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Commentary

Transplantation for TP53 mutant MDS: Room for improvement

TP53 mutations represent the most common genetic alterations in cancer, occurring in approximately 50% of all invasive malignancies [1]. TP53 mutant myelodysplastic syndrome (MDS) accounts for 5–10% of de novo MDS and 25–30 % of therapy-related MDS and represents a specific cohort with the worst outcome [1]. Treatment with hypomethylating agents leads to a median survival of 6–12 months with no difference between azacitidine and decitabine1 [2]. TP53 mutation has also been shown to predict inferior outcome for patients undergoing allogeneic stem cell transplantation (SCT) owing to a high risk of relapse [1,3–6]. The adverse prognostic effect was similar in patients who received reduced-intensity conditioning regimens and those who received myeloablative conditioning regimens [5].

A high variant allele frequency (VAF) may be an unfavourable prognostic factor [6], although this was not confirmed in other studies [2,4,5]. The presence of multiple TP53 mutations was not associated with survival after SCT [5]. However, the presence of a truncating TP53 mutation was associated with shorter survival than the presence of missense mutations, indicating a distinct biologic activity of loss-of-function TP53 mutations [5]. The presence of TP53 mutations is strongly associated with complex chromosomal abnormalities, and appears to be the critical driver of poor survival since patients with wild type TP53 and complex cytogenetic abnormalities do not experience inferior outcomes in the context of treatment with HMA or SCT [3,5].

In this issue of Leukemia Research, Kim et al analysed bone marrow samples within 6 weeks before SCT of patients with de novo MDS, excluding therapy-related MDS. They confirmed that TP53 mutation is an independent prognostic factor for overall survival and relapse risk, and that chronic graft-versus-host disease or increasing conditioning intensity could not overcome this effect. These observations have already been made, but the previous study populations were more heterogeneous and included therapy-related MDS and acute myeloid leukaemia (AML).

The most interesting finding in the study accompanying this editorial is the 5 year overall survival of 41% of patients with TP53 mutant MDS. This contrasts with the much lower 5 year survival in other recent studies with a larger number of patients (0–20%) [5,7].

Another exception to the rule of low survival in TP53 mutant MDS is a study in therapy-related MDS of Aldoss et al that also showed a high overall survival of 51.3% after 3 years [7]. The authors hypothesized that their use of fludarabine-melphalan instead of fludarabine-busulfan conditioning explained the difference between the outcomes of their cohort and patients in other studies. However, Kim et al used fludarabine-busulfan in their study and showed comparable survival data. Since the negative effect of TP53 mutation is independent of age, conditioning intensity and other clinical factors, another hypothesis could be that factors related to molecular analysis technique and type and timing of samples may explain the huge difference between those outcomes. If this is the case, than it will be difficult to extrapolate the observations from clinical trials to our daily practice.

Based on the results of Kim et al., MDS patients should not be excluded from treatment with SCT because they have a TP53 mutation. Still, survival is much lower than in patients with wild type TP53. Escalation of the intensity of the conditioning regimen in order to improve outcomes in patients with TP53 mutated MDS will not be successful [5]. These patients who have an exceptionally high risk of relapse-related death should be considered for investigative approached to conditioning or relapse-prevention strategies after SCT [5].

Clinical investigations in hematologic malignancies are increasingly focused on exploiting biological consequences of specific mutations as personalized therapeutic approaches. There is growing interest in compounds that reactivate mutant TP53, with APR-246 being the most advanced in clinical development [1,8–11]. One question is how these p53 reactivators can best synergize with current standard treatments, HMA and SCT.

Sallman et al. showed that survival is significantly better in patients who have clonal response to HMA, i.e. decrease of VAF to less than 5% [2]. Also, transplanted patients who achieved VAF < 5%, had improved survival. Therefore, it seems logical to combine HMA with p53 reactivators that cause tumour cell apoptosis to increase the probability of clonal response, and to use maintenance with HMA and/or p53 reactivators post SCT.

The downstream network of pathways impacted by transcriptional activation of p53 has to be investigated further, of course. Although mutant p53 was traditionally regarded as undruggable, several compounds are entering clinical trials [12]. Because of the very large number of patients with TP53 mutant hematological malignancies, hopefully these important trials will become widely available.

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