on the high or higher end levels of folate and their connection to the long-term outcome rather than investigating low levels and their connection to disease. Taken together, these data will support the consideration of novel public guidelines on the recommended level of folate that will keep one healthy and strong.

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Transplantation for therapy-related, *TP53*-mutated myelodysplastic syndrome – *not because we can, but because we should*

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To the man who only has a hammer, everything he encounters begins to look like a nail.
Abraham Maslow, and others

Transplant physicians have often been accused of performing allogeneic hematopoietic stem cell transplant (HSCT) in patients for whom no hope of cure, or even meaningful gain, was thought plausible, simply because HSCT was deemed possible. Exemplifying this is the concept of transplantation for therapy-related myelodysplastic syndrome (tMDS), or MDS associated with the most severe of genetic lesions, *TP53*, for which outcomes have historically been poor.

In this issue of *Haematologica*, Aldoss and colleagues from the City of Hope Medical Center compare the outcomes of patients with tMDS and *de novo* MDS who underwent allogeneic HSCT, and correlate molecular features with outcome.[1] Although the study was limited by small sample size, the authors noted no significant differences in all important post-HSCT clinical outcomes, including survival, between tMDS and *de novo* MDS patients, even when prior chemoradiotherapy was considered in multivariable models. This analysis therefore suggests that allogeneic transplantation for tMDS should be performed whenever it would be considered in the *de novo* MDS setting.

Perhaps even more importantly, the authors examine the impact of molecular lesions on transplant outcome in a subset of the patients. From the original cohort, 60 tMDS patients underwent a comprehensive molecular analysis: 30% had a *TP53* mutation, and the authors found that the presence or absence of a *TP53* mutation had no correlation with outcome among these tMDS patients, although sample sizes were limited. In this context, grouping a heterogeneous subset of patients with genetic changes associated with adverse outcome in the non-transplant setting did carry prognostic information. In patients with any one of five genes (*TP53*, *EZH2*, *ETV6*, *RUNX1*, *ASXL1*) associated with adverse risk (48% of molecularly characterized tMDS patients) the authors demonstrated an adverse impact on relapse-free survival (hazard ratio: 1.58). This difference was also not statistically significant due to small sample size. It is worth noting that in this single center, retrospective analysis, outcomes were generally favorable, with 5-year overall survival rates approaching 50%.

Numerous studies have now examined the outcomes associated with molecular mutations following allogeneic HSCT (Table 1); however, this is one of the largest to specifically examine tMDS patients and compare their outcomes with those of patients with *de novo* MDS. Initial studies examining molecular prognostic features demonstrated dismal results for patients with mutated *TP53*.[2] In a study of 87 MDS patients who underwent allogeneic HSCT at our institute, there were no long-term survivors in the subset with *TP53* mutations, with the majority of deaths occurring within the first 12 months following allogeneic HSCT. Fifteen of 18 deaths in this group were attributed to disease relapse. While sample sizes were exceedingly small, this result instantly changed the landscape of transplantation, with many centers deciding not to perform HSCT in *TP53*-mutated MDS patients at all.

Other larger series have now reported outcomes of *TP53*-mutated HSCT patients with slightly more promising results. For example, Yoshizato and colleagues

Table 1. Outcomes associated with molecular mutations in MDS patients following allogeneic HSCT.

	Sample size	Fraction of cases with *TP53* mutation	Impact on survival following transplant	Outcome influenced by complex karyotype?	Outcome influenced by variant allele fraction?	Outcome influenced by *TP53* mutation type?
Bejar *et al.*[2]	87	20.7%	HR 4.22, *P*< 0.001	Unknowna	Not studied	Not studied
Yoshizato *et al.*[3]	797	12.7%	HR 1.49	Yes	Yes	Not studied
Della Porta *et al.*[4]	401	13%	HR 1.82, *P*=0.022[b]	Not studied	No	Not studied
Lindsley *et al.*[5]	1514	19%	HR 1.96, *P*<0.001	No	No	Yes

[a]16/18 *TP53* mutated patients had a complex karyotype; [b]Considering MDS patients alone. HR: hazard ratio.

demonstrated in a cohort of nearly 800 subjects that while *TP53* mutations did adversely influence outcomes, complex karyotype had a strong influence.[3] While survival with a complex karyotype and a *TP53* mutation was poor, being as low as 10%, for those without a complex karyotype, results were quite good (73% survival at 5 years), although sample sizes were very small (n=12) because a number of patients with unrecognized complex karyotypes were excluded using sensitive sequencing-based copy-number analysis.

Della Porta and colleagues studied 401 patients with MDS or acute myeloid leukemia arising from MDS who underwent allogeneic HSCT.[4] The presence of a *TP53* mutation significantly affected outcomes in both groups of patients, but there was no influence of variant allele fraction on outcomes. Incorporating *TP53* (and other) mutation states into the revised International Prognostic Scoring System could improve prognostication. It is notable that in this analysis, the survival rate at 4 years was approximately 30%, but there were no survivors beyond 10 years in the presence of a *TP53* mutation, with more than half of deaths occurring prior to the 2-year mark.

In the largest analysis of molecular features and their influence on transplantation outcomes, Lindsley *et al.* examined 1514 subjects, 19% of whom had a *TP53* mutation. As in the other series, the presence of a *TP53* mutation significantly affected outcome; however, the 5-year survival rate was approximately 20%, suggesting, in contrast to prior reports, that long-term cure and survival are possible, even when an unselected registry population is examined. Importantly, 311 subjects analyzed had tMDS, and a high proportion of these (38%) had *TP53* mutations. In contrast to the analysis of Aldoss *et al.*, published in this issue of *Haematologica*, the presence of a *TP53* mutation in tMDS was strongly associated with inferior survival (hazard ratio 1.63; *P*<0.001) while the outcomes of tMDS patients without a *TP53* mutation were similar to those of *de novo* MDS patients.

While novel therapeutics might eventually improve non-transplant outcomes, at present, none is associated with favorable outcomes in *TP53*-mutated MDS. For example, a novel 10-day decitabine regimen was recently described by the Washington University group. In this experience, 21 subjects with *TP53*-mutated acute myeloid leukemia or MDS all attained a marrow remission (defined as <5% blasts); however, median survival was only 12.7 months for MDS patients with a *TP53* mutation, and fewer than 20% were alive at 2 years.[6] While transplantation was not prospectively assigned in that study, transplantation improved outcomes among all patients, and *TP53* mutation status did not have a negative impact on transplantation outcomes.

Can we rationally incorporate molecular features into prognostic modeling for transplantation outcomes? This question was asked by the GITMO group, who devised a four-category risk score incorporating marrow blasts, cytogenetic risk, responsiveness to chemotherapy and the presence of driver mutations in *ASXL1*, *RUNX1*, or *TP53*.[7] While this proof-of-concept risk score was devised from a relatively small number of patients (n=401), a much larger, multinational effort (n>2500) is underway to redesign the revised International Prognostic Scoring System, with incorporation of molecular risk factors analyzed on a common next-generation sequencing platform (R. Bejar, *personal communication*). Once validated, we can incorporate these risk scores into clinical decision making.

Based on the recently published literature and the new analysis by Aldoss and colleagues, we can now conclude that transplantation even in the context of *TP53* mutation should be performed in MDS patients, provided these patients are made aware of the negative prognostic impact of the mutation that their tumor cells harbor. Long-term survival can be attained in a minority of patients, and for these select few, the decision to transplant is as simple as hitting the nail on its head.

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