open access journal

hematology reports

ISSN 2038-8322 - eISSN 2038-8330 | www.hematologyreports.org

1st SOHO Italy Clinical and Biological School of Multiple Myeloma

Virtual Event, 15 – 17 December 2020

EDUCATIONAL BOOK

Hematology Reports 2020; 12:s2

Hematology Reports

ISSN 2038-8322 | eISSN 2038-8330

Publisher

PAGEPress Publications

Via A. Cavagna Sangiuliani 5

27100 Pavia, Italy

Tel. +39.0382.1549020 – Fax. +39.0382.1727454

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Day 0 — 15 Dec 2020

18.30 - 18.45 Introduction and presentation of SOHO School project - SOHO Italy Presidents: C. Cerchione - G. Martinelli - H. Kantarjian

18.45 - 19.00 Presentation of 1st SOHO Clinical and Biological School of Multiple Myeloma - Scientific Board: C. Cerchione - G. Martinelli - H.C. Lee - M.V. Mateos - K.C. Anderson

19.00 - 19.30 Lecture: How I manage Multiple Myeloma in Europe in 2020 – C. Cerchione

19.30 - 20.00 Lecture: How I manage Smoldering Multiple Myeloma in 2020 – M.V. Mateos

20.00 - 20.30 Lecture: How I manage relapsed/refractory Multiple Myeloma at MD Anderson Cancer Center – H. Lee

20.30 - 21.00 Lecture: Future of Multiple Myeloma - K.C. Anderson

Day 1 — 16 Dec 2020

Frontal Session

08.30-08.50 Opening and introduction to the project: C. Cerchione – G. Martinelli

Biology and MRD in Multiple Myeloma: N. Bolli – C. Terragna – G. Martinelli

08.50 – 09.10 Molecular pathogenesis of multiple myeloma - N. Bolli

09.10 – 09.30 Minimal Residual Disease Assessment Within the Bone Marrow of Multiple Myeloma – C. Terragna

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09.30 - 09.50 Exploring microenvironment – from biology to therapy – A. Romano

09.50 – 10.10 Importance of imaging for MRD evaluations – E. Zamagni

10.10 – 10.30 Future perspectives in MRD in Multiple Myeloma: where are we going? – G. Martinelli

10.30 – 10.50 break

Clinical Session 1 – C. Cerchione – K.C. Anderson – M.V. Mateos - H.C. Lee

10.50 - 11.10 Present and future of management of frontline Multiple Myeloma – M.V. Mateos

11.10 – 11.30 Present and future of management of relapsed/refractory Multiple Myeloma – C. Cerchione

11.30 – 11.50 Major differences between Europe and USA in the management of Multiple Myeloma – K.C. Anderson

11.50 – 12.10 Antibody-Drug Conjugates (ADCs) and Bispecific T-cell Engagers (TCEs) in Multiple Myeloma: How are they changing the current panorama – H. Lee

12.10 – 12.30 Discussion

Clinical Session 2 – A. Bosi – A. Olivieri - V. Montefusco
Frontline transplant-eligible setting

12.30 – 13.00 Transplant-eligible patients: old versus new – V. Montefusco

13.00 - 13.20 Role of allogenic stem cell transplantation in MM in novel agents era – A. Olivieri

13.20 - 13.30 Discussion

13.30 - 14.00 Mini lunch break

14.00 - 15.00 **Symposium**

Clinical Session 3 – F. Lanza, P. Tosi, D. Derudas
Transplant-inelegible setting and selected conditions

15.00 - 15.20 Transplant-inelegible patients: old and new options for elderly fit patients - P. Tosi

15.20 – 15.40 Transplant-inelegible patients: old and new options for elderly - unfit/frail patients - A. Larocca

15.40 – 16.00 Extramedullary disease and plasma cell leukemia D. Derudas

Clinical Session 4 – M. Martino, F. Di Raimondo, A. Vacca
Near future and new perspectives in Multiple Myeloma

16.00 - 16.20 CAR-T: lights and shadows in Italy – M. Martino

16.20 – 16.40 New Drugs on the Horizon – F. Di Raimondo

16.40 - 17.00 Endothelial cells and dendritic cells as immunosuppressive agents in patients with Multiple Myeloma – A. Vacca

17.00 - 17.30 Discussion – Questions and Answers

Day 2 **17 Dec 2020**

Young session

Selected oral presentations with project presentations in different categories

Chairs Big Faculty:
Cerchione C, Martinelli G, Lee HC, Mateos MV, Anderson KC, Bolli N, Bosi A, Cavo M, Derudas D, Di Raimondo F, Gay F, Lanza F, Larocca A, Martino M, Montefusco V, Olivieri A, Romano A, Terragna C, Tosi P, Vacca A, Zamagni E

15 min presentation + 15 min discussion)

Pre-clinical session

08.30 - 09.00 New targets and new approaches in Myeloma: extracellular vescicles as liquid biomarkers – Antonia Reale – Melbourne - Australia

09.00 - 09.30 The Myeloma-specific tumor suppressor FAM46C orchestrates plasma cell secretory capacity through its interaction with FNDC3 proteins – Enrico Milan – Milano

09.30 - 10.00 Targeting of the cell-adhesion system within the tumor microenvironment blocks angiogenesis, impairs diseases progression and dissemination in multiple myeloma – Antonio Giovanni Solimando - Bari

10.00 - 10.30 Functional role of bone marrow CD8+ tissue-resident memory T-cells in Multiple Myeloma - Melania Carlisi - Palermo

10.30 - 10.45 Questions and answers and discussion for future project/trials

10.45-11.00 break

11.00 - 11.30	Multiple Myeloma cell-derived MICA+ extracellular vescicles impair NKG2D-mediated NK cell immune surveillance – Elisabetta Vulpis - Roma
11.30 - 12.00	Endothelial cells and dendritic cells as immunosuppressive agents in patients with Multiple Myeloma – Ilaria Saltarella - Bari
12.00 - 12.30	Dissecting Daratumumab mechanisms of resistance at a single-cell level – Matteo Da Vià – Milano
12.30 - 13.00	Predictive parameters at first and second relapse, is there a role for sFLC? A real-life unicentric retrospective study in the era of novel agents – Uros Markovic – Catania
13.00 - 14.00	**Symposium** Introducing anti-CD38 in daily practice of Multiple Myeloma - C. Cerchione
14.00 - 14.30	Len/dex combination as first-line therapy of frail Multiple Myeloma patients: a monocentric real life study – Claudia Bellofiore - Catania
14.30 - 15.00	Evaluation of treatment approaches and outcome in newly diagnosed Multiple Myeloma patients, autologous stem cell transplant (ASCT) eligible or not, who presented early relapse or were refractory to first-line induction or first-line treatment – Francesca Fazio – Roma
15.00 - 15.30	Combined treatment with doxorubicin and ENPP1 inhibitor for improving anti-Myeloma innate immune response – Lorenzo Cuollo - Roma
15.30 - 16.00	Comparison of different imaging techniques in Multiple Myeloma patients – Sara Grammatico - Firenze

16.00 - 16.30 Addition of BCNU to Melphalan deepens responses without increasing toxicity thereby improving survival before second autologous stem cell transplant for relapsed Multiple Myeloma –
Joshua Thomas - Chicago - USA

16.30 - 17.00 Allograft in Multiple Myeloma: Experience of Multiple Myeloma GIMEMA Lazio group –
Federico Vozella – Firenze

17.00 - 17.30 Primary Plasma Cell Leukemia experience of 7 years in a Peruvian referral cancer center -
Jule Vasquez - Lima - Perù

17.30 - 18.00 Questions and answers and discussion for future projects/trials

After presentations, all projects will be started to be defined, with their teams, objectives and timepoints

18.00 - 18.30 Special Lecture
Present and future of European Myeloma Network (EMN) Clinical Trials - F. Gay

18.30 - 19.00 Conclusions and next steps
C. Cerchione, G. Martinelli

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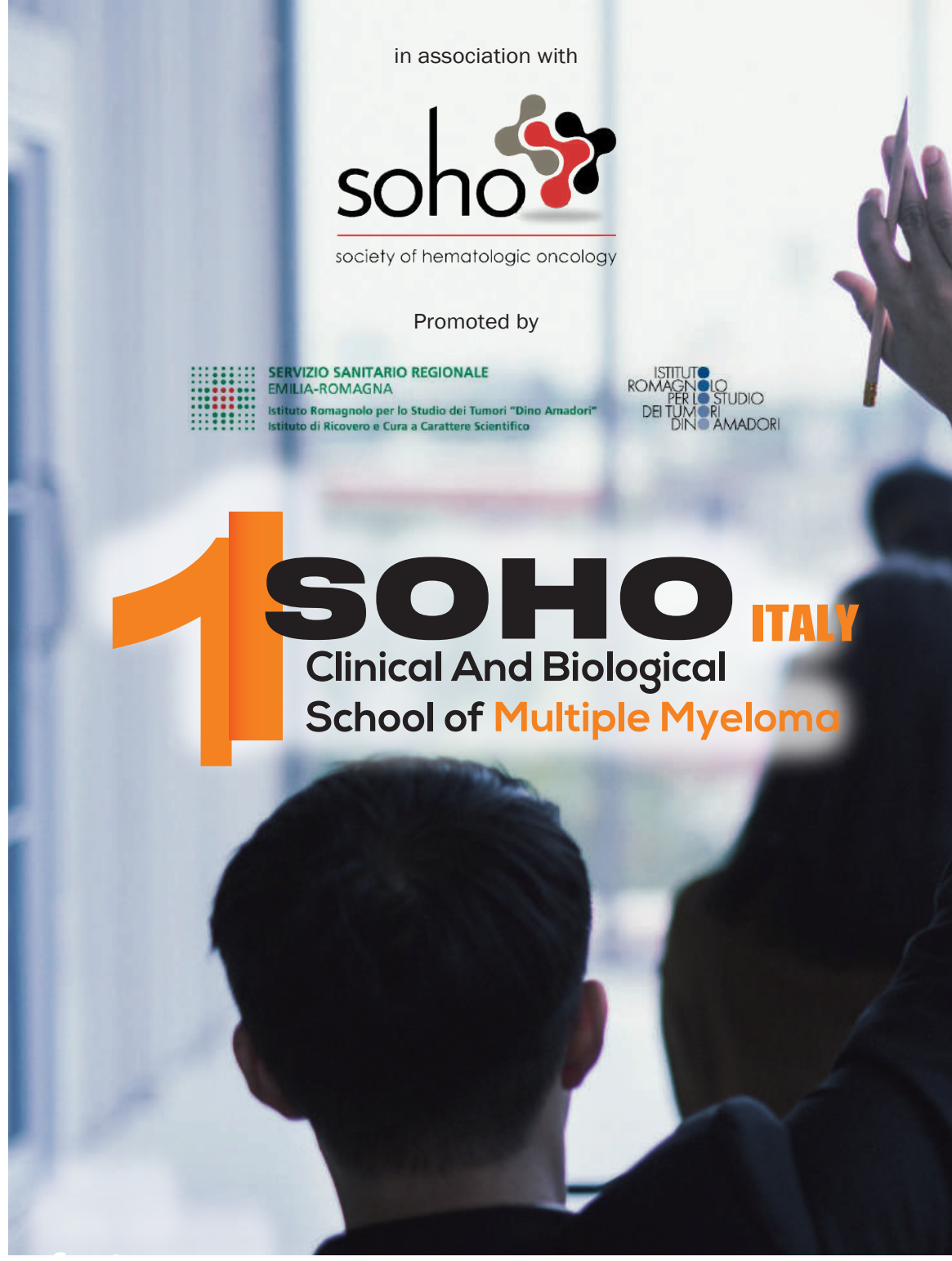

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How I manage frontline transplant-eligible multiple myeloma in Italy

Vittorio Montefusco,[1] Giovanni Martinelli,[2] Claudio Cerchione[2]

[1]Onco-Hematology, ASST Santi Paolo e Carlo, Milan; [2]Hematology Unit, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST) IRCCS, Meldola (FC), Italy

Abstract

The treatment of transplant-eligible multiple myeloma patients in Italy consists in an induction phase based on bortezomib plus thalidomide plus dexamethasone (VTd), followed by a single or tandem autologous stem cell transplantation (ASCT), followed by lenalidomide maintenance. This approach offers an overall response rate of 93% and a CR rate of 58% with acceptable toxicity. Lenalidomide maintenance adds a significant increase in disease control, with a progression free survival after ASCT of 53 months, and an overall survival of 86 months. Second primary malignancies represent the most concerning toxicity of lenalidomide maintenance with a 6.9% incidence. However, the benefit in terms of increased myeloma control largely outweigh this complication. The incorporation of daratumumab in this treatment schema will further improve these clinical results.

Introduction

Multiple myeloma (MM) accounts for 1% of all malignant diseases and 10% of all hematological neoplasms.[1] In the last two decades, the consolidation of the role of autologous stem cell transplantation (ASCT) and the incorporation of novel agents in the first line of therapy have significantly improved the quality of responses and the overall survival (OS).[2-4] Several studies have clearly demonstrated that ASCT is superior to standard therapy, also when the latter includes new drugs.[5-7] The upper limit of the transplant age has been progressively raised by the 60 years of the first ASCT studies,[8] to the 70 years currently adopted in the most recent protocols.[9] In several centers fit patients older than 70 years are considered for ASCT.[10] Therefore, since the transplant age threshold set at 70 years coincides with the average age of diagnosis of the disease, approximately half of MM are considered transplant eligible. In the following sections, I will discuss in detail the transplant approach adopted in Italy.

Management of transplant eligible patients in Italy

The goal of the first line of therapy consists in the achievement of the maximal depth of disease response, that translates into an optimal duration of disease control and OS. Presently, the first line of therapy consists in an induction phase, followed by a single or tandem ASCT, followed by a maintenance therapy. Each phase of the treatment program has specific characteristics.

Induction

Induction should have a remarkable quick effect, since patients frequently suffer from pain or renal failure, minimal nephrotoxicity, and low myelotoxicity, in order to not interfere with the subsequent stem cell mobilization. Induction should reverse end organ damage and improve the performance status. At present, the optimal induction combination consists in a triplet containing bortezomib plus an immunomodulatory drug (IMiD) plus dexamethasone.[11] In Italy bortezomib plus thalidomide plus dexamethasone (VTD) is by far the most commonly used triplet. The Italian collaborative group GIMEMA has conducted a phase III study comparing the combination VTD *versus* thalidomide plus dexamethasone (TD), at that time one of the standard treatments for induction. Patients were randomized in a 1:1 ratio to receive 3 cycles of VTD or TD, then tandem ASCT with 2 sequential doses of melphalan 200 mg/m^2 given 3 to 6 months apart, then 2 modified VTD or TD cycles, accordingly to the treatment arm. Dexamethasone maintenance was then used until disease progression, relapse, or toxicity.[12] The primary composite endpoint of the study consisted in the number of complete remisisons (CR) and near CRs (nCR) after the induction therapy. The trial enrolled 480 patients. After induction, a significant advantage for the VTD arm in terms of CR + nCR (31% *versus* 11%, p < 0.0001) was observed. After consolidation therapy, the CR plus nCR rate was again significantly higher in the VTD arm *versus* the TD arm (62% *versus* 45%, p=0.0002), and the ORR was 93% *versus* 79% in the VTD arm *versus* the TD arm, respectively (p<0.0001). CR rate was 58% in VTD and 41% in TD patients (p=0.0001). In the same period, the Spanish PETHEMA group conducted the PETHEMA/GEM study that compared 6 courses of VTD versus TD versus a combination of vincristine+BCNU+melphalan+cyclophosphamide+prednisone, and vincristine+BCNU+doxorubicin+dexamethasone, and bortezomib (VBMCP/ VBAD/B), as induction before ASCT.[13] The transplant phase consisted in a single ASCT conditioned with melphalan 200 mg/m^2. After transplant, patients were randomized to receive a 3-year maintenance with interferon α-2b versus thalidomide 100 mg per day orally versus thalidomide 100 mg per day orally plus one cycle of bortezomib on days 1, 4, 8, and 11 every 3 months. The primary endpoint consisted in CR rate after induction and after ASCT. The trial enrolled 380 patients. The overall response rate (ORR) was 85% in the VTD arm, 72% in the TD arm, and 75% in the VBMCP/VBAD/B arm. The CR rate after induction was higher in the VTD arm respect to the TD arm (35% *versus* 14%, p=0.001) or the VBMCP/VBAD/B arm (35% *versus* 21%, p=0.01).

The combination of bortezomib plus cyclophopsphamide plus dexamethasone (VCD) represents an acceptable alternative to VTD. The French phase III IFM2013-04 trial compared 4 VTD cycles to 4 VCD

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Key words: Multiple myeloma, bortezomib, autologous stem cell transplantation, lenalidomide.

Conflict of interest: VM has received honoraria and travel grants from Janssen, Celgene, Bristol-Myers Squibb, Amgen and Takeda.

Contributions: VM, GM, CC conceived the work and wrote the paper.

Acknowledgments: The author thanks Mr. And Mrs Ferrari for their funding. The author thanks also Amo La Vita ONLUS for their support.

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Hematology Reports 2020; 12(s2):8954
doi:10.4081/hr.2020.8954

cycles as induction before ASCT.[14] Three hundred and forty patients were enrolled. The primary endpoint was the post-induction VGPR rate. In the VTD arm 66.3% of patients achieved at least a VGPR *versus* 56.2% in the VCD arm (p=0.05). The CR rate was 13.0% in the VTD arm, and 8.9% in the VCD arm (p=0.22), ORR was significantly higher in the VTD arm, 92.3% *versus* 83.4% in the VCD arm (*P*=.01). Despite its minor cytoreductive efficacy, VCD can be considered for patients at high risk of peripheral neuropathy.

Since the optimal backbone for induction is represented by bortezomib and dexamethasone plus an IMiD, the rational evolution of this triplet was the replacement of thalidomide with lenalidomide (VRD). In the French phase III IFM 2009 study, transplant-eligible patients have been randomized between 3 VRD cycles followed by a single ASCT and a consolidation with 2 VRD cycles *versus* 8 VRD cycles without transplantation. All patients received lenalidomide maintenance for one year.[6] The primary endpoint was PFS. The study enrolled 700 patients. After the consolidation phase, and before maintenance start, the CR rate was 78% in the VRD-ASCT arm *versus* 69% in the VRD arm (p=0.03).

Despite the advantages of VRd, for regulatory reasons, at present, VTd is the standard induction in Italy.

Transplant

The transplant phase consists in two steps: peripheral blood stem cell (PBSC) mobilization and collection, and ASCT. There are two main options for PBSC mobilization. The first consists in the administration of chemotherapy, mostly cyclophosphamide 2-4 gr/sqm, followed by filgrastim injections until an adequate level of CD34+ cells in blood is achieved. The second is a steady-state approach, only based on filgrastim injections. Since the PBSC number obtained with this procedure is generally lower than the chemo-based approach,[16] it is frequently necessary to combine it with plerixafor, a chemokine-receptor 4 antagonist that enhances the PBSC mobilization activity of filgrastim.[17] The optimal stem cell dose for each transplant is 4-6 x 10^6 CD34+/Kg, while the minimum dose required for a safe transplant is 2 x 10^6 CD34+/Kg.[18] Notably, patients candidate to a tandem ASCT should collect the required amount of PBSC before the start of the transplant phase, since a second collection after ASCT is hardly feasible, in particular if done close to previous transplant.[19]

The optimal conditioning regimen for ASCT in MM is melphalan 200 mg/sqm. Patients with renal failure require a dose reduction of melphalan, but the procedure can be safely performed also in patients with dialytic replacement therapy.[20] Several attempts have been done to find a more efficient preparative regimen, but, to date, without success. In a phase II study intravenous busulfan plus melphalan has been compared with standard melphalan. Despite an increase in PFS, the response rate was similar to that observed in the control arm, and the toxicity was significantly increased.[21] The incorporation of bortezomib in the melphalan 200 mg/sqm conditioning has been evaluated in the phase III IFM 2014-02 trial, and compared with melphalan 200 mg/sqm standard regimen. The primary endpoint of the study was the CR rate at day 60 after transplant, and both arms had similar results (44% CR rate in bortezomib-melphalan arm versus 46% in the melphalan arm).[22,23]

In the GIMEMA trial, the CR or near CR (nCR) rate after consolidation was significantly higher in the VTD arm versus the TD arm (62% vs. 45%, p = 0.0002), and the ORR was 93% versus 79% in the VTD arm versus the TD arm, respectively (p<0.0001). With regard to survival endpoints, the 3-year PFS was longer in the VTD arm versus the TD arm (68% versus 56% p=0.0057), with a favorable hazard ratio (HR) (HR 0.63, p = 0.0061).[12] A recent update of this trial, with a median follow-up for surviving patients of 124 months, has shown that the 10-year PFS was 34% in the VTD, and 17% in the TD arms, respectively (HR 0.62, CI 0.50-0.77; p<0.0001). Ten-year OS was 60% in the VTD arm versus 46% in the TD arm (HR 0.68, CI 0.51-0.90; p=0.007). Median OS was not reached in the VTD arm, and 110 months in the TD arm.[24] Ten-year PFS of high risk cytogenetic patients, defined by the presence of either del(17p) or t(4;14), was 40% for standard risk VTD, 20% for standard risk TD, 17% for high risk VTD, and 3% for high risk TD patients. Ten-year OS of high-risk cytogenetic patients was 67% for standard risk VTD, 52% for standard risk TD, 42% for high risk VTD, and 22% for high risk TD patients.

A debated point is represented by the need to perform a single as opposed to a double ASCT. The EMN02/HO95 phase III trial addressed this question. A part of this trial was committed to compare the role of tandem ASCT respect to the single ASCT. It has been shown that tandem transplantation improved the depth of the response by 25%, and more than 50% of the patients achieved at least a CR.[7] PFS was not reached in the tandem ASCT arm versus 45 months in the single ASCT arm, and the 3-year PFS was 73%, and 60%, respectively (HR=0.66, CI=0.45-0.96; P=0.030).[25] Interestingly, the increase in PFS observed in the tandem arm was particularly evident in the subgroups of patients with high risk disease, either defined as bone marrow plasma cells >60% (HR=0.41, CI=0.22-0.77; p=0.006), elevated LDH (HR=0.52, CI=0.28-095; p=0.034), or high risk cytogenetics (HR=0.49, CI=0.24-1.02; p=0.057).

Consolidation

In some trials, the transplant phase is followed by a short-term period of non-intensive therapy. In the GIMEMA trial patients received either VTD or TD, according to their originally assigned arm.[12] VTD consolidation was able to upgrade the CR and nCR rate from 63% to 73%, while TD consolidation from 55% to 61%.[26]

In the EMN02/HO95 patients were randomized to two VRd consolidation cycles followed by lenalidomide maintenance *versus* direct start of lenalidomide maintenance.[7] The median PFS of patients in the consolidation arm was 59 months, respect to 46 months of the no consolidation arm (HR 0.77, CI 0.63-0.95; p=0.014).

At present, in Italy consolidation is not widely used, since this treatment is not reimbursed by the Italian healthcare system.

Maintenance

At least three studies have demonstrated the advantage of post-ASCT lenalidomide maintenance.

The IFM 2005-02 study enrolled MM patients with at least a stable disease after ASCT.[27] Patients were randomized to daily lenalidomide 10 mg for the first 3 months, afterwards increased to 15 mg if tolerated, or placebo. The primary endpoint was PFS. The study enrolled 614 patients. The median PFS was 41 months in the lenalidomide arm and 23 months in the control arm (HR 0.50; p<0.001). The CALGB 100104 study has a similar design to the previous study. This trial enrolled patients who achieved at least a stable disease after ASCT. Patients were randomized to daily lenalidomide 10 mg for the first 3 months, afterwards increased to 15 mg if tolerated, or placebo.[28] The primary endpoint was time to progression, defined as time to progressive disease or death from any cause after transplantation. The trial enrolled 460 patients. The median PFS was 39 months in the lenalidomide arm and 21 months in the con-

trol arm (HR 0.37, CI 0.26-0.53; p<0.001). Both studies highlighted an increased risk of developing a second primary malignancy in patients receiving lenalidomide treatment. In a meta-analysis of individual patient data including 3218 subjects, it has been shown that 5-year cumulative incidences of all second primary malignancies were 6.9% in lenalidomide maintenance patients and 4.8% in control patients (HR 1.55, CI 1.03-2.34; p=0.037).[29] The 5-year rate of solid second primary malignancies was 3.8% in lenalidomide patients, and 3.4% in control patients (HR 1.1, CI 0.62-2.00; p=0.72), while the 5-year rate of hematologic second primary malignancies was 3.1% in lenalidomide patients, and 1.4% in control patients (HR 3.8, CI 1.15-12.62; p=0.029). An important meta-analysis on lenalidomide maintenance included data from the IFM 2005-02, CALGB 100104, and GIMEMA MM-PI-209 trials.[30] A total of 1208 patients were included, 605 received lenalidomide maintenance, and 603 placebo or observation. The median PFS was 53 months for the lenalidomide group and 24 months for the placebo or observation group (HR 0.48, CI 0.41-0.55). Median OS was not reached in the lenalidomide group, and was 86 months in the placebo or observation group (HR, 0.75, CI 0.63-0.90; p = 0.001). Seven-year OS rate was 62% with lenalidomide maintenance and 50% with placebo or observation. This meta-analysis confirmed the increased number of second primary malignancies in patients on lenalidomide maintenance. However, the benefit in terms of improved myeloma control in lenalidomide maintenance patients was unquestionably superior to the intrinsic risk of developing a second primary malignancy.

Conclusion and future perspective

Presently, myeloma treatment of transplant eligible patients in Italy consists in 4-6 VTD cycles, followed by one or two ASCT, followed by lenalidomide maintenance. In case of high-risk disease, a tandem ASCT is recommended. This approach offers excellent results in terms of PFS and OS. However, the availability of more effective induction regimens, such as VRd or the combination of daratumumab with VTd or VRd are extremely promising in terms of long-term disease control.[6,9,31] The possible rescue of relapsed patients with newer immunotherapeutic approaches, such as CAR-T, bispecific antibodies and antibody-drug conjugates, along with new drugs paves the way to a very long term disease control.

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How I manage frontline transplant-ineligible multiple myeloma

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Abstract

The Multiple Myeloma (MM) is a plasma cells hematological malignancy with a median age of 69 years at diagnosis. The autologous stem cell transplantation is the standard of care for this disease but less than half of newly diagnosed patients are assessed for this treatment due to comorbidities or complications of disease. The management of transplant ineligible MM patients is based on the balance safety and efficacy of the new available regimen and a careful assessment of the frailty status is mandatory to define the goals. In this review we discuss of the clinical dilemmas in the management and define how to manage them based on the evidence from clinical trials and "real life" experience.

Introduction

Multiple Myeloma (MM) is an hematological malignancy characterized by an abnormal proliferation of monoclonal plasma cells. It accounts for 10% of all the hematological neoplasms.

The diagnosis requires the documentation of ≥10% monoclonal plasma cells and one or more markers of active disease defined with the acronym CRAB (C = elevated serum calcium, R = renal impairment, A = anemia, B = lytic bone lesions).[1] Recently new biomarkers of malignancy have been introduced as myeloma defining events (MDEs) in absence of CRAB features. These MDEs are represented by bone marrow clonal plasma cells ≥60%, an involved/uninvolved serum free light chains ratio ≥100 and/or presence of > 1 lytic lesions on magnetic resonance imaging (MRI).[2]

The median age at diagnosis of MM is 69 years, approximately 70% are older than 65 years and 40% are older than 75 years.[3-5] Moreover it is predictable the in 2050 434 million people in the world will be older than age 80[6] with 150000/ year newly diagnosed MM over 80 years.

In the last decades it has been observed a significant improvement either in the Progression Free Survival (PFS) and Overall Survival (OS) of the MM patients associated with the introduction of novel agents (immunomodulatory drugs, proteasome inhibitors, monoclonal antibodies) and mainly the more extensive use of high-dose therapy followed by autologous hematopoietic stem cell transplantation (aHSCT) and maintenance treatment.[7-9]

However several studies have shown a more marginal benefit in the elderly population (particularly over 75 years and older). That could be explained by an higher rate of comorbidities and organ dysfunction associated with the aging in this setting of MM patients, that exclude the most of this population from aHSCT.[7-9]

Either a close evaluation of the frailty with a geriatric assessment either a management of comorbidities is mandatory to exploit the efficacy of the association of the new agents and immunotherapy drug and to reduce the risk of treatment related toxicities with an improvement of the treatment efficacy in terms of PFS/OS and quality of life (QoL).

The management of elderly MM patients requires as first step the evaluation of transplant eligibility and then the assessment of frailty in order to define the best therapy available.

Evaluation of transplant-eligibility and frailty score

Historically the age cut-off accepted in clinical trials for eligibility for aHSCT was 65 years. But this limit excluded more than two-third of newly diagnosed MM patients considering the median age at diagnosis. In the clinical practice the age cut-off is extended to 70-75 years.[10,11]

The European Society of Medical Oncology (ESMO) recommended aHSCT up to the age of 70 years, contrariwise, the National Comprehensive Cancer Network (NCCN) did not set an age cut-off. [12,13]

Recently it has been documented an increasing use of aHSCT in the older population considering mostly retrospective or population based studies. A first analysis evaluated the trend of aHSCT in 31 European countries with a rate of aHSCT in patients older than 65 years of 3% between 1991 and 1995 versus 18% between 2006 and 2010. Costa et al. described similar data in USA and Canada.[14,15]

Subsequent trials demonstrated the feasibility of aHSCT in patients aged > 65. The most prolonged hospitalization and most frequent post- aHSCT complications observed in several clinical trials did not translate in higher treatment-related mortality (TRM) compared to younger patients, probably due to a reduction of conditioning regimen (from 200 to 100-140 mg/m^2 of melphalan). Data from trial including tandem transplant followed by consolidation and maintenance showed an increased TRM (19%) in patients older than 70 years compared with younger patients.[16-21]

These data encourage the use of aHSCT in older patients but only after a careful selection of patients, that must be based on the evaluation of the fitness with geriatric assessment (GA) tool, consideration of alternative therapies and the availability of caregiver collaboration, in order to reduce the rate of complication and TRM. In absence of clear data from clinical trials the optimal dose of melphalan has not been established. However in patients > 70 years, with renal impairment, and/or performance status less than 90% is reasonable to reduce the dose of melphalan to 100-140 mg/m^2.

Considering the efficacy of new combination with second-generation proteasome inhibitors, immunomodulatory agents and monoclonal antibodies the role of aHSCT in older patients is challenging. For example, recently the MAYA and ALCYONE trials including the addition of Daratumumab

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Key words: Multiple Myeloma; Stem cell transplantation; Frailty.

Conflict of interest: The authors declare no potential conflict of interest.

Hematology Reports 2020; 12(s2):8956
doi:10.4081/hr.2020.8956

with standard regimes in transplant-ineligible population (respectively Daratumumab plus Lenalidomide-Dexamethasone – DaraRd - and Daratumumab plus Bortezomib-Melphalan-Prednisone – DaraVMP) showed a significant decreasing of risk of death or progression (HR 0,56 and 0,43) and high rates of minimal residual disease (MRD) negativity (25%).[22,23]

Once defined the ineligibility for ASCT, the choice of the best regimen depends on the fitness of the patients. In fact the elderly population is heterogeneous and the aging is associated with a high rates of comorbidities and diseases that could exacerbate the side-effects of the available drug combination and increase the morbidity and mortality. For example, uncontrolled diabetes could lead to medical complication due to steroids treatment and increase myeloma-related mortality.[24]

Pre-existent peripheral neuropathy may limit the therapy with thalidomide and bortezomib. Cardiovascular diseases (cardiac arrhythmias, congestive cardiac failure, uncontrolled arterial hypertension) need a careful assessment in case of treatment with proteasome inhibitors (PI) particularly carfilzomib. Immunomodulatory drugs (IMIDs), as lenalidomide and thalidomide, could not be an optimal option in case of previous history of thrombosis. Renal failure affected a high proportion of patients with diagnosis of MM and could need an adjustment of the dosage of some drugs like lenalidomide.

The comorbidities, the decreased organ function and the frailty make the patients more vulnerable to the side effects of therapy with a reduced adherence to therapy, early discontinuation and decreased treatment efficacy. Bringhen et al. have showed in a large meta-analysis of 1435 elderly patients enrolled in 4 randomized trials treated with thalidomide and/or bortezomib, that the risk of death was higher in patients aged ≥75 years (HR 1,44, 95%, CI 1,20 - 1,72, $p < 0,01$), in patients affected by renal failure (HR 2,02, 95%, CI 1,51 - 2,70, $p < 0,01$) and in those that developed grade 3-4 infections and/or cardiac and gastrointestinal events during the treatment (HR 2,53, 95%, CI 1,74 - 3,64, $p < 0,01$). Also the patients that needed a discontinuation due to adverse events (HR 1,67, 95%, CI 1,12 – 2,51, $p = 0,01$) showed a worse increased risk of death. The estimated 3-years OS was 68% in patients £ 75 years and 57% in those ³ 75 years (HR 1,44, 95%, CI 1,2 - 1,72, $p < 0,01$).[25]

A frailty status may affect significantly the compliance to therapy: for example the management of oral therapy may be difficult in presence of mental or cognitive impairments with requirement of caregiver and, on the other hand, an intravenous or subcutaneous treatment, with the need of frequent hospital accesses, could be a limitation for patients with mobility impairment or in absence of caregiver. For these reasons recently different morbidity scores and GA tools were introduced and implemented to evaluate the fitness of patients and consequently define the goal of therapy with the best option available according to the frailty status by preventing and managing the side effects of chemotherapy and limiting the discontinuation of the treatment

In fact the terms aging and frailty represent different concepts. The aging is associated with a physiological reserve decline while the frailty is a complex syndrome characterized by an increased vulnerability and physiological decline. For this reason, because of heterogenicity of chronological and functional age, it is needed a multidimensional assessment that consider the age, comorbidities, performance status, nutritional status, polypharmacy, cognition, socioeconomics factors to define the frailty of transplant- ineligible MM patients.

The International Myeloma Working Group (IMWG) frailty index categorizes MM patients as fit (score 0, 39%), unfit (score 1, 31%) and frail (≥2, 30%)) using as domains age, comorbidities (Charlson Comorbidity Index) and functional status of patients (Katz Activities of Daily Living, ADL and Lawton's Instrumental Activities of Daily Living, IADL).[26] This tool has not been validated in "real life" but only in clinical trial[27] and the patient aged > 80 years are defined as frail by definition. The IMWG frail score defines a worse PFS and OS with increased discontinuation of therapy for the frail category. The fit group shown an 3-years OS of 84%, the intermediate fit 76% and frail population 57% (HR 3,57: $p < 0,01$). The frail patients documented also a higher risk of grade 3/4 non hematological toxicities compared with the other groups (HR 1,57; 95%; CI 1,12 - 2.2). This score can be calculated with web application *http://www.myelomafrailtyscorecalculator.net/*.

Another tool, the revised myeloma comorbidity index (R-MCI), categorizes the patients according to Karnofsky Performance Status (KPS), frailty, age, lung and renal function and cytogenetics. It was set in Germany on a cohort of 801 newly diagnosed MM (NDMM) consecutive patients. The categorization is between fit (Index ≤ 3), intermediate (Index 4-6), frail patients (Index > 6) with a median OS of 10,1, 4,4 and 1,2 years respectively.[28]

Regarding other fitness assessment, the Cancer and Aging Research Group Geriatric assessment tool has been used to define the ASCT eligibility and the Health-related Quality of Life assessment represents an important tool in the clinical trials to define complementary endpoints particularly in transplant-ineligible MM patients.

Unfortunately there is not an accordance between the different GA tools: for example a comparison of IMWG frailty score with Freiburg Comorbidity Index (based on renal function, KPS and Lung impairment) shown a discordance of 57% in patients categorization.[29]

The frailty assessment, regardless the tool available, is, in conclusion, mandatory in this setting of patients to tailor and optimize treatment both in clinical trial and in the real-life practice.

In our Department we select the fit patients for aHSCT between 65-70 years by IMWG frailty assessment and availability caregiver support. The patients non eligible to HSCT are stratified by IMWG frailty assessment upfront and during relapse.

The treatment of newly diagnosed transplant-ineligible MM patients

Once defined the ASCT ineligibility and the fitness status, the goal of treatment must lead the choice of the best regimen (Table 1).

In the last decades the introduction of novel agents has expanded dramatically the availability of effective regimen. The backbone of the treatment in this setting was the alkylator-based therapy, typically oral melphalan-prednisone (MP). The first novel agent associated with MP was thalidomide (MPT). Seven randomized clinical trials tested this regimen[30-36] in transplant ineligible population: all the trials demonstrated an improvement in PFS but only four out of seven showed a benefit in order of OS. However the introduction of thalidomide was associated with a increased risk of deep venous thrombosis, peripheral neuropathy, constipation and high rates of treatment discontinuation and dose reduction. For these reasons this regimen is currently replaced by other effective and less toxic treatments.

Another association of new drugs with MP is the triplet bortezomib – melphalan – prednisone (VMP). The VISTA trial[37,38] showed superiority versus MP in terms of PFS and OS (median 24 *vs* 16,6 months, HR 0,48 p < .001 and median 56,4 *vs* 43,1 months, HR 0,695 p < .001 respectively) and these results was confirmed in different sub-groups by age (≥75 years), disease stage (ISS stage III) and renal function

(eGFR < 60 ml/min). Because of the high rates of peripheral neuropathy associated with Bortezomib it was introduced a one-weekly and sub-cutaneous dosing with reduction of the side effects incidence without difference in efficacy.[39,40]

In the GIMEMA-MM-03-05 trial the regimen VMP-thalidomide followed by bortezomib-thalidomide (VT) maintenance (VMP-VT) for 2 years was compared with VMP.[41,42] The median PFS after a follow-up of 54 months and the 5 -years OS was superior with VMP-VT regimen.

An alkylator-free regimen was evaluated by the PETHEMA group with the comparison of bortezomib-thalidomide- prednisone (VTP) versus VMP.[43,44] After induction the patients were randomized between VT and bortezomib-prednisone (VP). The trial showed a median PFS of 32 months for VMP and 23 months for VTP (p =.09) with a prolonged OS in the VMP arm (median 63 *vs* 43 months; HR:0,67, p =.01). No difference was observed in OS between the two maintenance arms with PFS pf 32 months for VT *vs* 24 months of VP. The VT regimen was affected by a higher rate of cardiovascular adverse events. Most recently, considering the high rates of side effects associated with thalidomide, different trials tested preferably lenalidomide in combination for the treatment of transplant ineligible MM patients.

The association of lenalidomide with MP (MPR) was evaluated in two trial, ECOCG E1A06 and MM-015,[45,46] the first in comparison with MPT and the last versus MP and MPR-R (maintenance with continuous lenalidomide). The trials fail to demonstrate a superiority of MPR to MPT or MP in terms of PFS and PS. The MM-015 study shown only a PFS advantage in the MPR-R arm versus MPR because of the maintenance with Lenalidomide. Notably it was found high rates of grade III/IV hematological adverse events in the MPR arm, particularly for older patients (≥75 years).

The unacceptably hematological toxicity of the association of lenalidomide with melphalan shows that lenalidomide is not an optimal partner with alkylating agents highlighting the need of different combination.

The FIRST trial is a three arms trial that compared fixed therapy with Rd (18 cycles, Rd18) versus MPT and continuous Rd. This study demonstrated the superiority of continuous Rd combination versus MPT and Rd18 in terms of reduction of risk of death (HR 0,72, p =.0006 and HR 0,70, p = .0001) without difference in median PFS between MPT and Rd18. These advantages were observed in different subgroups (age, ISS, renal function, performance status) but not in the high risk population (defined for high-risk cytogenetics or elevated LDH). No difference in OS was observed between continuous Rd and Rd18 but Rd increased OS of patients compared with MPT. Notably a quality of life assessment was performed with a better result in the group of continuous Rd versus MPT, also because a low rate of side effects.[47,48]

The association of lenalidomide with bortezomib and dexamethasone (VRd) in comparison with Rd was explored in the SWOG S0777 trial that enrolled newly diagnosed MM patients without an intent of immediate ASCT. A twice-weekly intravenous bortezomib schedule was defined for this trial. The study showed an improved PFS (43 *vs* 30 months, HR 0,712; p = 0.0038) and OS (75 *vs* 64 months; HR 0.709; 0.025) in the VRd arm if compared with Rd regimen. The advantages remain after age-adjusted multivariate analysis. Evaluation of the population > 75 years old shown a better PFS and OS in the VRd arm. As expected the rate of grade 3/4 peripheral neuropathy was superior in the VRD arm (33% *vs* 11%) and grade 3/4 toxicities were described in 82% of VRd arm versus 75% in Rd arm.[49] Despite the encouraging results no clear conclusions can be made because the trial was not restricted to transplant ineligible patients.

In a Phase II dose-reduced association of lenalidomide, bortezomib and dexamethasone (VRd-lite), lenalidomide was administered as a single day dose of 15 mg (days 1-21), bortezomib subcutaneous at a dose of 1,3 mg/m^2 once-weekly (days 1-8-1-5-22) and dexamethasone at dose of 20 mg (days 1,2-8,9-15,16 and 22,23) if < 75 years old or on days 1-8-15-22 for patients

Table 1. Selected regimens in newly diagnosed transplant-ineligible multiple myeloma.

Study	Regimen	Median age in years (range)	ORR (%)	Grade 3 AE rates (%)	Median PFS (months)	Median OS (months)
Fayers *et al.*	MPT *vs* MP meta-analysis of six randomized trials n=1685)	72-78,5 y	NR	NR	20,3 *vs* 14,9 (HR 0,68: $p < 0,001$)	39,3 *vs* 32,7 (HR0,83; $p = 0,004$)
San Miguel et al.	VMP *vs* MP (n=682)	71 (57-90) *vs* 71 (48-91) y	≥PR 71 *vs* 35	81 *vs* 71	mTTP: 20,7 *vs* 15 (HR 0,54; $p < 0,001$)	56 *vs* 43 (HR 0,7; $p < 0,001$)
Benbouker *et al.*	cRd *vs* Rd18 vs MPT (n=1623)	73 (44-91) *vs* 73 (40-89) vs 73 (51-92) y	75 *vs* 73 *vs* 62	85 *vs* 80 *vs* 89	25,5 *vs* 20,7 (HR 0,7; $p < 0,001$) *vs* 21,2 (HR 0,72; $p > 0,001$)	4 years OS: 59% *vs* 56% (HR 0,9; $p = 0,31$) *vs* 51% (HR 0,78; $p = 0,002$ compared to cRd)
Durie *at al.*	VRd *vs* Rd *vs* 6 Maintenance Rd in both arms (n=525)	63 (56–71) y	82 *vs* 72	82 *vs* 75	43 *vs* 30 (HR 0,71; $p = 0,002$)	75 *vs* 64 (HR 0,709; $p = 0,025$)
Mateos *et al.*	D-VMP *vs* VMP (n=700)	71 (40-93) vs 71 (50-91) y	91 *vs* 74	41,6 *vs* 32,5	18-months PFS: 72 *vs* 50% (HR 0,5; $p < 0,001$)	OS data immature
Facon *et al.*	DRd *vs* Rd (n=737)	73 (45-90) y	VGPR: 79 *vs* 53	NR	NR *vs* 31,9 (HR 0,55; $p < 0,0001$)	OS data immature
Palumbo *et al.*	MPRx9 f/b R maintenance *vs* MPRx9 *vs* MPx9 (n=459)	71 (65-87) *vs* 71 (65-86) vs 72 (65-91) y	77 *vs* 68 *vs* 50	Grade 4 neutropenia/ thrombocytopenia: 3%/11% *vs* 32%/12% *vs* 12%/4%	31 *vs* 14 (HR 0,49; $p < 0,001$) *vs* 13 (HR 0,4; $p < 0,001$ compared to MPR-R)	3-years OS: 70% vs 62% (HR 0,79; $p = 0,25$) *vs* 66% (HR 0,95; $p = 0,81$ compared to MPR-R)

cRd: continuous lenalidomide-dexamethasone; HR: hazard ratio; D-VMP: daratumumab-bortezomib-dexamethasone; DRd. daratumumab-lenalidomide-dexamethasone; MP: melphalan-prednisone; MPT; melphalan-prednisone-thalidomide; MPR: melphalan-prednisone-lenalidomide; NR: not reported; ORR: overall response rate (partial response or better); OS: overall survival ; PFS: progression free survival; PR: partial response; R = lenalidomide; Rd: lenalidomide-dexamethasone; Rd18: lenalidomide-dexamethasone for 18 cycles; SAE: serious adverse events; TTP: time to progression; VRd: bortezomib-lenalidomide-dexamethasone; VMP: bortezomib-melphalan-prednisolone; VGPR: very good partial response

older than 75 years. Every cycle was administered over 35 days. The median age was 73 years (range 65-91 years).

The overall response rate was 81,8% with an acceptable safety profile.[50]

The new proteasome inhibitor carfilzomib in association with MP was compared with VMP in the phase III CLARY-ON trial. No statistical differences were found between the two arms in terms of PFS and OS. As expected in the VMP was described a higher rate of peripheral neuropathy and the KMP arm was characterized by an elevated incidence of cardiovascular events.

Two studies evaluated the role of daratumumab, anti-CD38 antibody, in the treatment of transplant ineligible MM patients.

The first one is the ALCYONE trial[51] that compared 9 cycles of VMP with or without daratumumab (Dara-VMP). In the Dara-VMP arm daratumumab continued as maintenance until disease progression. The study was tailored for transplant-ineligible patient and showed in the Dara-VMP arm a reduced risk of progression and death (0,5; 95% CI) and an increased rate of MRD negativity (10^{-5}). The result in terms of PFS was confirmed in the high-risk group, but is was not statistically significant. The safety report showed an increased rate of pneumonia (grade 3/4) in the daratumumab group.

The second trial incorporating daratumumab was the MAIA trial,[52] with the association of the monoclonal antibody with Rd (Dara-Rd) compared to Rd. Also for this trial the population considered was the transplant ineligible patients and the randomization was stratified according to age and geographic region. The treatment was continued until progression. After a median follow-up of 28,8 months the PFS was not reached in the Dara-Rd arm versus 31,9 months in the Rd arm. The overall response rate was superior in the daratumumab arm as well as the rate of deeper responses and MRD negativity to the level 10^{-5}. Dara-Rd arm remains superior in all the subgroups analyzed but no conclusion was derived about the high-risk cytogenetic group due to the small number of patients.

There are no clinical trials tailored for transplant ineligible patients with high risk disease, for which the only information that it can be used for the treatment of this population derived from subgroup analysis of clinical studies. Despite the absence of clear survival benefit for the association available in the high-risk patients, the IMWG recommends combination of proteasome inhibitor with immunomodulatory agent and dexamethasone like RVd-lite in this setting. Conclusive data regarding new agents as carfilzomib and daratumumab are not available

According to the regimens in use, the frailty stratification and the personalized goal of therapy, the following treatment selection could be proposed (Figure 1):

1. fit patients should achieve a complete response and MRD negativity with an increased PFS and OS by full dose triplets or new quadruplets (Dara-VMP, Dara-Rd, VRd, VCd, VMP, Rd) if not assessed for ASCT.
2. intermediate fit patients need a reduced-intensity regimens (weekly VMP, weekly VCd, Vd, Rd, Rd-R, VRd lite) to results in a good response, relieve symptoms and increase the overall response rate (ORR) and PFS.
3. the goal in the treatment of frail population is improve the quality of life and relieve the symptoms trough a low-toxic and dose-adjusted regimens (rd, vd). Palliation and supportive care represent an option for many of this setting of patients.

Different treatment approaches are applied in Europe compared with the USA and other countries because of the difference in approval processes by European Medicines Agency (EMA) and Food and Drug Administration (FDA) as well as the heterogeneity of national health care systems.

In Europe,[12] the two regimens approved by EMA are the VMP and Rd. About the other combination either MPT either MPR are available according with EMA statement but are not used in the clinical practice because of their high toxicity and low efficacy compared with Rd.

Notably the association bortezomib, cyclophosphamide and dexamethasone (VCD) is widely used but is not approved by EMA because of lack of confirmed data.

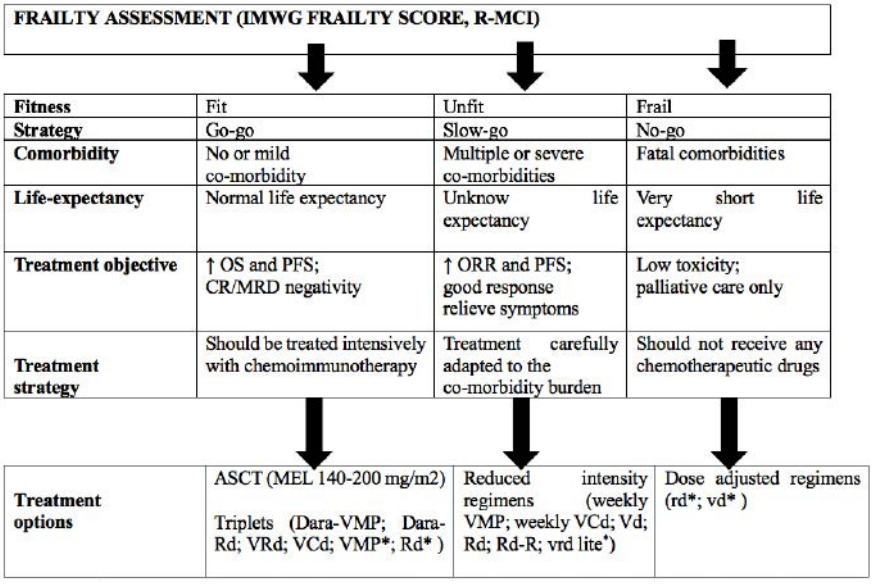
In the USA,[53,54] the FDA approved various regimens comprised the association with daratumumab with VMP and Rd.

The preferred and most widely used regimen is VRd (8-12 cycles followed by Lenalidomide maintenance) and second option is DaraRd (adding cost and long term toxicity). The VCD is also recommended for treatment of this population because of high response rate.

Unlike European approach, melphalan-based regimens are not recommended and used in this population due the concern of the development of stem cell damage followed by secondary myelodysplastic syndromes and leukemia.

In Italy the standard regimens approved by the Italian Drugs Agency, named AIFA (Agenzia Italiana per il Farmaco) are VMP and Rd. In the clinical practice is preferred the VMP association with subcutaneous and once-weekly bortezomib administration. A randomized trial comparing the two standards is ongoing (REAL trial). The choice, waiting for the results of the trials, is based on the patient and disease features, compliance, patient preference and logistics.

In our Department we consider that the



ASCT: autologous stem cell transplantation; MM, multiple myeloma; Rd, lenalidomide and dexamethasone; Rd-R, lenalidomide and dexamethasone followed by lenalidomide maintenance; R-MCI, revised myeloma comorbidity index; VCd, bortezomib, cyclophosphamide, dexamethasone; VMP, bortezomib, melphalan, and prednisone; VRd/vrd, bortezomib, lenalidomide, and dexamethasone. (*) If daratumumab-based combinations or VRd are unavailable. (°) The lowercase letter indicates a reduced dose.

Figure 1. Management of transplant-ineligible MM patients according to frailty score

patients with the high-risk disease may benefit from proteasome inhibitor in a weekly subcutaneous VMP regimen and in presence of renal failure bortezomib represents the gold standard. The Rd, considering the oral administration and long-term tolerability in absence of peripheral neuropathy represents an optimal option particularly in patients frail, without caregiver and living far from the Hospital. The VCD is a widely used in patients with renal failure and intermediate fit population.

The treatment of relapsed/refractory transplant-ineligible MM patients

In clinical practice an asymptomatic biochemical relapse is currently managed according to the "wait and watch" strategy.[55] In the other hand in case of rapid increasing (3 months) of monoclonal component or the onset of clinical sings and/or symptoms the treatment must be started. Different factors should be considered before the choice of the therapy and its aggressiveness: age, fitness status, type and duration of response to the previous therapy, cytogenetic status.

In general it is preferred a treatment with drug with non-cross reagent mechanism of action. The re-challenge could be considered if the previous therapy was associated with an interval response between 6 and 12 years, low toxicities and good tolerance.

Alternately a short duration of remission and suboptimal response need a different therapeutic strategy. New agents as second-generations proteasome inhibitors (carfilzomib and ixazomib), monoclonal antibodies (daratumumab and elotuzumab) and Immunomodulators agents like pomalidomide are effective in this setting of patients.

Particularly ixazomib, an novel proteasome inhibitor structurally different from Bortezomib, in association with Rd seems to be safe and efficacious in this population and its oral administration attractive in elderly patients.[56-58] Elotuzumab, an anti-CS1 monoclonal association, is associated with an increased PFS when associated with Rd and is quite safe with a low rate of infusion reaction.[59,60]

Carfilzomib administered with dexamethasone and daratumumab in association with Rd or Vd maintain efficacy in terms of PFS even in patients > 75 years.[61-64]

According with the refractoriness of patients to Lenalidomide or Bortezomib is possible to add new agents like carfilzomib, daratumumab, elotuzumab or ixazomib to Rd and daratumumab to Vd.

Unfortunately there is a lacking of trials tailored to elderly relapsed/refractory MM patients for which is to date difficult to translate clinical information in the "real life" practice.

Conclusions

The majority of patients affected by MM are > 65 years old and, despite the increased PFS and OS observed in the past 20 years, this advantage have not translated entirely in this population.

There are various medical unmet needs in the management in transplant ineligible MM patients:

The eligibility of ASCT has to be defined by strictly parameters widely recognized to spread this option also in the elderly population.

An accurate assessment of fitness and frailty status are mandatory to define the goals, plan the best treatment available and tailor the therapy. Therefore, it is needed GA tools reliable and efficacy to achieve this goal.

There is a lack of trials tailored for regimens according to frailty status

Different subgroups of this population, as frail and high-risk patients, are underrepresented in clinical trials.

Different treatment approaches and drugs availability, particularly between European countries and North-America translate in a heterogeneity in the management of this population.

According to the data from clinical trials and the application of concept of frailty, despite the limitations described above, to date the management of transplant ineligible patients is based in a tailored treatment with dose adjustment and careful supportive care. The introduction of second -generations agents are currently ongoing and new regimens will be exploited soon for these patients to achieve an improvement of survival and quality of life, similar to younger MM patients.

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How I treat relapsed and/or refractory multiple myeloma

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Abstract

The expanding therapeutic landscape of relapsed and/or refractory multiple myeloma (RRMM) has contributed to significant improvements in patient outcomes. These have included combinations of proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), monoclonal antibodies (mAbs), histone deacetylase inhibitors, and/or alkylating agents. More recently, the approval of the first-in-class nuclear export inhibitor selinexor and the first-in-class B-cell maturation antigen (BCMA) antibody-drug conjugate (ADC) belantamab mafodotin has helped address the current unmet need in patients refractory to PI, IMiD, and anti-CD38 mAb directed therapy, otherwise known as triple class refractory myeloma. With the growing number of treatment options in the RRMM therapeutic landscape, the choice and sequencing of drugs and combinations has become increasingly complex. In this review we discuss our approach and considerations in the treatment of both early and late RRMM based on best available data and our clinical experience.

Introduction

Outcomes in multiple myeloma patients have improved substantially over the last 10-15 years due to the incorporation of immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies (mAbs) to standard myeloma treatment regimens. In relapsed and/or refractory multiple myeloma (RRMM), a number of treatment options exist based on randomized phase 3 trials that have led to the regulatory approval of various combinations of PIs, IMiDs, mAbs targeting CD38 or SLAMF7, and histone deacetylase inhibitors. Moreover, based on recent phase 2 studies, the first-in-class nuclear export inhibitor selinexor and the first-in-class B-cell maturation antigen (BCMA) antibody-drug conjugate (ADC) belantamab mafodotin were recently approved, helping address an unmet need in myeloma refractory to PIs, IMiDs, and anti-CD38 mAbs, otherwise known as triple-class refractory myeloma. With the growing number of treatment options in the RRMM therapeutic landscape, the choice and optimal sequencing of agents has become increasingly complex. In this review we discuss our approach and considerations in the treatment of RRMM based on the best available data and our clinical experience through several representative cases. While the preferred approach is to enroll on a clinical trial, we will focus our discussion on drugs and regimens that are currently commercially available for use in routine clinical practice.

Case 1

A 64 year-old woman was diagnosed with IgG kappa multiple myeloma with lytic bone lesions and anemia (hemoglobin 8.8 g/dL) on initial presentation. Initial M-protein was 3.6 g/dL. Fluorescence *in situ* hybridization (FISH) demonstrated standard risk disease with del 13q. She was treated with frontline therapy with bortezomib, lenalidomide, and dexamethasone for four cycles, followed by high-dose melphalan and autologous stem cell transplantation (ASCT). Subsequently she was started on maintenance lenalidomide, achieving a compete response (CR) to therapy. However, 34 months after her ASCT, she now has evidence of a new lytic lesion in her right humerus on positron emission tomography/computed tomography (PET/CT) and reappearance of her M-protein at 0.8 g/dL.

Case 1: discussion

The patient in Case 1 represents probably the most common scenario encountered at first relapse in myeloma today given the prevalence of maintenance lenalidomide use in both transplant and non-transplant patients. In this case, the patient has both biochemical progression and clinical relapse, warranting a change in therapy.

In a daratumumab naïve, lenalidomide refractory patient, incorporating anti-CD38 directed therapy in the patient's 2nd line of therapy would be our treatment of choice. Several randomized trials in early RRMM have demonstrated the benefit of combining anti-CD38 mAbs and PIs, which would provide a class switch away from an IMiD-based regimen in this case. Daratumumab in combination with bortezomib and dexamethasone (DVd) was the first anti-CD38 mAb and PI combination to gain regulatory approval based on the CASTOR study which showed an improvement in progression free survival (PFS) compared to bortezomib and dexamethasone (Vd).[1] However, among 18% of patients in the DVd arm who were refractory to lenalidomide in their last line of therapy, median PFS was only 9.3 months.[2] More recently, results from randomized phase 3 studies evaluating daratumumab (CANDOR) or isatuximab (IKEMA) in combination with the second generation PI carfilzomib and dexamethasone (Kd) versus Kd alone have been reported. In the CANDOR study, among the subset of lenalidomide refractory patients, median PFS was significantly higher in the daratumumab-Kd arm (not-reached) versus the Kd arm (11.1 months, hazard ratio (HR) 0.47, 95% confidence interval (CI) 0.29-0.78).[3] Likewise among patients who were lenalidomide refractory in the IKEMA study, a beneficial trend was seen with the addition of isatuximab to Kd versus Kd alone (hazard ratio 0.60, 95% confidence interval 0.34-1.06).[4] When choosing an anti-CD38 mAb and PI combination, our preference would be daratumumab-Kd or isatuximab-Kd in this setting based on a stronger PFS efficacy signal compared to daratumumab-Vd. However, in older patients or those with pre-existing cardiac conditions, daratumumab-Vd should be

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Key words: Multiple myeloma; Relapsed; Refractory.

Acknowledgements: H.C.L. would like to acknowledge support from the Baer Family Fund and the Goff-Street Foundation.

Conflict of interest: H.C.L. declares consulting fees from Amgen, Celgene, GlaxoKlineSmith, Janssen, Sanofi, and Takeda and research funding from Amgen, Celgene, Daiichi Sankyo, GlaxoKlineSmith, Janssen, Regeneron, and Takeda.

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Hematology Reports 2020; 12(s2):8955
doi:10.4081/hr.2020.8955

considered. The use of the third generation IMiD in combination with an anti-CD38 mAb would also be an option in this setting. While randomized phase 3 data is awaited from the APOLLO study (NCT03180736) evaluating the benefit of adding daratumumab to pomalidomide and dexamethasone (Pd) in early RRMM, two phase 2 studies have demonstrated the strong efficacy of this combination.[5,6] In particular, the phase 2 MM-014 study enrolled patients with early RRMM with 1-2 lines of prior therapy. Among 84 lenalidomide-refractory patients, median PFS was 21.8 months, suggesting that durable responses can be attained even without a class switch away from IMiD-based therapy in patients progressing on lenalidomide.

Based on these data, daratumumab-Pd is frequently utilized in our routine clinical practice in patients progressing on lenalidomide. Given several strong therapeutic options in this setting (daratumumab-Kd, isatuximab-Kd, and daratumumab-Pd), other important considerations include any patient comorbidities that may affect the tolerability of certain treatment options based on known drug adverse event profiles. In addition, patient preferences on route of administration (oral, subcutaneous, or intravenous) and frequency of clinic visits for treatment administration also becomes an important consideration.

Case 2

A 76 year-old man is diagnosed with kappa light chain myeloma with anemia (hemoglobin 8.3 g/dL) on presentation. Myeloma FISH studies demonstrated standard risk disease. He underwent induction therapy with bortezomib, lenalidomide, and dexamethasone for 8 cycles achieving a CR to therapy. Afterwards, due to personal preference, he stopped myeloma therapy and elected observation. Approximately 15 months later, he developed asymptomatic biochemical recurrence of disease that was initially observed but now has clear acceleration in the kinetics of disease progression with a serum free kappa light chain level of 330 mg/L and a free light chain ratio of ratio 44.2. A repeat bone marrow biopsy shows no high-risk FISH markers.

Case 2: discussion

Unlike case 1, this patient is considered to have lenalidomide sensitive disease, despite previous exposure, given the prolonged period of time (>60 days) between treatment discontinuation and disease progression. In this case, retreatment with a lenalidomide-based regimen would be a preferred choice. Options with regulatory approval based on randomized phase 3 data include elotuzumab in combination with lenalidomide and dexamethasone (Rd, ERd),[7] ixazomib in combination with Rd (IRd).[8] carfilzomib in combination with Rd (KRd)[9] and daratumumab in combination with Rd (DRd).[10] Both ERd[11] and KRd[12] have demonstrated overall survival (OS) benefit with long term follow-up when compared to the Rd backbone alone, and it is likely that DRd will achieve similar results as data matures based on a median PFS of 45.8 versus 17.5 months in the Rd arm and strong HR ratio 0.43 (95% CI 0.35-0.54).

Given several options in this setting, therapeutic considerations may again depend on patient comorbidities that may affect the tolerability to certain drugs and patient preferences on route of administration. If efficacy was the only consideration, DRd would be our preferred option in this case given the fact that the patient is naïve to anti-CD38 mAb therapy and the impressive median PFS and median PFS2 of this combination that has been reported with longer follow-up.[13]

Case 3

A 55 year-old man was diagnosed with IgG kappa multiple myeloma with lytic bone lesions on presentation. FISH demonstrated t(11;14) and amplification of +1q21 with 4 copies of *CKS1B*. He was treated with bortezomib, lenalidomide, and dexamethasone for 3 cycles, followed by high-dose melphalan and ASCT, followed by maintenance bortezomib, lenalidomide, and dexamethasone given his high-risk disease in a risk-adapted maintenance approach. His best response was a minimal residual disease (MRD) negative CR. After 29 months on maintenance therapy, patient had disease progression at which time he was treated with second line daratumumab-Pd. After 15 months on daratumumab-Pd, the patient now again has evidence of disease progression.

Case 3: discussion

This patient has had 2 lines of prior therapy and is now triple class refractory to PIs (bortezomib), IMiDs (lenalidomide, pomalidomide), and an anti-CD38 mAb (daratumumab). The patient is not refractory to the second generation PI carfilzomib and alkylating agents, and their use in combination with a regimen such as carfilzomib, cyclophosphamide, and dexamethasone would be one option.[14.]

The presence of t(11;14) also makes the off-label use of the Bcl-2 inhibitor venetoclax a consideration. While the phase 3 BELLINI trial of venetoclax, bortezomib, and dexamethasone versus bortezomib and dexamethasone demonstrated a trend towards inferior OS in the venetoclax arm, a PFS benefit and a trend towards OS benefit was retained in the subset of patients with t(11;14).[15] Preliminary safety and efficacy data have also been reported with carfilzomib, venetoclax, and dexamethasone with patients with t(11;14) showing the strongest efficacy signal.[16] The role of venetoclax is still evolving in RRMM as data continue to mature so should be used judiciously in this setting and be limited to t(11;14) patients.

Other considerations of lower priority would be combining the histone deacetaylase inhibitor panobinostat with proteasome inhibitors. In particular, the combination of panobinostat, bortezomib, and dexamethasone is approved for RRMM patients who have received at least two prior regimens including bortezomib and an immunomodulatory agent (IMiD). While the pivotal PANORAMA 1 study that led to the regulatory approval of this regimen excluded bortezomib-refractory patients,[17] the phase 2 PANORAMA 2 study enrolled only bortezomib-refractory patients which demonstrated an ORR 34.5%, median duration of response 6 months, and median PFS of 5.4 months.[18] Phase 1 and 2 data with the combination of carfilzomib and panobinostat have also been reported.[15,19]

While the patient has not been on an elotuzumab-IMiD combination, the expected NK depletion from recent daratumumab therapy may diminish any potential efficacy,[20,21] given the role of NK cell-mediated antibody-dependent cellular cytotoxicity (ADCC) as a major mechanism of action of elotuzumab. Therefore, as the patient is also IMiD refractory, we would deprioritize the use of an elotuzumab-IMiD based combination in this setting.

Case 4

A 67 year-old woman presents to the clinic for discussion of treatment options for her relapsed IgA lambda multiple myeloma. She has had 6 lines of prior therapy including high-dose melphalan and autologous stem cell transplantation. She is refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, daratumumab, and cyclophosphamide. Most recently, she has been treated with isatuximab, pomalido-

mide, and dexamethasone and now has progressive disease.

Case 4: discussion

This patient is both triple class refractory and penta-refractory to all five major drugs in myeloma treatment including lenalidomide, pomalidomide, bortezomib, carfilzomib and the anti-CD38 mAb daratumumab (and isatuximab). Hyperfractionated cyclophosphamide-based cytotoxic chemotherapy regimens such as DT-PACE,[22] modified-CBAD,[23] or DCEP,[24] have historically been used in this setting but are often poorly tolerated in late RRMM and associated with high morbidity and mortality rates.

The recent regulatory approval of belantamab mafodotin (belamaf), the first-in-class BCMA antibody-drug conjugate (ADC) and from a broader standpoint, the first BCMA-targeted therapy, would be our preferred consideration in this patient. While the ORR of 31% at the approved 2.5 mg/kg belamaf dose in the DREAMM-2 study is comparable to other recent single-agent approvals in RRMM,[25-27] the depth of response (≥ VGPR 19%) and median duration of response of 11 months were particularly promising.[28] A multidisciplinary team of oncologists and eye care specialists is needed to safely treat patients with belamaf given its association with frequent yet reversible corneal ocular adverse events, which are managed effectively by dose delays and dose reductions based on ocular exam findings and symptoms.

The first-in-class oral nuclear export inhibitor selinexor would also be a consideration for this patient based on an ORR of 25%, median DOR of 4.4 months, and median PFS of 4.7 months in the pivotal STORM registration study targeting triple class refractory myeloma patients.[27] Aggressive supportive care is also important when administrating selinexor to mitigate adverse events, including prophylactic anti-nausea agents with a 5-HT3 antagonist (e.g. ondansetron) in combination with olanzapine and/or a neurokinin 1 (NK1) receptor antagonist.[29]

Conclusions

The therapeutic landscape in RRMM is rapidly evolving, in relation to both efficacy and treatment tolerability, which has led to continued improvement in the overall survival of myeloma patients over the last two decades. With a plethora of therapeutic options, particularly in early RRMM, the choice of therapy should also be individualized based on patient- and disease-related factors such as previous therapies, duration of prior responses, nature of relapse (biochemical or clinical), and patient comorbidities in relation to known drug adverse event profiles. In late RRMM, triple class refractory myeloma remains a therapeutic challenge, an area where the recent approvals of selinexor and belamaf have helped address. The anticipated approvals of other novel therapeutic agents such as BCMA-targeted chimeric antigen receptor T-cells (CAR-T) and bispecific antibody T-cell engagers will bolster this area of unmet need. While having many treatment options is clearly advantageous, the choice and sequencing of therapeutic options in RRMM remains a challenge in the absence of randomized clinical data that address common clinical scenarios.

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How we manage smoldering multiple myeloma

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Abstract

Smoldering myeloma (SMM) is an asymptomatic stage characterized by bone marrow plasma cells infiltration between 10-60% in absence of myeloma-defining events and organ damage. Until the revision of criteria of MM to require treatment, two main prognostic models, not overlapping each other, were proposed and used differently in Europe and in US. Novel manageable drugs, like lenalidomide and monoclonal antibodies, with high efficacy and limited toxicity, improvement in imaging and prognostication, challenge physicians to offer early treatment to high-risk SMM. Taking advantage from the debates offered by SOHO Italy, in this review we will update the evidence and consequent clinical practices in US and Europe to offer readers a uniform view of clinical approach at diagnosis, follow-up and supportive care in the SMM setting.

Introduction

For long time, the two terms of Smoldering and Indolent myeloma were variably used in an undefined manner,[1,2] until 2003 when the International Myeloma Working Group (IMWG) defined SMM as an asymptomatic stage of plasma cell disorder, defined by the presence of a serum monoclonal component of at least 30 g/L and/or more than 10% plasma cells in the bone marrow (BMPC),[3] higher than those generally seen in monoclonal gammopathy of uncertain significance (MGUS), in absence of myelomadefining events, like hypercalcemia, renal failure, anemia, or bone disease (also collectively known as CRAB symptoms). In 2014, IMWG included BMPC>60%, elevated immunoglobulinfree light chains (in which the involved light chains are 100 times more numerous than the uninvolved ones), and 2 or more bone focal lesions identified by magnetic resonance imaging (MRI)[4] as additional myeloma-defining events, that address earlier patients to first-line treatment.

SMM accounts for about 15% of all the patients with newly diagnosed MM[5] and it carriers a higher risk of progression to symptomatic MM compared to MGUS.[6,7]

In the first 5 years after diagnosis the risk of progression to MM in SMM is approximately 10% per year[8] and decreases thereafter, differently from MGUS in which the rate of progression to MM is 1% per year, constant overtime.[9] The difference in clinical behavior in SMM is due to genetic heterogeneity[10] as deciphered by application of novel technologies.[10-12] While transcriptome trajectory is invariant,[13] genomic events associated to progression from SMM through active MM can follow two main patterns, as revealed by whole-genome sequencing approach.[11] The first, in which the sub-clonal architecture is retained and the progression is consequence of linear increase of disease burden; the second, due to a change of the sub-clonal architecture, in which progression is associated to stochastic additional complex genomic events.[12,14] Like in active MM, cytogenetics can identify high-risk SMM patients[8] and will likely be incorporated in future comprehensive models for risk stratification.[15] As a whole, BMPC external factors, like microbiote composition[16] or immune dysfunction,[17-21] can play a role still to investigate.

Initial diagnostic work-up

While there are no significant differences between Italy and US in the initial diagnosis work-up, to exclude myelomadefining events,[4] there are some emerging differences about the way to attribute risk class and further follow-up requirements.

According to 2014 IMWG MM diagnostic criteria[4] and 2016 ESMO guidelines,[22] BM evaluation by aspirate and or biopsy is the standard way to evaluate the number, immune phenotype (to check aberrancies like the absence of CD19 and/or CD45 expression, decreased expression of CD38, and overexpression of CD56)[23] proliferative index[24,25] and genetic aberrations (by FISH and/or conventional cytogenetics) of BMPC. Moreover, BM evaluation can provide additional information, like the presence of dysplastic hematopoiesis, an emerging prognostic factor for active MM.[26] A BM evaluation should be offered to all patients, even if asymptomatic, with a serum monoclonal component higher than 1.5 g/dL, based on a large Italian study showing that the probability of detecting a plasma cell infiltration ≥10% in asymptomatic patients with a serum M-protein ≤15 g/L is 4.7% for IgG subtype.[27] The absence of significant tumor burden with an M protein of <15 g/L and a normal FLC ratio seem to predict an MGUS-like behavior.[28]

In several European centers the evaluation is deferred in asymptomatic patients with apparent IgG MGUS if the serum M- protein is ≤15 g/L and without end-organ damage, until there is evidence of progression to symptomatic disease.[29] Accordingly, the European Myeloma Network does not routinely recommend bone marrow evaluation when patients have a serum IgG M-protein ≤15 g/L or IgA M-protein ≤10 g/L without CRAB symptoms.[29] A recent large retrospective series including patients presenting with low risk MGUS profile and no CRAB signs, confirmed that the risk of missing a diagnosis of SMM and MM by omitting bone marrow aspirate and biopsy was less than 1%. Thus, based on comorbidities, frailty,[30] age and amount of monoclonal component bone marrow evaluation could be deferred, preferring clinical and laboratory monitoring.[24,29]

After the initial diagnosis of SMM, in our Center we repeat laboratory tests,[31] including a hemogram, biochemistry tests, serum free

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Key words: Smoldering multiple myeloma.

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Conflict of interest: the authors declare no potential conflict of interest.

Hematology Reports 2020; 12(s2):8951
doi:10.4081/hr.2020.8951

light chain (sFLC) ratio, serum and urine[30] protein studies in 3 months to confirm the stabilization of the monoclonal component, as well as the absence of anemia, kidney impairment, and hypercalcemia. Shift from negative to positive urine immune-fixation and Bence Jones proteinuria are predictor markers of progression to active MM.[30,32,33] Dynamic monitoring of sFLC[34] and M component are helpful to identify evolving SMM type,[35] with an emerging prognostic role.[36] Based on the pioneering work of Dr. Dispenzieri and colleagues who evaluated disease progression in 273 SMM patients at Mayo Clinics, an involved/uninvolved FLC ratio of ≥8 is a significant risk factor for progression,[37] and if sFLC ratio rises to ≥ 100, the 2 year risk of progression approaches 80%, thus to be considered a myeloma-defining event in the IMWG guidelines.[38]

Imaging: the emerging role of whole-body MRI

Imaging is required in the initial work-up of any suspected plasma cell disorder,[22,30] to collect detailed information about the BM involvement, by whole-body MRI[39] and to early identify osteolytic bone lesions, preferentially by low-dose whole-body CT.[40] In 20% SMM patients the X-rays scans is silent due to bone loss<30%,[40] thus whole-body CT screening for bone lesions can lead to change clinical management in almost one third of patients in the real-life setting.[41] Latest IMWG guidelines recommended to perform WBCT (either CT alone or as part of an FDG-PET/CT protocol) as the first imaging technique at suspected SMM and, if these images are negative or inconclusive, to perform whole-body MRI.[42] Indeed, 18F fluorodeoxyglucose (FDG) integrated with computed tomography (18F-FDG PET-CT) provides information more valuable than whole body X-rays for the assessment of myeloma bone disease in areas not covered by MRI.[43,44]

Imaging can also provide prognostic additional information. Moulopoulos et al. first demonstrated that in patients with asymptomatic myeloma, time to progression (TTP) was shorter (16 vs 43 months) for patients with abnormal MRI (due to presence of focal, diffuse or variegated pattern) versus normal MRI.[45] An abnormal marrow signal of MRI of the spine in a patient with SMM was associated with a significant factor for progression to symptomatic myeloma (median 15 months) and confirmed by similar findings in independent cohorts, leading to the new IMWG criteria to identify MM patients.[39]

Since in MM imbalanced distribution of active lesions is frequently observed in medical imaging, associated to spatial heterogeneity,[46,47] integrative imaging, like whole body MRI or immunoPET, can add valuable information diagnosis and prognosis. The preliminary results of immunoPET scans based on antibody-based radiotracers targeted for CXCR4, BCMA or CD38[48] are shifting imaging from a metabolic toward a functional technique to monitor overtime and in different body areas potential therapeutic targets.[44,48] The imaging biomarker speed of growth, defined as development of the total tumor volume over time as detected by whole-body MRI, can identify 63.2% of SMM patients who progress within 2 years, including a high-risk group with a 2-year progression rate of 82.5%.[49] In newly-diagnosed MM significant splenic signal loss on diffusion-weighted MRI (DW-MRI) images, was seen in 24% patients and preserved in MGUS, reflecting increased tumor burden and associated to inferior outcome [50], but its role has never been tested in SMM.

Risk assessment

After the diagnosis of SMM, it is necessary to evaluate the risk of progression to symptomatic disease, integrating several parameters that should be taken in account to predict the risk of progression to symptomatic MM and address potential therapeutic interventions.

The Level and the Type of Serum M Protein Concentration: the size and type of the serum M-protein are two independent significant risk factors for progression in MM.[2,6,51,52] In a large retrospective series, the median time to progression (TTP) in patients with a component ≥4g/dL was 18 months vs 75 months in patients with a lower serum M protein; the median TTP was significantly shorter in patients with IgA versus IgG M-protein[6]: however, re-classifying SMM patients according to 2014 IMWG criteria for active MM, size and quality of M-protein have lost their prognostic meaning.[8] Evolving changes in M-protein and hemoglobin,[35,36] associated to FLC ratio≥8, and BMPC≥20% clearly identify those patients to requiring restaging with BM biopsy and imaging to validate progression.[53]

Percentage of Bone Marrow Plasma Cells: Based on two large independent series,[6,37,54] BMPC>20% is associated to shorter time progression. This cut-off has been validated in a large series of patients with SMM diagnosed according to 2014 IMWG criteria for active MM and it is part of the 20/2/20 IMWG score.[8]

Genomic and transcriptomic abnormalities Genomic aberrancies are associated to increased risk of progression through active MM.[14,55-57] Among findings available in clinics, the presence of del (17p13), t(4;14), +1q21 and hyperdiploidy is associated to inferior TTP.[58,59] Based on a cohort of 331 patients with MGUS and SMM, Dhodapkar and colleagues identified a gene expression profiling (GEP70-gene signature) signature as an independent predictor of the risk of progression to MM.[60] The same group identified four genes that can predict high risk of progression from smoldering to symptomatic MM.[61] However, these techniques are note reproducible in all centers, require a specific expertise, and are burdened with technical issue such as the necessity to enrich neoplastic plasma cells and to avoid bone marrow hemodilution. Further efforts are required for quality control, harmonization and standardization before wider use in routine practice.[62]

Immunophenotyping: The Spanish group found that 60% SMM patients have aberrancies in the immunephenotype of BMPCs similar to MM, where >95% of PCs are aberrant and only <5% of the detected PCs are normal, with a median TTP to symptomatic MM of 34 months.[23] Similar aberrancies in the phenotype can be monitored also in peripheral blood, looking at circulating Plasma Cells (PBPC).[63] Patients with high circulating PBPC have a higher risk to progress to active disease within 2 years compared with patients without high circulating PC (71 versus 25%, respectively). However, the detection of circulating PC is still not standardized and difficult to reproduce,[64] despite in the last years a terrific effort is challenging data interpretation and prospective clinical trial design of subsequent studies to incorporate and harmonize flow cytometry for[65] disease assessment in both smoldering and active MM.[62,63,66]

Immunoparesis: the suppression of one or more uninvolved immunoglobulins is a significant risk factor for progression in SMM, as shown by two independent large series. In the Mayo Clinics' experience, the median TTP was 159 months for patients without immunoparesis, 89 months in those with a reduction of only one isotype, and 32 months in patients with reduction in two isotypes of uninvolved immunoglobulins. The Spanish group reported similar findings, with a median TTP of 31 months in SMM patients carrying one or more reduced uninvolved immunoglobulins.[23]

Serum-Free Light-Chain Ratio: Based on the first work of the Mayo Clinic group, including 273 SMM patients, an involved/uninvolved FLC ratio of ≥8 is a significant risk factor for progression.[37] When the involved/uninvolved FLC ratio rises to ≥ 100, the median TTP is only 15 months, and the 2-year risk of progression approaches 80%. Therefore, this can be considered as a biomarker of early progression and such patients are now classified as MM.[38] However, recent studies suggest that this cut-off for sFLC may not confer as high a risk as initially defined,[67] and additional factors should be added, thus conveying that a single biomarker cannot be predictive for evolutionary trajectory in SMM trough progression to symptomatic MM.[15]

Prediction models In lack of a single reliable biomarker, clinical and laboratory findings should be integrated. To this end, several models and relevant scores have been developed and tested in clinical trials.[15]

In US the risk assessment of progression to MM in SMM is largely based on the Mayo Clinic (version 2007, 2008 developed before the 2014 update in the MM criteria[4,22] and Arkansas models.

The Mayo 2007 score takes in account only two lab findings, BMPC ≥ 10% and serum M protein ≥ 3 g/dL to identify three groups of patients with the risk of progression to active MM at 5 years of 15%, 43% and 69% respectively. Adding FLC ratio > 8, the 5-year progression rates were 25%, 51%, and 76%, in the presence of one, two, or three risk factors respectively, in the Mayo 2008 score.[37] Taking in account the 2014 update of the MM criteria the score has been further improved in the 20/2/20 Mayo 2018 version, combining the presence of BMPCs>20%, a value of M-component >2 g/dL and sFLC ratio>20 to identify three groups of patients with the risk of progression to active MM at 5 years of 22.5%, 46.7% and 81.5% respectively.[8]

The Arkansas risk-stratification model is based on gene-expression of 4 genes, M protein ≥ 3 g/dL and albumin level <3g/dL to identify three groups of patients with the risk of progression to active MM at 2 years of 5%, 44.8% and 85.7% respectively.[68]

In Europe, the Spanish group proposed the PETHEMA score, developed before the 2014 update in the MM criteria[4] on a cohort of 106 patients, combining the presence of aberrant BMPCs (aPCs/BMPC ≥ 95%) and immunoparesis to address the risk of progression to active MM at 5 years is 4%, 46%, and 72%, for patients with none, 1, or 2 risk factors respectively.[23] The Danish group suggested a model derived form a population-based study, involving 297 patients, in which combining M protein ≥ 3 g/dL an immunoparesis could distinguish three groups of patients with the risk of progression to active MM at 5 years of 9%, 24% and 55% respectively.[69]

So far, the Mayo 2008 and the PETHEMA models have been used and validated in prospective trials. However, the two models do not overlap and there are many patients that are differently classified according the two models,[70] thus most investigators use the 20/2/20 Mayo 2018 score based on parameters (M-protein size and the amount of BMPCs) available and reproducible in all centers.

Follow up

Outside the clinical trial setting, additional examinations should be recommended only in case of clinical evidence for progressive disease from the routine work-up. Subsequent follow-up should be individualized, based on risk of progression, evaluated by application of one of the above-mentioned scores and life expectancy.

The EMN and IMWG recommends follow-up 3 months after the initial SMM diagnosis, and if the results are stable, follow-up should be every 4-6 months for a year, and then every 6- 12 months.

Since the likelihood of finding bone lesions at skeletal survey is very low for M-protein IgG ≤15 g/L (2%) and IgA ≤10 g/L (0.0%),[27] in Europe imaging evaluation is not routinely recommended when patients have a serum IgG M-protein ≤15 g/L or IgA M-protein ≤10 g/L without bone pain,[29] and for asymptomatic patients with limited life expectancy.[29] In US, based on IMWG recommendations, imaging MRI is performed on an annual basis for at least 5 years and later based on clinical suspicion of progression, according to the findings of a large study at Mayo Clinics that suggested new cut-offs for prognostic variables to risk stratify SMM patients, the Mayo score 20/2/20, showing a stabilization of risk progression at 3%-5% per year beyond 5 years of follow-up.[8]

In our Center, we generally use the 20/2/20 Mayo 2018 prognostic scoring system,[8] associated to CT-scan findings, evolving nature of the M-protein and sFLC, and Bence Jones proteinuria and distinguish SMM patients for further the follow-up in three categories:

- *low risk*, with a probability of progression at 5 years less than 10%, that should be followed similarly to MGUS patients, every 6 months in the first two years and then every 12 months
- *intermediate risk* with a probability of progression at 5 years less than 50%. They represent the true SMM patients that should be followed every 3-6 months
- *high risk*, with a probability of progression at 2 years more than 50%, for whom is under investigation the need of early treatment. Based on current evidences, outside of the clinical trial setting, treatment for SMM or MGUS is not recommended and treatment should be given only in case of symptomatic progression, as detected by the presence of one of the myeloma-defining events.[4,22]

In our Center, we propose at baseline CT-scan, bone marrow biopsy and aspirate to asymptomatic patients when M-component in serum is higher than 1 g/dL for IgA subtype and 15 g/L for IgG subtype,[27,29] and to all patients with Bence Jones proteinuria due to the increased probability to progress to high-risk SMM and active MM.[32,33,71] Further imaging by CT-scan or MRI is performed every 18-24 months in lack of bone pain or if not differently clinically indicated.

The dynamic evaluation of additional lab findings can be helpful, including the increase of at least 25% of M-protein or s-FLC over time and hemoglobin reduction by at least 0.5 g/dL within the first year, that prompt us to reduce the follow up lag time to every 2 months, to detect the presence of one of the myeloma-defining events which require active anti-MM treatment. If after the second year of follow up M-protein, s-FLC and hemoglobin remain stable, the follow-up schedule can change to one visit per year. In addition, at least once a year we evaluate Pro-BNP and total urine protein to detect any cardiac or renal impairment that could lead to a diagnosis of amyloidosis.

Clinical management and treatment

Currently, management of SMM, especially of high-risk patients, is challenging, also because the available risk stratification models do not help to predict accurately the risk of progression. In the uncertainty to overtreat asymptomatic patients without improving quality of life or overall survival, waiting for mature results of completed or ongoing clinical trials (see below), no drugs are approved for the treatment. For each individual patient a close observation remains the standard of care,

taking in account the requirements of supportive and preventive measures to reduce the incidence of impaired bone mineral density, recurrent infections and cardiovascular disease and to optimize timing to start treatment when MM is diagnosed[72], even if the contribution of previous diagnosis of asymptomatic disease has been formally shown only for MGUS patients,[73,74] and this approach reflects the importance of monitoring tumor load in a linear evolution from asymptomatic through active MM.[6-8]

Supportive care

In MGUS and SMM patients there is an increased incidence of reduced bone mineral density,[75] osteoporosis and atraumatic fractures, associate to lower levels of vitamin D.[76] In these cases, beyond a careful evaluation of myeloma defining event by imaging as discussed above, supportive care should include monitoring and supplementation of vitamin D and calcium could be helpful, despite data from large prospective cohorts miss.[76] In the past, early intervention with zoledronic acid did not show any advantage in increase overall survival,[77] but they could still be used to prevent myeloma-related skeleton events.

Clinical implication of immunoparesis is the secondary antibody deficiency, whose biological contribution to MM evolution is still under investigation [78]. As consequence of both innate and cellular immunity,[18-20,26,79-81] immunosenescence,[82] T-cell anergy and addiction of neoplastic plasma cells to TLR4 signaling [83,84], SMM patients have increased risk to develop bacterial and viral infections.[69,85] In patients with active MM, both 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) can increase anti-pneumococcal antibodies, and preliminary observations suggest that vaccination is negatively correlated with disease progression.[78,86] Even if these preliminary observations have not maturely shown in the SMM setting, it is reasonable that a policy to improve the prevention of viral and bacterial infection should be tested in each single center and offered to all SMM patients with a positive anamnesis for recurrent infections, including immunoglobulin replacement, as suggested by the Canadian group.[87] We suggest that clinical evaluation and anamnestic aspects are fundamental to decide if may be helpful to prescribe or not substitutive therapy in MM. In our Center, we recommend seasonal flu vaccination and anti-pneumococcal vaccination, with either PCV13 or PPSV23 and offer sub-cutaneous, home delivered, immunoglobulin replacement when more than 3 infective episodes are registered in the previous 6 months,[88] based on promising results of this approach in MM patients.[89]

Since potentially clonal and dysplastic hematopoiesis may co-exist with MGUS and MM,[26,90] associated with increased risk of atherosclerotic arterial disease, there is an emerging interest in defining the cardiovascular risk due to M-component.[91-93] Despite data are not available for SMM, a retrospective series found an increase of cardiovascular events (coronary, peripheral and cerebrovascular) in both MGUS and MM patients,[75] suggesting that the same could happen in SMM setting. In lack of any trial-derived evidence of specific prophylactic strategy to adopt, cooperative studies involving US and European Institutions of well-identified and classified SMM patients could clarify in a near future how to profile and manage cardiovascular risk in SMM.

Treatment options based on outcome goal: delay progression or curative attempt?

When ESMO guidelines have been released in 2016 only 15% MM patients could be cured and for this reason immediate treatment for patients with indolent myeloma could not be recommended, strongly encouraging enrollment in clinical trials for high-risk SMM.[4] After failing of thalidomide in preventing progression through MM.[94-97] in the last five years the scenario has been changed and more than 50 trials are ongoing to test the feasibility, safety and efficacy of drugs active in MM that alone or in combination could be offered to high-risk SMM. Both European and US groups have shown that the early addition of lenalidomide to treatment significantly prevents SMM progression to active MM.[98]

However, there are still major concerns about study design, in particular primary endpoint (time to progression versus overall survival) and inclusion criteria, since the first trials included, in a variable proportion, patients who are classified as MM according to 2014 IMWG criteria, using uniform stratification risk models, to make the results comparable each other and the urgent need of additional surrogate endpoints, like achievement of minimal residual negativity.[62]

There are two main strategies arising from the study designs: delay MM onset or eradicate MM cells in the attempt to offer a cure. According to the first goal, a gentle approach, fixed-term and steroid-free, has been proposed by US investigators; on the opposite, a most aggressive approach, including a total therapy, with induction, autologous stem cell transplantation (ASCT) and maintenance regimen with a curative intention is under investigation.[72,99]

With the main goal to find a cure for MM, investigators from both the Spanish Myeloma Group in Europe and the Mayo Clinics in US, have shown that the early addition of lenalidomide to treatment significantly prevents SMM progression to active MM.

In the Spanish randomized phase 3 study early intervention consisting of nine cycles of lenalidomide– dexamethasone induction, followed by lenalidomide maintenance, compared with observation only in patients with high-risk SMM, defined according to the PETHEMA score, showed longer TTP and OS for the lenalidomide–dexamethasone group (median TTP: not reached vs. 21 months; 3-year OS: 94% vs. 80%).[98] The PETHEMA trial demonstrated for the first time that early treatment with lenalidomide and dexamethasone delayed time to progression to active disease, and provided a significant improvement in overall survival,[99] confirmed by the updated follow up at ten years presented at EHA 2020 (Abstract #EP950). However, major concerns raised from the inclusion criteria, based on the PETHEMA score that are not reproducible in all centers. In addition, in this study the bone lesions were evaluated by X-rays skeleton survey, reflecting the standard practice at that time, and that is probably one of the reasons of the exceptionally short median TTP of 24 months in the arm control. The ancillary substudy of the QUIREDEX trial support the importance of lenalidomide to delay the progression to MM due to recovery of T-cells activation and proliferation.[100]

To better define the contribution of lenalidomide exposure to delay MM onset in SMM patients, reducing the bias associated to steroids, the E3A06 trial investigated continuous exposure to lenalidomide 25 mg versus observation, achieving in the experimental arm 91% 3-yrs PFS, confirming the promising role of lenalidomide in delay onset of MM-defining events or end-organ damage but confirming that the benefit of lenalidomide treatment is limited to high-risk SMM patients.[101]

Other pilot trials are investigating the role of immunotherapy using monoclonal antibodies as single agents,, including *elotuzumab (anti-SLAMF7)* tested in a phase II study,[102] *daratumumab (anti-CD38)* tested in a phase II study,[103] *siltuximab (anti-IL-6)*[104] *and pembrolizumab (anti PD-1)*[105] extensively described in an excellent recent review,[106] we recommend our readers for

further details.

Additional single agents that more directly engage the immune system, tested in phase I-II studies, include pan-KIR2D inhibitor IPH2101,[107] the anti-human anti-intercellular adhesion molecule-1 monoclonal antibody BI-505,[108] rice bran arabinoxylan and curcumin.[109,110]

The GEM-CESAR phase II single-arm clinical trial led by Spanish Myeloma Group enrolled 90 high-risk SMM (defined according to PETHEMA score) patients who received induction with six 4-week cycles of carfilzomib, lenalidomide and dexamethasone (KRd) regimen, followed by single ASCT, KRd consolidation and maintenance with lenalidomide. Preliminary results from 77 patients who completed induction, HDT-ASCT, consolidation, and 1 yr of maintenance, showed that 81% of patients achieved ≥ CR and 62% were MRD negative (Mateos. ASH 2019. Abstr 781).

The safety and efficacy of KRd regimen have been confirmed in a small cohort of high-risk SMM treated at MSKCC in New York, with more 90% of MRD-negative responses, but longer follow-up is required for definitive conclusions.[111]

There are still open questions before to prime treatment to all SMM patients:

1. What characteristics of immune status, singularly or in cooperation, and mutational signatures co-vary with racial/ethnic differences for asymptomatic MM onset and how these factors influence progression to active MM?
2. Are there differences in immunological triggers (e.g. microbiote composition, dietary and life style) that could modify the evolution pattern and response to treatment?

Conclusions: unmet clinical needs and open questions

In conclusion, to manage each newly diagnosed SMM patient, it is necessary to identify the risk of progression to individualize follow-up schedule, taking in account all the available data, in a dynamic perspective. Waiting for the results of ongoing clinical trials enrolling SMM patients defined according to the 20/2/20 score, the primary goal of clinical management is delaying onset of CRAB symptoms and improving quality of life. Real-world life experiences will be needed in a near future, to explore the impact of advanced age, co-morbidities and the possibility to reduce drug dosage and exposure.

If early treatment could cure SMM patients, conveying sustained MRD negativity and longer overall survival, without giving unreasonable adverse events and secondary neoplasms, is a challenging paradigm of near future.

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The molecular pathogenesis of multiple myeloma

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Abstract

Multiple Myeloma (MM) is characterized by uncontrolled proliferation and accumulation of clonal plasma cells within the bone marrow. However, the cell of origin is a B-lymphocyte acquiring aberrant genomic events in the germinal center of a lymph node as off-target events during somatic-hypermutation and class-switch recombination driven by activation-induced-deaminase. Whether pre-germinal center events are also required for transformation, and which additional events are required for disease progression is still matter of debate. As early treatment in asymptomatic phases is gaining traction in the clinic, a better understanding of the molecular pathogenesis of myeloma progression would allow stratification of patients based on their risk of progression, thus rationalizing efficacy and cost of clinical interventions. In this review, we will discuss the development of MM, from the cell of origin through asymptomatic stages such as monoclonal gammopathy of undetermined significance and smoldering MM, to the development of symptomatic disease. We will explain the genetic heterogeneity of MM, one of the major drivers of disease recurrence. In this context, moreover, we will propose how this knowledge may influence future diagnostic and therapeutic interventions.

Introduction

Random mutagenesis is a frequent and likely ubiquitous phenomenon in replicating tissues, stemming from slight intrinsic infidelity of DNA replication and repair processes, and enzymatic modification of DNA bases.[1] Additionally, exogenous processes may increase this mutation rate. Rarely, these events will result in creation of a variant conferring a proliferative or survival advantage to the cell. In such case, a small pre-clinical proliferation will be observed.[2] Further acquisition of additional variants may then dictate evolution from these small clonal proliferations, never recognized in clinical practice, to a clinically evident cancer following natural selection acting on the resulting phenotypic diversity.[3] The complex multicellular microenvironment, the competition for metabolites, oxygen, growth factors, and the necessity for immune escape[4] will also dictate which clone is the fittest for growth. Genomic plasticity, conferred by the loss of DNA-repair mechanisms and/or acquisition of a hypermutator phenotype, will certainly facilitate the ability to adapt of the tumor cells.

Plasma cell dyscrasias are frequent hematological malignancies, and are usually regarded to as a more complex disease from a genomic point of view as compared to leukemias and lymphomas.[5] The most frequent conditions, forming a continuous spectrum that can often be observed over time in the same patient, are clinically categorized as monoclonal gammopathy of unknown significance (MGUS), smoldering multiple myeloma (SMM) and active MM.

The diagnosis of MGUS requires the presence of a serum monoclonal protein of <3 g/dL and <10% clonal bone marrow (BM) plasma cells, in the absence of myeloma defining events or amyloidosis. MGUS may progress to the more advanced asymptomatic stage of SMM, defined by a serum monoclonal protein of ≥3 g/dL or 24h urinary monoclonal protein ≥500 mg, and/or 10–60% clonal BM plasma cells in the absence of myeloma defining events or amyloidosis. Active MM in turn is diagnosed in presence of clonal BM plasma cells >10% and/or a biopsy proven bony or extra- medullary plasmacytoma, and one or more myeloma-defining events: end-organ damage (hypercalcemia, renal failure, anemia, lytic bone lesions), ≥60% bone marrow clonal plasma cells, serum free light-chain (FLC) ratio ≥100 (for kappa) or <0.01 (for lambda), and >1 focal lesion on MRI.[6]

These categories reflect differences in management to prevent the development of end-organ damage, or its prompt recognition and treatment.[6] From a genomic point of view, the question then is whether this clinical evolution is paralleled by a similar biological evolution of the neoplastic clone, from initiating lesions to those associated with progression and development of an aggressive disease, and whether this can be exploited clinically.

In this review, we will describe recent advances on the molecular pathogenesis of MM. Cell-intrinsic factors involved in the initiation processes of monoclonal gammopathies will be described in the context of the normal B-cell development. We will then focus on the different patterns of evolution from asymptomatic to aggressive stages of disease and the impact MM heterogeneity has in this process.

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Key words: Multiple myeloma, tumor evolution, next-generation sequencing, personalized medicine.

Received for publication: 14 December 2020.
Accepted for publication: 15 December 2020.

Conflict of interest: the Authors declare no potential conflict of interest.

Hematology Reports 2020; 12:9054
doi:10.4081/hr.2020.9054

Initiating events

Asymptomatic clonal expansion of hematopoietic cells are nowadays well recognized at the expense of plasma cells,[7] having been found decades ago through the identification of a monoclonal antibody in the serum through protein electrophoresis. On the contrary, the presence of an asymptomatic clonal B-lymphocytosis has been identified more recently thanks to flow cytometry.[8] Stem cells can also show similar instances of asymptomatic clonal expansions, identified through next-generation sequencing (NGS).[9,10] All these evidences confirm the multi-step nature of cancer evolution. In fact, it is thought that all MMs are preceded by an MGUS stage, even if not clinically evident.[11]

Contrary to lymphoproliferative diseases, plasma cell dyscrasias are not classi-

fied based on the cell of origin, since the latter – a post-germinal center B-lymphocyte- is morphologically different from the neoplastic cell encountered in the bone marrow at the time of diagnosis – a plasma cell.

Events leading to transformation of a naïve B cells upon antigen encounter within the germinal center (GC) of lymph nodes are thought to arise from errors during class-switch-recombination (CSR) and somatic hypermutation (SHM) of the B-cell receptor (BCR). These are two processes aimed at increasing antigen affinity to a peculiar antigen and conferring specific effector functions, catalyzed by the activation-induced-deaminase (AID) enzyme. Through the creation of double strand breaks and mutations, AID activity is at risk of off-target mutations and rearrangements.[12] It is unknown if the transformed cell would need some priming in the form of pre-existing mutations or genomic lesions permissive to the survival upon this AID off-target activity, but this is subject of intense research. Another question is whether this transformation is favored by a germline predisposition. Indeed, the risk of developing a plasma cell dyscrasia is increased twofold in relatives of MM patients,[13] and germline transmission of several risk alleles has been described.[14,15]

The transformed B-cell will then home to the BM and differentiate into a plasma cell, giving rise to the clonal expansion clinically recognized as MGUS. Importantly, crucial to this process is the interaction with the microenviroment.[16]

MGUS therefore displays common genetic features with MM: it carries either recurrent translocations of oncogenes with switch regions of the IGH locus or an hyperdiploid (HD) karyotype. The latter consists in multiple trisomies of odd chromosomes with the exception of chromosomes 13 and 17.[17] IGH translocations are caused by aberrant CSR promoted by AID, as proved by the fact that the rearrangement hotspot is close to the canonical CSR breakpoints. Furthermore, translocation partner genes show mutations with a signature of AID-induced mutations, consistent with a germinal center origin of the event.[18] Subsequent to the translocation, Ig enhancers promote the overexpression of the recurrent partner genes, consisting in the known oncogenes *CCND1*, *WHSC1*, *MAF*, *MAFB*, *CCND3* in t(11:14), t(4:14), t(14:16), t(14:20) and t(6;14) respectively. Being initiating events, IGH translocations are almost always clonal, mutually exclusive with each other and with the HD karyotype.[12,19] On the contrary, mechanisms leading to the generation of an HD karyotype are less clear. In hyperdiploid acute lymphoblastic leukemia, the HD karyotype is thought to derive from a single abnormal cell cycle duplication.[19] However, analysis of the activity of mutational processes with a constant mutation rate on trisomic chromosomes showed that the number of pre-gain and post-gain mutations if often different from chromosome to chromosome. This implies that different trisomies can be acquired in different time windows.[20] Furthermore, only mutations in HD chromosomes acquired before the gain show an off-target AID signature, while mutations acquired after the gain don't show any sign of AID activity.[21] This demonstrates a germinal center origin of the trisomy. Last, mechanisms linking trisomy to neoplastic transformation are unclear, but may be linked to the expression of oncogenes within the duplicated chromosomes.[22]

The same analysis of the activity of mutational signatures with a constant activity over time has provided bases to enquire when the transformation happens in the life of the patient. Using serial samples from the same patients, the activity of these mutational processes could be extrapolated back in time, concluding that the transforming event could take already in the second or third decade of life.[21] Subsequently, decades of clonal proliferation and acquisition of additional events would ensue before the clone becomes clinically evident in the form of MGUS.

Genomic features of MGUS

In MGUS, differently from MM, clonal BM plasma cells are low to absent, the monoclonal protein in the serum is low, and there are no signs of end-organ damage, active MM or amyloidosis.[23]

IGH translocations and HD are transforming events, however they are not sufficient for MM development. In fact, MGUS may display these abnormalities and remain clinically stable. This is the case for the majority of cases, since MGUS progresses at an average rate of 1% of cases each year, and this rate does not increase even after decades.[24] This argues against a model of continuous acquisition of additional lesions to drive progression, and on the contrary suggests that clonal sweeps may be driven by stochastic events. The question is therefore what additional genomic events are required for progression. From a point of view of prevalence, the t(11;14) is more frequent in MGUS, while all other translocations are more prevalent in MM. On the contrary, del(13) and other copy-number alterations (CNAs) are more prevalent in MM. This suggests a differential propensity towards transformation conferred by karyotypic events that can be assessed by FISH or SNP-arrays.[25–27] Furthermore, the fact that many CNAs can be found at the subclonal level confirms their acquisition after the PC clone has been established.

NGS has the potential to allow a much deeper analysis of the genome of MGUS, highlighting initiating events beyond recurrent translocations and CNAs. However, single-cell RNAseq studies have clearly highlighted how at this stage there is a large number of contaminating, non-clonal PC which may hamper bulk cell analysis.[28] However, initial targeted DNA-sequencing studies highlighted recurrent mutations in the myeloma genes *NRAS, BRAF, KRAS, DIS3, EGR1* and *LTB*. Mutations were less frequent than in active MM and within each case allelic frequencies were suggestive of a late acquisition of the mutation.[27,29] Importantly, no mutations have been detected in tumor suppressor genes such as TP53, or in genes involved in DNA repair mechanisms as *ATM* or *ATR* usually enriched in more advanced phases of the disease. Indeed, MGUS does not display an early and specific single-nucleotide mutational activity that may explain expansion of the tumor clone. This is very different, for example, from what observed in NPM1-mutated acute myeloid leukemia,[30–32] and is more in line with a slowly evolving disease driven by structural events as seems to be the case for most mature lymphoid neoplasms.

Very recently, through the combination of multi-parametric flow-sorting strategy and low-input whole genome library preparation, the genome of highly purified clonal MGUS PCs has been sequenced.[33] With the addition of SMM and MM cases, a comprehensive analysis of progressive vs non-progressive asymptomatic cases and their comparison to active MM cases has been possible. Results suggested a quite striking difference between MGUS and SMM cases that remained stable in the long term. Stable asymptomatic conditions displayed very little activity of mutational processes besides the AID-activity responsible for disease initiation,[34] along with reduced numbers of CNAs. Interesting, while the number of trisomies in HD cases were not significantly different between the various conditions, stable asymptomatic cases showed fewer instances of chr(1q) gain or amplifications, del(6q), gain(8q24) involving the *MYC* locus, del(16q) as compared to progressive cases. Finally, structural variants and partic-

ularly complex events like chromothripsis and templated insertions[20] were strikingly enriched in progressive cases, suggesting that in the future a molecular signature may prognosticate indolent asymptomatic cases much better than the current clinical and laboratory parameters.

Genomic features of SMM

SMM carries a higher disease burden than MGUS, as by definition clonal plasma cells in the BM must be >10% and <60%. The rate of progression of SMM is 10% per year in the first 5 years, then declines to 3% for the next 5 and to 1% after ten year from diagnosis.[35,36] SMM is therefore quite heterogeneous from a clinical point of view, suggesting its definition includes patients ranging from an actual active MM that does not yet satisfy criteria for diagnosis to others with a biologically indolent form similar to MGUS just with more BM PCs.

MGUS patients do not routinely undergo BM examinations during follow-up, therefore it is unusual to catch an evolution from MGUS to SMM even if this is what it is supposed to happen in all progressing cases. This makes it hard to ascertain events associated with initial progression of this asymptomatic conditions, and most of what we know about SMM comes from cases diagnosed *ab initio* as such. Furthermore, since SMM itself can be stable for years, our knowledge of its evolution is biased towards more aggressive and more rapidly evolving cases.

From a genomic point of view, SMM appears to carry similar genetic abnormalities to active MM, just at a lower frequency.[29,37,38] An interesting observation came from the whole-genome analysis of paired samples from ultra-high risk SMM progressing to MM. At baseline, the genomic structure of SMM was similar to MM in terms of driver events. This included translocations, CNAs and gene mutations but particularly complex structural events. Known secondary CNAs such as del(13q), del(6q), del(8p), del(16q) and amp(1q) were also frequent. Differently from MGUS, the structure of high-risk SMM was therefore very similar to that of MM.[39] Comparing the genome of paired samples, clonal evolution followed one of two main modalities. Authors described a "static progression model", where the subclonal structure grows unchanged from SMM to MM, and a "spontaneous evolution" model, where the subclonal structure of SMM changes because of the acquisition of one or more subclones and/or loss of others at the time of progression to MM. On average, patients would progress in less than one year in the static model, and at a much slower pace in the spontaneous evolution model. Furthermore, analysis of mutational processes active in each subclone was also particularly revealing. AID activity was preponderant in the ancestral clone of each case, again confirming a germinal center origin of the disease. Subclones evolved later in the disease course and responsible for progression showed instead enriched activity of the APOBEC family of DNA deaminases, an aberrant mutational process active across a variety of cancers[40], shedding some light onto aberrant genomic processes responsible for the acquisition of additional genomic lesions.

More recent studies on much larger sample cohorts have further expanded these findings, and translated them into information that could be used in clinical practice. In particular, *MYC* translocations[41] or *MYC* abnormalities, mutations in MAPK genes or DNA repair genes and the t(4;14) all independently predicted progression to MM.[42] This evidence makes it tempting to assume that genomics can really help prognostication of SMM by identifying at diagnosis cases that will behave like MGUS, and will rarely progress in years owing to the acquisition of additional genomic events, and cases that are de facto MM and already show all features of an aggressive neoplasms. This also highlights the inadequacy of current prognostic scores, mostly based on the tumor burden of SMM[43].

Genomic features of MM

Genomic studies in MM have much changed the perception of the disease in the last 10 years. Dozens of mutated genes, mutational processes, CNAs and complex structural events have been added to the genomic landscape of what initially seemed to be a disease with few karyotypic events[44] and gene mutations. Initial enthusiasm for the discovery of actionable mutations such as *BRAF* V600E[45] has nevertheless been curbed by the evidence that MM at diagnosis is a highly heterogeneous disease,[18,46,47] so that targeted treatment can trigger rapid subclonal outgrowth outcompeting the main

Table 1. Main genomic features of MGUS (1a), SMM (1b) and MM (1c).

Stage of disease	Genomic features
Stable asymptomatic cases	Fewer instances of chr(1q) gain or amplifications, del(6q), gain(8q24) involving the MYC locus, del(16q) as compared to progressive cases
Progressive cases	Structural variants and particularly complex events like chromothripsis and templated insertions are strikingly enriched
Table 1a MGUS	
Genomic feature	**Clinical significance**
MYC abnormalities/translocations, MAPK or DNA repair genes mutations t (4; 14)	Indipendently predict SMM progression to MM
Table 1b SMM	
Genomic feature	**Clinical significance**
Mutations in CRBN t (11;14)	Predict IMIDs and PI resistance Predict targeted treatment (venetoclax) responsiveness
High-risk lesions: - bi-allelic events in tumor suppressors, - amp(1q), - acquisition of an APOBEC signature	Simultaneously resistance to PIs and IMiDs and worse prognosis
Table 1c MM	

clone at diagnosis.[48] At the same time, this wealth of information has failed to improve a biological classification of the disease. This is still based on the main cytogenetic events, confirming these are the initiating events that shape the subsequent trajectory of evolution, providing some constraint on the type of alterations required for progression[20]. HD and IGH-translocated cases still provide the mainstay of classification. Within HD cases, about a third associate with CNAs – mostly del(1p), amp(1q), del(13q), del(14q), del(16q) – and the other two thirds with mutations, with a preponderance of mutations of the RAS family. T(4;14) cases cluster in two categories, frequently associate with del(13q), and in the first they also associate with CNAs, in the second they show fewer CNAs but mutations in *DIS3* and *FGFR3*. t(11:14) cases also fall in two different categories, one with *CCND1* and *IRF4* mutation, and one with *TP53* bi-allelic inactivation. A seventh category is not characterized by any particular structural event, but by a hypermutated genotype.[20] This evidence reinforces the notion that gene mutations are late events, whose impact is not strong enough to define a genetic category of the disease. Furthermore, most mutated genes are not even expressed in MM.[49,50] On the contrary, and similar to solid cancers, structural events – many of which are complex and non-recurrent, yet impacting recurrent driver genes – are the events that drive and define the disease.[51]

However, genomic analysis has revealed several important prognostic correlates, most of which are not captured by the R-ISS[52]. A well-known example is what is somehow improperly referred to as "double-hit" multiple myeloma, *i.e.* cases with ISS stage 3 and chr(1q)amp, or cases with TP53 bi-allelic inactivation.[53] The definition is somewhat improper since it has been observed how several combinations of genomic events have prognostic relevance, some showing a clear interaction, others simply highlighting an additive effect.[54,55] Other events associated with worse prognosis include a high activity of the APOBEC mutational process,[56] IGL-MYC translocations,[57] *TP53* mutations.[58] While this list is not at all inclusive, the main examples are cited to stress the point that the use of genomic analysis for MM prognostication is still in its infancy, and a comprehensive analysis will be required over large datasets to understand the independent prognostic role of these and other variables to inform clinical decisions.

Aside from prognostic markers, genomics has also opened the search for predictive markers, i.e. events that correlate with response to a specific treatment or lack thereof. However, no such biomarkers have been found to correlate with response to proteasome inhibitors (PIs) or immunomodulatory drugs (IMiDs), the two most used drug classes in induction. Indeed, mutations in *CRBN* in IMiD-resistant cases[59] and in proteasome subunit genes in PI-resistant cases[60] account for a tiny fraction of cases and are not found -or are found at the subclonal level- in the majority of cases that do not respond to such treatments.[50,61] Indeed, analysis of cases that are simultaneously resistant to PIs and IMiDs suggested instead that chemoresistance in MM is achieved through the acquisition of high-risk lesions, such as bi-allelic events in tumor suppressors, amp(1q), and acquisition of an APOBEC signature.[50] The described subclonal heterogeneity is responsible for this dynamic evolution of the tumor through lines of treatment and is especially visible in cases of extra-medullary evolution.[18,62]

Potential clinical applications of genomic technologies in plasma cell dyscrasias

The recent progress prompted by genomics discoveries in MM raised the question as to whether these merit incorporation into routine clinical practice. The paradigm has been set by myeloid malignancies and particularly AML, where genomics has dramatically impacted classification[63] and prognostication,[64] prompting the development of clinical-grade NGS sequencing panels.[65–67] In MM, the nature of the genome of the disease requires that translocation in IGH regions and copy-number abnormalities are captured along with gene mutations, posing additional hurdles to the design of the panel. While several NGS attempts have been successful at matching or outperforming the accuracy of FISH for the detection of such structural events,[68–70] the perception still is that NGS is a much complicated technique and the extra-information added to common FISH panels is not going to change the way we make clinical decision soon.

This perception may soon be challenged. Starting from SMM, novel prognostic markers incorporating cytogenetic events have been validated,[71] accepting the notion that disease biology should be more relevant than disease burden for SMM prognostication.[72] In newly diagnosed MM, treatment paradigms still follow a "one-size fits all" approach, but the example of venetoclax, a new drug class in relapsed-refractory MM that seems to offer a survival advantage in cases with t(11;14) but a disadvantage in other subgroups[73] will open the field for personalized treatment in MM based on patient-specific gene lesions. Furthermore, several trials are exploring a risk-adapted approach, if not a "basket" design where personalized treatment is offered based on each patient's gene mutations.[74] The most immediate application of NGS to the clinic will nevertheless be that of reliable measurement of minimal-residual disease through the sequencing of the patient-specific B-cell receptor rearrangement. The prognostic value of this technique seems to be extremely high,[75] and this is likely explained by the fact that this technique may overcome the heterogeneity of other phenotypic and genotypic markers of the tumor clone.

Limits of NGS in MM could be represented by the difficulty of obtaining enough DNA from bone marrow aspirates, and by the spatial heterogeneity of the disease.[62] In this respect, analysis of circulating tumor cells or cell-free tumor DNA could represent a suitable alternative for longitudinal disease monitoring. While initial approaches in MGUS and SMM have been in part disappointing,[76,77] MM at diagnosis seem to offer more circulating cells and cfDNA thus allowing a more informative analysis.[78,79] Limiting amounts of circulating DNA seem also to limit the analysis of peripheral blood to track disease response to treatment so far[80]. However, there is little doubt that knowledge banks built on thousands of cases of MM, including genomic and clinical details are highlighting prognostic groups that can't be captured by FISH alone.[55,53] More such efforts are underway and will likely soon reach a consensus on a reduced set of genomic lesions that may explain most of the risk of MM at diagnosis and may amenable to routine clinical-grade detection. Furthermore, the advent of new drug classes will improve the treatment landscape of MM, but potential benefits may be offset by increased costs and toxicity. This mandates that novel biomarkers are found to rationalize treatment, implying that genomic analysis will become routine clinical practice at diagnosis and at each relapse.[81]

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