Low dose Azanucleosides for high risk (s)MDS and AML

Azanucleosides like 5-aza-2’deoxyctydine (Decitabine=Dacogen) and 5-azacytidine (Vidaza) are both cytosine analogues, already synthesised in 1964, tested for there cytotoxic capacity when applied in high doses. Using high dose Decitabine therapy for AML patients it became clear that there was a good antileukemic activity but also a high toxicity. When administered in low dose however, these drugs are known to have a strong DNA demethylating effect and therefor are epigenetically active for instance by reactivating tumour suppressor genes that have been silenced by hypermethylation.

Although hypermethylation of the 5’region of gene like for instance p15 seems important it was made clear by Tamm et al that not all genes that were upregulated by Decitabine showed CpG hypermethylation in the promoter region suggesting also a methylation independent effect of Decitabine.

Head to head comparison of the two drugs has as yet not been done, it might be expected by the differences between the mode of action that Decitabine is the most active of the two. This is supported by in vitro data. Both drugs are successfully applied in patients with primary - and secondary MDS, AML and blast crises from CML. In CMMIL patients, now according the new WHO classification regarded more as a myeloproliferative disorder, this drug has shown activity as well.

Drug administration

The dosing schedules used in the phase II and phase III studies with Decitabine was $135 \text{ mg/m}^2$ per day for three days with therapy cycles every 6 weeks. With this dosage schedule it was shown that Decitabine could induce DNA demethylation, gene reactivation and protein expression of the p15 INK4B gene. The promotar of this inhibitor of cyclin dependent kinase that is often found to be hypermethylated in (high risk) MDS.

Alternate dose schedules are proposed and might be more active. The most efficient dose schedule based on data measuring DNA demethylation has as yet to be established. Higher doses seem not to be more effective and are certainly more toxic Lower doses like $2 \text{ mg/m}^2$/day for 7 days administered by continuous intravenous infusions gives a significant genomic DNA hypomethylation. Longer duration of the therapy cycle might be more effective whereas more convenient dose scheduling might improve quality of life. Vidaza was always administrated during a longer period. Seven days schedules every 4 weeks were used with a dosage of $75 \text{ mg/m}^2$/day. There are no studies that compared the demethylating activity of both drugs in patients.

Although both drugs are tested i.v. most studies with Vidaza are done with the s.c. administration form. In these studies Vidaza is administered s.c with a minimum of 7 months of treatment in cases reaching a CR or till progressive disease in responding patients. Patients treated with Decitabine received a minimum of 4 cycles (when CR after 2 cycles) and a maximum of 8. From the data of retreated patients we concluded that prolongation of the Decitabine therapy might benefit MDS patients. A s.c form of Decitabine is under study at this moment. For several theoretical reasons combination therapy with drugs that can alter histone acetylation is of interest. Lübbert et al studied the combination of Decitabine with ATRA. Especially combination with Valproic acid a known histone deacetylase inhibitor. The MD Anderson group have tested this option in phase I/II trials. Both combination were shown to be very well tolerable.
Treatment results in MDS patients

The first phase II studies performed in MDS patients showed comparable results for Vidaza as for Decitabine with perhaps a somewhat higher CR rate for patients treated with Decitabine. It became clear that with Decitabine high risk MDS patients even with high risk cytogenetic abnormalities like complex karyotypes or chromosome 7 abnormalities had a fairly good response rate and perhaps a survival benefit. It was noted that with this therapy complete cytogenetic responses were observed for the first time with low intensity therapy in these patients. We were also able to show that the neutrophils of these patients were of polyclonal origin after treatment. Furthermore remarkable platelet responses were seen often as the first sign of therapy effect. The phase III studies are somewhat difficult to compare because in the Decitabine study more intermediate 2 and high risk patients are included. The response duration was comparable in the two studies.

The time to AML or death in the Decitabine treated patients with a intermediate 2 or high risk MDS was significant better than in the control arm. In the Vidaza study also a significant improvement was seen but since a cross over was allowed for patients in the control arm overall survival was difficult to determine. In both studies an improvement of the quality of life was seen, often already rather soon after start of the therapy. The toxicity profile of low dose azanucleoside therapy is rather low. Most toxicity is due to marrow suppression in patients with already severe cytopenias. The toxic death rate (death due to all courses during therapy) in this high risk group included in the phase II studies was only 7%.

sMDS

Also in both studies patients who were previously treated for a non haematological malignancy were included. However no separate analysis was published if patients with a secondary MDS did respond. In the phase II studies with Decitabine a few patients were included who were previously treated for non haematological malignancies. Responses were observed in some of these patients.

Myeloproliferative/myelodysplastic syndrome

A total of 28 patients diagnosed with CMML are included in the Decitabine studies. Similar demographics and disease characteristics were observed in all 3 studies, with an average age of 70.2 years and 71% of patients male. A baseline WBC of >20,000 was observed in 8/28 (29%) patients and baseline bone marrow blasts >5% were observed in 11/28 (39%) patients. The ORR was 25% (14% CR + 11% PR), thus comparable with the responses seen in mDS patients. Hematologic improvement was observed in 11% of patients and stable disease in 39% of patients. Responses were seen both in the dysplastic type (WBC < 20.000) as well as in the proliferative type (WBC > 20.000).

AML

Because already in the phase II studies it became clear that number of blast cell were certainly not a bad prognostic parameter looking to response rate, it seemed logic to study these drugs also in AML patients. Moreover the DNA methylator phenotype of AML also offers a biological rationale for treating also AML patients with doses of demethylating agents which act by reverting the hypermethylated state to an unmethylated state rather than by “classic” cytotoxicity mechanisms typically associated with higher doses.

The new WHO criteria using a blast cell count of >20% for the diagnosis of AML makes retrospective analysis for the group of patients who have a blast cell count between 20% and 30% of interest. The response rate (CR and PR) for these patients who developed AML from MDS was for Decitabine 32%. 17% of these patients showed an hematological improvement. A median survival of 13 months was seen in these patients. This survival did not differ from the one seen in patients with blast cell count between 20% and 30%.
10% and 20%. With Vidaza this response rate was between 10-17% with a hematological improvement between 17% and 32%.

Lübbert et al. showed that also AML patients with > 30% blasts in the bone marrow aspirate responded to the treatment with low dose Decitabine. 31% of the patients responded to low dose Decitabine. Some of them received rather long maintenance therapy indicating that with low intensity therapy long survival is possible.

If the response rate improved by adding ATRA to this therapy has to be established. The group of Issa was able to show that in AML patients hypomethylation corresponded with the response on low dose Decitabine. A CR rate of 19% was observed in often pretreated AML patients with an overall response rate of 39%.

**Blast crisis from CML**

Also in patients with a myeloid blast crisis evolving from CML responses were observed. The response rate of patients with a myeloid blast crises treated with intensive therapy was equal to that seen in patients treated with Decitabine with a comparable overall survival.

**References**


Wijermans P, Lübbert M, Verhoef G, Klinek V, Bosly A. An epigenetic approach to the treatment of advanced MDS; the experience with the DNA demethylating agent 5-aza-2’-deoxycytidine (decitabine) in 177 patients. Ann Hematol 2005 84; 9-17.


