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The Bottom Line

Induction, Bridging, or Straight Ahead: The Ongoing Dilemma of Allografting in Advanced Myelodysplastic Syndrome

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Allogeneic stem cell transplantation is still the only curative treatment option, and the number of allografts is steadily increasing in international registries [1]. Since large retrospective studies from european society for blood and marrow transplantation (EBMT) and center for international blood and marrow transplant research (CIBMTR) have shown that the number of blasts in patients with myelodysplastic syndrome (MDS) and chronic myelomonocytic leukemia (CMML) at the time of transplantation has a significant impact on outcome because of a higher risk of relapse [2,3], attempts have been made to reduce the number of blasts before transplantation by induction chemotherapy or hypomethylating agents (HMAs). Despite the lack of randomized studies, international experts recommend performing cytoreductive therapies before allogeneic stem cell transplantation in high-risk patients with MDS with ≥10% marrow blasts [4].

The study from Schroeder et al. [5] in this issue compared retrospectively upfront transplantation with induction chemotherapy and HMAs before stem cell transplantation in 165 patients with MDS and secondary acute myeloid leukemia (sAML). Despite a trend for improved survival in patients receiving upfront transplantation, no significant difference could be seen for upfront versus chemoinduction versus HMA induction with respect to overall survival and relapse-free survival. Other retrospective studies already have reported that HMAs before allogeneic stem cell transplantation did not improve outcome in comparison to upfront transplantation [6,7]. One might argue that the potency of HMA to induce complete remission is significantly lower than intensive chemotherapy and that HMAs are more likely used for "bridging" rather than "induction," aiming to avoid disease progression until a suitable donor is found. Indeed, also in the reported study by Schroeder et al. [5], the median number of HMA cycles was only 4, although it is known that most remission after HMA therapy was seen between 4 and 6 cycles or even beyond 6 cycles [8]. However, in the presented study as well as in line with other studies, induction chemotherapy induces a higher rate of complete remission than HMA, but this did not translate into a better outcome after transplantation [9,10]. In a recent EBMT registry study, patients who received induction chemotherapy or HMA had a similar outcome after transplantation, and only primary refractory disease resulted in worse outcome [11]. Also in studies comparing induction with no-induction therapy, no clear benefit could be observed for those who received induction therapy [6,12]. Any benefit was seen only in those who achieved a complete remission. As in other retrospective studies, a major concern is patient selection and those who received some form or induction or bridging therapy but did not undergo allogeneic stem cell transplantation because of reduced performance status caused by long-lasting myelosuppression and organ toxicity or treatment-related mortality. Treatment-related mortality up to 16% has been reported in patients with high-risk MDS who were candidates for allogeneic stem cell transplantation [13]. Investigators tried to overcome long-lasting myelosuppression of induction chemotherapy by a sequential approach using first anthracycline-based chemotherapy, followed after only 3 days of rest by the reduced or myeloablative conditioning regimen, which was also used in 73% of the upfront transplantation patients in the presented study. The impact of this sequential approach is currently being tested in a randomized FIGARO trial (ClinicalTrials.gov 50855000), and results are eagerly awaited. Even after HMAs that in general are considered less toxic, patients might lose their eligibility for allogeneic stem cell transplantation during treatment. In a recent

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Table 1.
Retrospective Studies Investigating Induction Therapy before Allogeneic Stem Cell Transplantation in MDS

Author	Treatment	RFS	*P* Value	OS	*P*value
Schroeder et al. [5]	Upfront (n = 67)	5 yr: 38%	.90	5 yr: 61%	.10
	Chemotherapy (n = 64)	5 yr: 41%		5 yr: 50%	
	HMA (n = 34)	5 yr: 38%		5 yr: 45%	
Potter et al. [11]	HMA (n = 77)	3 yr: 29%	.60	3 yr: 42%	.30
	Chemotherapy (n = 132)	3 yr: 36%		3 yr: 41%	
Damaj et al. [9]	Chemotherapy (n = 98)	3 yr: 37%	.90	3 yr: 48%	.07
	HMA (n = 48)	3 yr: 42%		3 yr: 55%	
	HMA → chemotherapy (n = 17)	3 yr: 36%		3 yr: 32%	
Damaj et al. (only RIC/NMA) [6]	Upfront (n = 88)	3 yr: 42%	.80	3 yr: 53%	.70
	HMA (n = 40)	3 yr: 37%		3 yr: 53%	
Alessandrino et al. [12]	Chemotherapy (n = 209)	NA	NA	HR: 1.07	.50
	Untreated (n = 148)	NA			
Nakai et al. [13]	RAEB-T	NA	NA	54% (only CR)	.80
	Chemotherapy (n = 111)	NA	NA	20% (if no response)	.10
	Untreated (n = 28)	NA		57%	
	RA + RAEB	NA		58% (only CR)	
	Chemotherapy	NA		50% (if no response)	
	Untreated	NA		73%	
Gerds et al. [10]	Chemotherapy (n = 33)		.10	1 yr: 36%	.20
	HMA (n = 35)	HR: 0.62		1 yr: 57%	
Field et al. [7]	HMA (n = 30)	1 yr: 41%	.30	1 yr: 47%	.25
	Upfront (n = 24)	1 yr: 51%		1 yr: 60%	

RFS indicates relapse-free survival; OS, overall survival; RIC, reduced intensity conditioning; NMA, non-myeloablative conditioning; NA, not applicable; HR, hazard ratio; RAEB-T, refractory anemia with excess of blasts in transformation; CR, complete remission; RA, refractory anemia; RAEB, refractory anemia with excess of blasts.

reported prospective trial in older patients with high-risk MDS, allogeneic stem cell transplantation was planned for patients with an HLA-matched donor. During a donor search, 4 cycles of 5-azacitidine were planned as a bridge to transplant to induce remission or at least prevent progression until transplantation. The fact that 33% who started 5-azacitidine treatment could not undergo allogeneic stem cell transplant because of death (19%), progress (10%), or toxicity suggests an advantage for upfront transplantation [14]. Concerns about using pretransplant chemotherapy or HMAs came from recent investigators who analyzed clonal evaluation in patients with MDS who relapsed after allograft. They showed that a small subclone before transplant could drive progression after allografting, but also newly acquired structural variants were present in expanding subclones at progression, and pretransplant therapy with 5-azacitidine influenced the mutation spectrum and evaluation of the subclone postallografting [15]. This might explain—but does not prove—why upfront transplant patients responded better to HMA salvage therapy after relapse than others in the reported study from Düsseldorf [5].

Overall, after the only randomized study from the EBMT had to be closed because of poor recruitment, all reported retrospective studies did not answer properly whether to induce, bridge, or perform allogeneic stem cell transplantation without any pretransplant in patients with advanced MDS (see Table 1). The available results and the biological clonal evaluation studies question seriously the usefulness of pretreatment in patients with MDS who are considered for an allogeneic stem cell procedure, but they remind us about the still existing clinical need for a well-designed prospective study assessing this issue.

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