### Myelodysplastic syndromes

**UPDATE ON LENALIDOMIDE AND AZACITIDINE**

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#### TRIAL SUMMARIES: 1. Lenalidomide in MDS patients with del5q not associated with risk of AML progression but with survival benefit

Kuendgen A, Lauseker M, Alan F et al. Lenalidomide treatment is not related to AML progression risk but is associated with a survival benefit in RBC transfusion-dependent patients with IPSS Low- or Int-1-Risk MDS with del5q: Results from a comparative study. ASH 2011, Abstract 119.

This study compared the risk of progression of myelodysplastic syndromes (MDS) to acute myeloid leukemia (AML) and death in lenalidomide-treated patients in the MDS-003 and -004 studies (n=295) with MDS patients with del5q from patient registries in Europe, US and Australia (n=459) receiving best supportive care (BSC). Baseline characteristics of lenalidomide patients and BSC patients (at the time of diagnosis) were similar and are shown with the study results in Table 1.

In the final Cox proportional hazards models, neither lenalidomide treatment (HR 0.939; p=.860) nor one cytogenetic abnormality in addition to del5q (HR 1.111; p=.755) increased the risk of AML progression. Significant factors associated with an increased risk of AML progression were complex cytogenetics (p=.002), higher transfusion needs (p=.029) and elevated marrow blast count (p=.016). The authors concluded that lenalidomide was not associated with higher risk of AML progression but led to reduced risk of death (p=.012).

#### 2. Cytoreduction with azacitidine alone prior to ASCT


This retrospective study reported on 405 consecutive MDS patients (median age 54 years) who underwent ASCT between January 1999-December 2009 in 26 centres in France and Belgium.

Prior to transplant (Table 2), 45 patients received azacitidine alone and 32 patients received azacitidine preceded or followed by intensive chemotherapy (azacitidine+CT). Of the remaining patients, 166 received intensive CT alone and 162 were managed with BSC. The azacitidine alone cohort was older (p=.025), more frequently had higher-risk MDS (p=.013) and more commonly underwent reduced-intensity conditioning stem cell transplantation (RICT) (p=.005) from an unrelated donor (p=.007). Overall, 45% of all patients were considered to be in partial remission (PR) or complete remission (CR) at the time of ASCT; response rates for each subgroup are shown in Table 2, along with other key outcome measures (median followup 4.6 years).

Multivariate analysis confirmed a significantly inferior OS in the azacitidine+CT group (p=.003), even though 60% of the patients in that group had achieved at least PR at ASCT. However, compared to the other 3 groups, cytoreduction with azacitidine alone prior to ASCT led to a favourable outcome in older patients with poor-risk MDS.

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**TABLE 1: Lenalidomide vs BSC MDS patients with del5q**

<table>
<thead>
<tr>
<th></th>
<th>Lenalidomide (n=295)</th>
<th>BSC (n=125)</th>
</tr>
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<tbody>
<tr>
<td>Median age (years)</td>
<td>65</td>
<td>66</td>
</tr>
<tr>
<td>Median time from diagnosis to study entry (years)</td>
<td>2.7</td>
<td>0</td>
</tr>
<tr>
<td>Median observation time (years)</td>
<td>4.3</td>
<td>4.6</td>
</tr>
<tr>
<td>Baseline RBC transfusion burden</td>
<td>6 [1-25]</td>
<td>2 [1-10]</td>
</tr>
<tr>
<td>2-year/5-year cumulative AML incidences</td>
<td>7%/23%</td>
<td>12%/20%</td>
</tr>
<tr>
<td>2-year/5-year cumulative OS probabilities</td>
<td>90%/54%</td>
<td>74%/41%</td>
</tr>
<tr>
<td>Median OS, years (95% CI)</td>
<td>5.2 (4.5-5.9)</td>
<td>3.8 (2.9-4.8)</td>
</tr>
</tbody>
</table>

BSC=best supportive care; MDS=myelodysplastic syndromes; RBC=red blood cells; AML=acute myeloid leukemia; OS=overall survival.

**TABLE 2: Key outcomes for patients given azacitidine±CT vs BSC before ASCT**

<table>
<thead>
<tr>
<th>(%) of total patients</th>
<th>azacitidine alone n=45 (11%)</th>
<th>azacitidine/CT n=32 (8%)</th>
<th>BSC n=162 (40%)</th>
<th>CT n=166 (41%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (PR/CR) at time of ASCT (% of subgroup)</td>
<td>32 (71%)</td>
<td>19 (60%)</td>
<td>6 (4%)</td>
<td>121 (73%)</td>
</tr>
<tr>
<td>3-yr OS (p=.033)</td>
<td>60%</td>
<td>28%</td>
<td>52%</td>
<td>49%</td>
</tr>
<tr>
<td>3-yr TRM (p=.055)</td>
<td>13%</td>
<td>29%</td>
<td>34%</td>
<td>20%</td>
</tr>
<tr>
<td>3-yr relapse rates (p=.169)</td>
<td>31%</td>
<td>41%</td>
<td>29%</td>
<td>38%</td>
</tr>
</tbody>
</table>

CT=intensive chemotherapy; BSC=best supportive care; PR=partial remission; CR=complete remission; OS=overall survival; TRM=transplant-related mortality.
**LANDMARKS**

**Special report from the American Society of Hematology (ASH) Annual Meeting**

**COMMENTARY:** Recent evidence has shown that del5q patients who do not respond to lenalidomide have an increased risk of AML transformation, particularly in the presence of p53 mutations. This has raised the concern that lenalidomide may promote transformation of MDS to AML in some situations. The findings of the study from Kuendgen et al suggest that treatment of lower-risk MDS patients with lenalidomide does not increase the risk of this transformation. Furthermore, the investigators’ comparative analysis provides support for lenalidomide being associated with a survival benefit in lower-risk del5q MDS. However, their analysis has its limitations in that the lenalidomide-treated cohort was a median of 2.7 years from diagnosis at study entry, raising the possibility that these patients may have had more biologically stable disease with a more favourable prognosis than the registry patients. In addition, molecular analysis for p53 mutations was not done in either cohort.

The use of azacitidine to cytoreduce MDS patients prior to ASCT is becoming increasingly popular in light of its simplicity of administration and its favourable toxicity profile, especially when compared to intensive CT. As was the case in the study from Damaj et al, this is a particularly attractive option for older patients who are being planned for RICT. The results from this retrospective study are interesting but certainly do pose a clinical conundrum. Patients who responded to azacitidine alone and subsequently went on to SCT had the lowest transplant-related mortality (TRM) and essentially equivalent relapse rates to other patient groups which resulted in a superior OS (60% at 3 years). Conversely, patients who required azacitidine+CT had both a higher TRM and the highest relapse rates with a significantly inferior OS (28%). The question for the clinician is: which MDS patients should receive azacitidine cyto reduction prior to SCT, since failure to respond to this therapy will lead to an inferior outcome to that observed for patients receiving CT alone (OS of 49% at 3 years). The answer may lie in patient selection which almost certainly was a factor in this retrospective analysis. The response rate (PR/CR) in the azacitidine±CT group (66%) is at least twice that reported in the prior randomized trials with this agent. Since only patients who actually underwent ASCT were included in this study, this suggests that many patients who received azacitidine±CT did not respond adequately to proceed to ASCT. This selection bias was likely not as much of an issue in the intensive CT patients in whom the PR/CR rate of 71% was more consistent with response rates previously reported in MDS patients given induction CT. A further difficulty in interpreting the data from the Damaj study is that the value of a “PR” with azacitidine and a “PR” with intensive CT may be different. This is especially true for patients proceeding to ASCT, where outcomes for MDS patients who have failed CT are known to be unsatisfactory. The final publication from this study may provide further insight into these questions but it is more likely that a randomized study comparing pre-SCT cyto reduction with azacitidine vs intensive CT will be needed to provide a definitive answer.

**IN BRIEF**

**Already known**

- Recent evidence has shown that del5q patients who do not respond to lenalidomide have an increased risk of AML transformation, particularly in the presence of p53 mutations; concern exists that lenalidomide may promote transformation of MDS to AML in some situations.
- The use of azacitidine to cyto reduce MDS patients prior to ASCT is increasingly popular because of ease of administration and favourable toxicity profile, especially vs intensive CT.

**What these studies showed**

- Treatment of lower-risk MDS patients with lenalidomide does not increase the risk of AML transformation.
- Len is associated with a survival benefit in lower-risk del5q MDS.
- Patients who responded to azacitidine alone and subsequently went on to SCT had the lowest TRM and equivalent relapse rates vs other patients.
- Patients who required azacitidine+CT had both a higher TRM and the highest relapse rates with a significantly inferior OS (28%).

**Next steps**

- A randomized study comparing pre-SCT cyto reduction with azacitidine vs intensive CT is needed.

**AZACITIDINE IN CMML**

Previous randomized studies of azacitidine in MDS have excluded patients with therapy-related MDS (tMDS) and have only included a small number of individuals with chronic myelomonocytic leukemia (CMML). The efficacy of azacitidine in 76 patients with tMDS was reported by Komrokji and colleagues at ASH 2011 (abstract 1712). This study showed clear evidence of azacitidine response rates in this patient population (PR+CR+histologic improvement [HI] of ~40%) that were similar to what has been reported in primary MDS. However, both the median number of azacitidine cycles delivered (only 4) and the OS (~15 months) appeared inferior to what was achieved in the Phase III studies in primary MDS. Two studies presented at ASH 2011 addressed the use of azacitidine in CMML with the first (Pleyer et al; abstract 1715) reporting a 46% response rate (including 4 CRs) in 26 patients (median age 75 years) and a median OS of 12.7 months. The second study (Ades et al; abstract 1726) reported a 43% response rate (5 CRs) in
79 patients (median age 70 years) with CMML. These investigators also noted that inferior response rates could only be correlated with younger age. Median OS was 21.8 months in this study with an inferior outcome in patients with CMML-2, splenomegaly or a white blood cell count (WBC) >13x10^9/L. Although none of these reports on azacitidine in tMDS or CMML came from a randomized study, they do provide practical information to clinicians that can be used in treatment decision for patients with these 2 hematologic disorders.

References
1. Göhring G, Giagounidis A, Büsche G et al. Patients with del(5q) MDS who fail to achieve sustained erythroid or cytogenetic remission after treatment with lenalidomide have an increased risk for clonal evolution and AML progression. Ann Hematol 2010;89:365-74.

Disclosure
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