To date, most patients with Hodgkin’s lymphoma (HL) can be cured with chemotherapy, radiotherapy or combined modality treatment. However, current treatment is associated with severe side effects and late toxicities such as infertility, cardiovascular damage and secondary malignancies. Moreover, a fraction of patients suffers from refractory disease and cannot be cured with current approaches including high dose chemotherapy and stem cell transplant.

In HL cellular and soluble tumor-cell derived factors CD30/sCD30, TARC and others inhibit local and systemic anti tumor immunity. In addition, there is a specific expression of tumor cell antigens such as CD30, CD15 and CD25 on malignant Hodgkin-Reed-Sternberg cells (HRS cells) making HL an ideal candidate for immunotherapeutic strategies.

Current immunotherapeutic approaches include unconjugated monoclonal antibodies, radioimmunconjugates, immunotoxins and – very recently – novel immunomodulatory compounds.

This talk will summarize current and novel approaches in the immunotherapy of Hodgkin’s Lymphoma and discuss its possible role in the future.
SGN-30 was generally well tolerated and the MTD was not reached in this study. One complete remission was observed in a patient with Anaplastic Large Cell Lymphoma. However, activity in HL patients was somewhat disappointing with four patients achieving stable disease duration ranging from 6 to 16 months and no PRs or CRs.

Similarly, the fully humanized anti-CD30 antibody MDX-060 was tested for safety in a phase I/II open-label, dose-escalation study in patients with relapsed or refractory Hodgkin’s Lymphoma or CD30+ NHL without any dose-limiting toxicities occurring. Consequently, a phase II trial was done with patients receiving MDX-060 at 10 or 15 mg/kg. MDX-060 was tolerated well in this study, serious adverse events occurred in five patients. There was moderate clinical activity, responses were observed in four of the 63 treated HL patients including 2CRs and 2PRs.

In conclusion, unconjugated anti-CD30 antibodies are well tolerated in HL showing only moderate activity in refractory and relapsed patients. Since in vitro data suggests favorable combination activity with conventional chemotherapeutics, future clinical trials could evaluate combination strategies.

Immunotoxins

Immunotoxins or antibody-drug-conjugates consist of a specific antibody linked to a cytotoxic agent. Few of the numerous preclinically developed constructs have been tested in clinical trials.

Ricin A, a ribosome inactivating toxin, was used as an effector in phase I studies in relapsed and refractory patients linked to either an anti-CD25- or an anti-CD30-directed antibody. Both constructs were moderately toxic with vascular-leak syndrome being the most relevant sign of toxicity and in both studies approximately 40-50% of the patients produced human-anti-ricin-antibodies (HARA) in response to the treatment. Response rates were comparable in both studies with ORR (overall response rate) around 15% and no CRs observed.

Other immunotoxins include an anti-CD30-saporin construct which was tested in two studies in 12 patients overall resulting in some activity (four PRs, three MRs); and an anti-CD25-pseudomonas-exotoxin-A construct with moderate activity.

Very recently, Younes and colleagues reported preliminary results of an ongoing phase I dose-escalation trial in relapsed and refractory HL patients with 0.1-3.6 mg/kg SGN-35, an anti-CD30-antibody- monomethylauristatin E (MMAE) conjugate. SGN-35 was designed to be stable in the blood and to release MMAE only upon internalization into CD30-expressing tumor cells. 36 HL patients have been treated so far and SGN-35 was reported to be generally well tolerated.

In these heavily pretreated patients, a total of five CRs and seven PRs were reported which occurred in the higher dose levels, fifteen patients had stable disease.

Radioimmunotherapy

Since HLs are highly sensitive to radiation, radioimmunotherapy appears to be a promising approach. In addition, radiolabeled antibodies consisting of a tumor-targeted specific antibody labeled with an alpha- or beta-emitter have the advantage of killing not only the tumor cells but also cells of the microenvironment that might be substantial for tumor growth (cross fire effect).

In early clinical trials, Yttrium90- or Iodine131-labeled polyclonal antiferritine antibodies were tested including myeloablative and non-myeloablative strategies in multiple
relapsed and refractory HL patients. This approach led to remission rates around 20-80% depending on schedule and administered dose with considerable mostly hematological toxicity (reviewed in reference 5).

In a recently published phase I trial, 22 relapsed or refractory patients were treated with murine Iodine131-labeled anti CD30 (Ki4) antibody resulting in an ORR of 27% including one CR, five PRs and three minor responses. The median duration of response was four months and the most significant toxicity was severe myelosuppression consisting of grade IV hematotoxicity 3-5 weeks after treatment in 8 patients.12

Anti CD20-antibody rituximab

HL can be classified into classical HL (cHL) the clinically and histologically distinct subtype Lymphocyte-predominant Hodgkin’s Lymphoma (LPHL), the latter accounting for about 5% of all HL cases. In contrast to cHL, LPHL typically shows strong expression of CD20 along with CD30 and CD15 in the malignant cell population. Clinically, LPHLs show a more indolent course compared to cHL and patients mostly present in early stages of the disease. Treatment of LPHL using standard HL protocols is highly effective leading to complete remission in more than 95% of patients. Given the indolent course of the disease, LPHL patients are likely to be overtreated with current cHL-derived protocols. Particularly early stage LPHL patients have an excellent prognosis and are more likely to die from treatment-associated late toxicities than from the disease itself.14

Given the indolent clinical course and the strong CD20 expression in LPHL tumors, the monoclonal anti-CD20 antibody Rituximab was suggested to be a non-mutagenic, less toxic alternative treatment for LPHL. The German Hodgkin Study Group (GHSG) recently reported the results of a phase II trial of rituximab (375 mg/m² in 4 doses) in 21 relapsed or refractory NLPHL patients.15 15 of the 21 enrolled patients were evaluable with confirmed diagnosis of LPHL and were analyzed resulting in an overall response rate of 94%, including 8 patients with complete remission (CR) and 6 patients with partial remission (PR). With a median follow-up of 63 months (range 3-84), the median time to progression was 33 months, with the median overall survival (OS) not reached. Similar results were reported from another study of standard dose Rituximab in 22 patients with relapsed LPHL resulting in an ORR of 100% with CR in 41%, CRu 5% and PR in 54%.16

In conclusion, these highly promising results suggest a change of paradigm in the treatment of LPHL; however, further investigation is warranted.

In classical HL, the malignant cells express CD20 in only about 25-30% of cases. However, CD20 is strongly expressed by the tumor infiltrating B-cells which contribute to HL tumor growth by providing antiapoptotic signals for the malignant HRS cells via CD30-CD30L and CD40-CD40L crosstalk. Moreover, recent findings suggest that similar to mechanisms observed in leukemias and solid tumors, malignant HRS cells in HL tumors might arise from a CD20+ “Hodgkin’s Stem Cell”. Based on this rationale, 22 patients with relapsed CD20+ or CD20- cHL were treated with weekly infusions of 375 mg/m² Rituximab in a pilot study. Responses were observed in 22% of patients with CR in one patient. Interestingly, responses were seen in both, CD20+ and CD20- HL cases.

These results and the low rate of adverse effects associated with Rituximab have led to the implementation of Rituximab in combination into large first-line trials in Hodgkin’s Lymphoma. The recently initiated HD18 trial...
for advanced stage cHL from the GHSG will evaluate the efficacy of Rituximab in combination with the dose-escalated BEACOPP regimen.

**Adoptive Immunotherapy and bispecific antibodies**

Eppstein Barr Virus (EBV) antigens EBNA1, LMP1 and LMP2 can be detected in HRS cells of approximately 40% of the HL cases. Since no effective cellular anti-EBV response is observed in these patients, *in vitro* generation and subsequent administration of autologous EBV-specific T-cells has been tested in pilot studies and phase II clinical trials. In the most extensive study, Bollard and colleagues treated 14 relapsed or refractory patients who had measurable disease or were considered at high risk for relapse with (LMP2-) EBV-specific T-cells. They observed *in vivo* expansion and anti-viral activity of EBV-specific T-cells and reported some activity including complete remissions.

Unfortunately, targeting EBV is limited to the EBV+ HL cases and the generation of EBV-specific T-cells is time consuming and complex, which might be obstacles to the clinical application.

Bispecific monoclonal antibodies simultaneously bind to the tumor cells, and, with a second binding site, to an immune effector cell. Until now, bispecific constructs using NK-cells and monocytes/macrophages as effector cells have been tested in clinical trials. The murine Bi-MAb HRS-3/A9 binds to CD30 on HRS cells and CD16 on NK cells and was tested in a phase-I/II study in 15 patients with relapsed or refractory HL. HRS-3/A9 was well tolerated in this study without reaching the MTD and responses included one CR, one PR and three MRs. In an attempt to further activate the effector NK-cells, HRS-3/A9 was co-administered with IL-2 and GM-CSF in a second trial involving 16 refractory patients. Response included one CR and three PRs with comparable tolerability.

A bispecific construct containing CD30-binding Ki-4 fragments and domains binding CD64 expressed on human monocytes was tested in a phase I dose-escalation trial in ten patients with relapsed or refractory HL. The MTD was not reached, and side effects were moderate. Responses observed included one CR and three PRs; four patients had stable disease.

As novel class of compounds, the immunomodulatory drugs (IMIDs) thalidomide and its derivative lenalidomide have been approved for the treatment of hematological malignancies as multiple myeloma and myelodysplastic syndrome. Besides possessing anti-angiogenic and possibly direct anti-tumor-cell-activity, these IMIDs stimulate T cell proliferation and enhance NK cell function via IL-2 and IFN-γ. The alliance of direct anti-tumor activity with anti-angiogenic and immunostimulatory properties was the rationale for the treatment of multiple relapsed and refractory HL patients in a named patient program in Cologne and other German sites. Although these are only case experiences, a number of complete remissions observed in this group of heavily pretreated patients has led to the initiation of clinical trials testing the activity of lenalidomide in HL.

**Conclusions and perspective**

Different immunotherapeutic concepts have been tested for the treatment of Hodgkin’s Lymphoma including unconjugated monoclonal antibodies, immunotoxins, radioimmunoconjugates and, most recently, immunomodulatory compounds. Some strategies, in particular radioimmunotherapeutic
approaches and immunotoxins have already shown significant effectiveness. First experiences with relatively non-toxic immunomodulatory compounds have implemented a whole new kind of immunotherapy in or LPHL the anti-CD20-antibody Rituximab might be the future effective but less toxic treatment. Therefore, the question is not whether there is a role for immunotherapy in HL but how immunotherapeutic concepts can be implemented into the current treatment concepts the best way in order to conserve or even improve the good long term survival in HL patients and to reduce toxicity and long-term side-effects. One challenge for the development of any new concept remains the recruitment of patients in clinical trials since HL is a rare disease and the majority of patients can be cured with conventional chemotherapy. International cooperations could be the solution to this problem.

References