Best Practice & Research Clinical Haematology 32 (2019) 104–113

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/issn/15216926

Can allogeneic hematopoietic cell transplant cure therapy-related acute leukemia?

Yazan F. Madanat, Aaron T. Gerds*

Leukemia and Myeloid Disorders Program, Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH, USA

ARTICLE INFO

Keywords:
Leukemia
Myeloid
Therapy-related
Transplantation
Allogeneic

ABSTRACT

Therapy-related myeloid neoplasms (t-MN) include both therapy-related myelodysplastic syndromes as well as therapy-related acute myeloid leukemia. These two entities were grouped together in the World Health Organization classification of AML due to having similarly poor outcomes and disease biology. Exposure to prior radiation therapy or chemotherapy for other malignant or benign conditions, namely autoimmune diseases or solid organ transplants, constitutes the principal risk factor to develop t-MN. Mechanisms for the development of t-MN include direct genotoxic damage from prior chemotherapy or radiation therapy exposure and the selection of pre-existing clones with malignant potential that are able to evolve with time and manifest as new cancers. Patients with t-MN are generally considered high-risk at the time of diagnosis and are commonly referred for consideration of an allogeneic hematopoietic cell transplantation, however, this patient population poses unique challenges, and little is known about the ideal sequence and timing of treatment. In this review, we summarize the data pertaining to transplant options, focusing on patient and disease characteristics in which transplantation may be most useful and populations where non-transplant options may also be considered.

1. Introduction

The outcome of patients with therapy-related myeloid neoplasia (t-MN) is poor and allogeneic hematopoietic cell transplantation (allo-HCT) remains the only treatment modality that has demonstrated curative potential in treating patients with t-MN. However, it may not be the best approach for all patients, and its use is somewhat controversial. Prospective trials specifically designed to address the utility of transplant in t-MN are lacking, moreover, patients with t-MN are often enrolled on clinical trials designed for de-novo disease and are available for subset analysis only. Therefore, we have to rely on retrospective datasets to aid in treatment decisions [Table 1] [1–8]. Also, these studies have significant limitations; they are not contemporary [1–8], and do not include patients treated with newly approved targeted agents in AML [9–13], or patients treated with newer induction chemotherapy regimens [14]. Finally, several improvements in allo-BMT have occurred since then, including the management of graft versus host disease and infectious complications, which impact outcomes [15].

The WHO definition for t-MN is somewhat broad and encompass a wide range of disorders including therapy-related myelodysplastic syndromes (t-MDS), therapy-related acute myeloid leukemia (t-AML) and therapy-related myelodysplastic/

* Corresponding author. Leukemia and Myeloid Disorders Program, Department of Hematology and Medical Oncology, Cleveland Clinic Taussig Cancer Institute, 9500 Euclid Ave, CA-60, Cleveland, OH 44195, USA.

E-mail addresses: madanay@ccf.org (Y.F. Madanat), gerdsa@ccf.org (A.T. Gerds).

https://doi.org/10.1016/j.beha.2019.02.011
Received 26 January 2019; Received in revised form 18 February 2019; Accepted 22 February 2019

Table 1
Post-transplant outcomes of therapy-related myeloid neoplasms.

Study [reference]	Total Number (t-MDS/t-AML)	t-AML Cohort	Time of outcome measure (years)	Outcome Measure (%)			Factors impacting NRM	Risk Factors impacting OS
				NRM/TRM	Relapse	mOS		
Litzow et al. [1]	868	545	5	48	31	22	–	Unfavorable: Age > 35 years Poor-risk cytogenetics Non-remission status pre-transplant Donor Status (less well-matched)
Kroger et al. [2]	461	308	3	37	31	35	Age Calendar year	Favorable: Calendar year Age (< 40 years) Normal cytogenetics
Chang et al. [3]	257	103	5	28-61*	33 for t-AML 12–36 for t-MDS	33	Lowest with tBUCY conditioning	–
Witherspoon et al. [4]	111	71	5	42-58*	40 for t-AML 0–26 for t-MDS	NA	–	–
Finke et al. [5]	79	67	5	23	42	38	Favorable: Karnofsky score ⩾90%	None
Yacoub-Agha et al. [6]	70	39	2	49	42	30	–	–
De Witte et al. [7]	67	NA	3	46	36	35	–	–
Alam et al. [8]	65	32	2	31	30–33	34	Donor type (NRM 20% vs 60% related vs unrelated)	Unfavorable: Adverse Cytogenetics (HR 2.7) Unrelated donor (HR 2.7)

Abbreviations: t-MDS = therapy-related myelodysplastic syndrome, t-AML = therapy-related acute myeloid leukemia, NRM = non-relapse mortality, TRM = treatment-related mortality, mOS = median overall survival, tBUCY = targeted busulfan cyclophosphamide. *Range reported based on conditioning regimen.

myeloproliferative neoplasms (MDS/MPN) overlap syndromes [16,17]. Therapy related myeloid neoplasms constitute 7–20% of newly diagnosed AML, MDS or overlap syndromes [17–19]. While some patients may have prior exposure to chemotherapy, radiation therapy, or immune suppressive agents, the time between the exposure and development of t-MN does not quite fit temporally with known patterns. There are certainly karyotypic associations between exposure to a specific chemotherapeutic agents and cytogenetic abnormalities, such as that with topoisomerase II inhibitors and abnormalities involving the long arm of chromosome 11 (11q23/KMT2A/MLL), as well as that with the exposure to alkylating agents, radiation therapy or immune suppressive chromosome 5 or 7 abnormalities [20–23]. Overall, the majority of patients with t-MN have a poor risk karyotypic profile and high risk molecular features. The most common molecular abnormality in t-MN involves mutations in the tumor suppressor gene, *TP53*, which carries a poor prognosis and conveys a high risk in both *de novo* and therapy-related disease [24,25]. In the next sections, we will focus on the unique challenges of caring for this patient population, summarizing non-transplant treatment options, and highlighting those who may derive the most benefit from undergoing an allo-HCT.

2. Mechanisms and unique challenges of transplant in this population

Pound-for-pound, the treatment of t-MN is more complex than that of its *de novo* counterpart. First, while t-MNs are lumped together, this group is very heterogeneous and multiple mechanisms have been described could lead to the development of a t-MN [26]. These include; the direct induction of a fusion oncogene by cytotoxic agents or radiation therapy, induction of genomic instability which will in turn lead to complex abnormalities [24], selection of pre-existing malignant clones [27–29] and possibly a hereditary pre-disposition to develop more than one malignancy [26,30,31]. The hereditary predisposition may have implications during donor selection at the time of hematopoietic cell transplantation. In most large transplant centers, a matched sibling donor remains the preferred donor source. However, over the past several years, hereditary syndromes in myeloid malignancies have become more recognized and the association of specific gene abnormalities with hereditary syndromes (such as *GATA2*, *RUNX1* or *DDX41*) or a strong family history of myeloid malignancies should trigger early referral for genetic counseling and potential germline mutational testing [32,33]. Matched sibling donors carrying the same genetic abnormality and risk to develop myeloid malignancies are not suitable as the risk of donor-derived leukemia is too great.

Despite the pathogenic variation leading to t-MN, these patients share high-risk disease features. This was exemplified in an analysis of 3026 AML patients, 200 of which had t-AML [34]. Patients with t-AML were older vs *de novo* respectively (57.8 vs 53.2 years; $P < .0001$), and had lower median white blood counts and platelets. T-AML patients had higher percentage of abnormal karyotypes (75% vs 51%, $P < .0001$) most commonly involving chromosomes 5 and 7, t(v; 11)(v; q23), 17p or having complex and monosomal karyotypes. Although the type of AML had no impact on induction-remission rates, having t-AML adversely impacted relapse free and overall survival in a multivariable model that accounted for cytogenetic abnormalities [34]. Patients with t-MN have specific molecular profiles and adverse molecular features when compared to patients with *de novo* disease. In a study characterizing somatic mutations in 266 patients with t-MN, mutations in *TP53* and *KIT* were significantly enriched in the t-MN cohort (odds ratio 2.6 and 6.0 respectively) [35]. The use of somatic mutations to define AML ontogeny classified 101 patients with t-AML into 3 molecular groups. The first group (23%) had *TP53* mutations, the second (33%) had "secondary type" mutations as *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR or STAG2* and a third group (47%) had "*de novo*" or pan-AML abnormalities [36]. The authors in this study were not able to define at a molecular level any specific t-AML ontogeny. Clinically, those with "secondary type" mutations closely resembled patient with secondary AML, those with "*de novo*/pan-AML" mutations resembled *de novo* disease and those with *TP53* mutated AML with or without a history of prior therapy were associated with complex, monosomal karyotypes, often involving chromosome 5 or 7 [36]. While some of the clinical characteristics (age, male: female ratio and number of driver mutations) were similar in this study between patients with t-AML vs those with sAML/*de novo* disease with similar genomic profile, t-MN patients are inherently different.

Patients developing a t-MN are an older population and may have more medical co-morbidities. The prior exposure to chemotherapy or radiation therapy can have long lasting effects on the hematopoietic system. This, in turn, can weaken the regenerative ability of hematopoietic tissue, prolonging the duration of cytopenias and bone marrow recovery as a result [37]. Additionally, some patients have active primary cancer at the time of t-MN diagnosis, which affects outcomes and further complicates treatment decisions for t-MN. Another unique cohort of patients are those with a history of a prior solid organ transplantation or an active rheumatologic condition requiring ongoing immune suppressive therapy. This can render patients more frail and susceptible to infection-related complications while undergoing treatment of t-MN. T-MN post solid organ transplantation carries dismal outcomes [38]. The disease (cytogenetic, molecular) and patient characteristics (age, comorbidities, primary disease amongst others) are some of the features that complicate treatment decisions and make this population unique.

3. Weighing the risks and benefits of transplant per disease subgroup

3.1. Myelodysplastic syndromes

The first question is whether or not our current scoring systems adequately predict risk associated with treatment-related myelodysplastic syndromes (MDS). The international prognostic scoring system (IPSS) [39] and its revised version (IPSS-R) [40] are commonly used to risk stratify patients with *de novo* MDS, however, both scoring systems excluded patients with therapy-related MDS in their original derivation. A study of a cohort of 1837 patients with t-MDS demonstrated that when the IPSS/IPSS-R scoring systems are applied to this population, they will underperform in predicting transformation to AML or overall survival and are thus suboptimal for this patient cohort. In this population, the revised IPSS risk categories were 8%, 20% and 17% (total 45%) in very low, low and intermediate risk groups and 23%, 32% (total 55%) in the high or very high-risk groups respectively. It was clear that although the majority of patients fell in the higher risk groups, 28% of patients fell in the very-low and low risk categories and a large number of patients had good risk cytogenetics. Recognizing these limitations, the international working group is currently developing a more specific t-MDS scoring system in order to better predict outcomes and tailor therapy [41]. Of note, the majority (28%) of patients with t-MDS received prior therapy for non-Hodgkin lymphoma, followed by breast cancer therapy in 16% in this database.

In *de novo* MDS patients, allogeneic transplantation is recommended for patients with higher risk disease per IPSS (i.e. intermediate II or high risk groups), due to a survival and quality of life advantage as demonstrated in a series of Markov analyses [42]. The outcomes of a large cohort of 660 patients with t-MDS or oligoblastic AML using IPSS-R were compared to *de novo* MDS; patients with t-MN had worse outcomes in each of the 5 risk groups, particularly those in very low and low risk categories [43]. Although upfront allo-HCT is not recommended for patients with low-risk *de novo* MDS, it should be considered in those with lower-risk t-MDS as their outcomes with non-transplant therapies are comparable to high-risk disease.

3.2. T-AML: favorable-risk cytogenetics

In t-AML, the cytogenetic subtypes that are considered favorable in *de novo* disease, including t(15; 17) or core binding factor leukemia with t(16; 16)/inv16, t(8; 21), can occur [44]. These subtypes may achieve similar remission rates when compared to patients with *de novo* AML [45,46] and in turn, some have questioned the benefit of allo-HCT in first remission and elect to treat those patients similar to their *de novo* counterparts [47]. Again, it can be challenging to discern whether they are truly t-MNs or a second *de novo* disease as the WHO definition of t-MN cannot truly distinguish between the two.

3.2.1. Core binding factor t-AML

AML with inversion 16 has been linked to exposure to topoisomerase II inhibitors [48]. In a study of 48 patients with t-AML with inv16 cytogenetic abnormality, the median time to development of t-AML was 22 months. The complete remission rates were 85% with intensive chemotherapy [46]. In another study of 16 patients with inv(16) t-AML, the complete remission rate with intensive chemotherapy was 86% with a 2-year disease-free survival of 54% [49]. While remission rates are high with induction chemotherapy, survival rates remain poorer for therapy-related core binding leukemia than its *de novo* counterpart [50,51]. Similarly, induction chemotherapy can result in high complete remission rates for t-AML with t(8:21) [52]. The remission rates in a study that included 13 patients with t(8; 21) t-AML were similar to 38 patients with *de novo* AML with t(8; 21). However, the outcomes of the t-AML cohort were worse with a median overall survival of 19 months for t-AML versus “not reached” for *de novo* AML with t(8; 21) ($p = .002$) [53].

With overall survival in core binding factor t-AML akin to that of high-risk disease, allo-HCT is warranted in this population, however, there are conflicting results on the matter. In another study of 139 patients with t(8; 21) AML, 22 patients had therapy-related AML. Patients receiving intensive induction chemotherapy regimens (72%, n = 16/22) were included in the survival analysis. The 2 year overall survival was not statistically different between therapy-related vs *de novo* AML with t(8; 21) (46.8% vs 78.4%, p = .061) [54]. No difference in outcomes were observed in 9 t-AML with t(8; 21) as compared to 128 patients with *de novo* disease [55]. In a multicenter analysis of 26 patients with therapy-related t(8; 21) AML, The majority of patients (76%, n = 16/21) achieved complete remission with intensive chemotherapy and the 2 year disease free survival was 47% [49].

High quality evidence to have firm recommendations are currently lacking for core binding factor therapy-related AML. However, based on the sum of available data, we recommend intensive chemotherapy followed by consolidation with high-dose cytarabine for patients with t-AML and t(8; 21), inv(16), t(16; 16) and in the absence of additional high-risk features, reserve allogeneic transplant at the time of relapse [47].

3.2.2. t-AML with t(15; 17) or t-APL

Therapy for acute promyelocytic leukemia (APL) has taken a leap forward with the introduction of all-trans-retinoic acid (ATRA) and arsenic trioxide (ATO). The final analysis of a phase III trial in low- or intermediate-risk APL demonstrated a 100% complete remission rate for patients on the ATRA/ATO arm. The event-free survival, cumulative incidence of relapse, and overall survival at 50 months for those patients were 97.3%, 1.9%, and 99.2%, respectively. ATRA/ATO has since become the standard of care in this population [56,57]. Moreover, there are no reports of t-MN in patients treated with this chemotherapy-free regimen. The use of ATRA and anthracycline-based chemotherapy for APL was associated with a 2.2% incidence of t-MN [58].

In one study of 41 patients with therapy-related APL, the median time to develop t-APL after prior exposure was 29 months. The complete remission rate in this cohort was 69%, however the use of ATRA was inconsistently reported at the time this study was conducted [46]. Another retrospective analysis reported on the outcomes of 29 patients with t-APL treated with ATRA/ATO (n = 19) or ATRA plus anthracycline-based chemotherapy (n = 10). Patients treated with ATRA/ATO had a complete remission rate of 89% as compared to 70% in the ATRA plus chemotherapy arm [59].

The overall response rates and outcomes are excellent for *de novo* as well as t-APL and the treatment with ATRA/ATO combination is thus justified, especially for patients with low-intermediate disease (Fig. 1). Allogeneic transplantation, therefore, is not recommended in first remission for patients with t-APL.

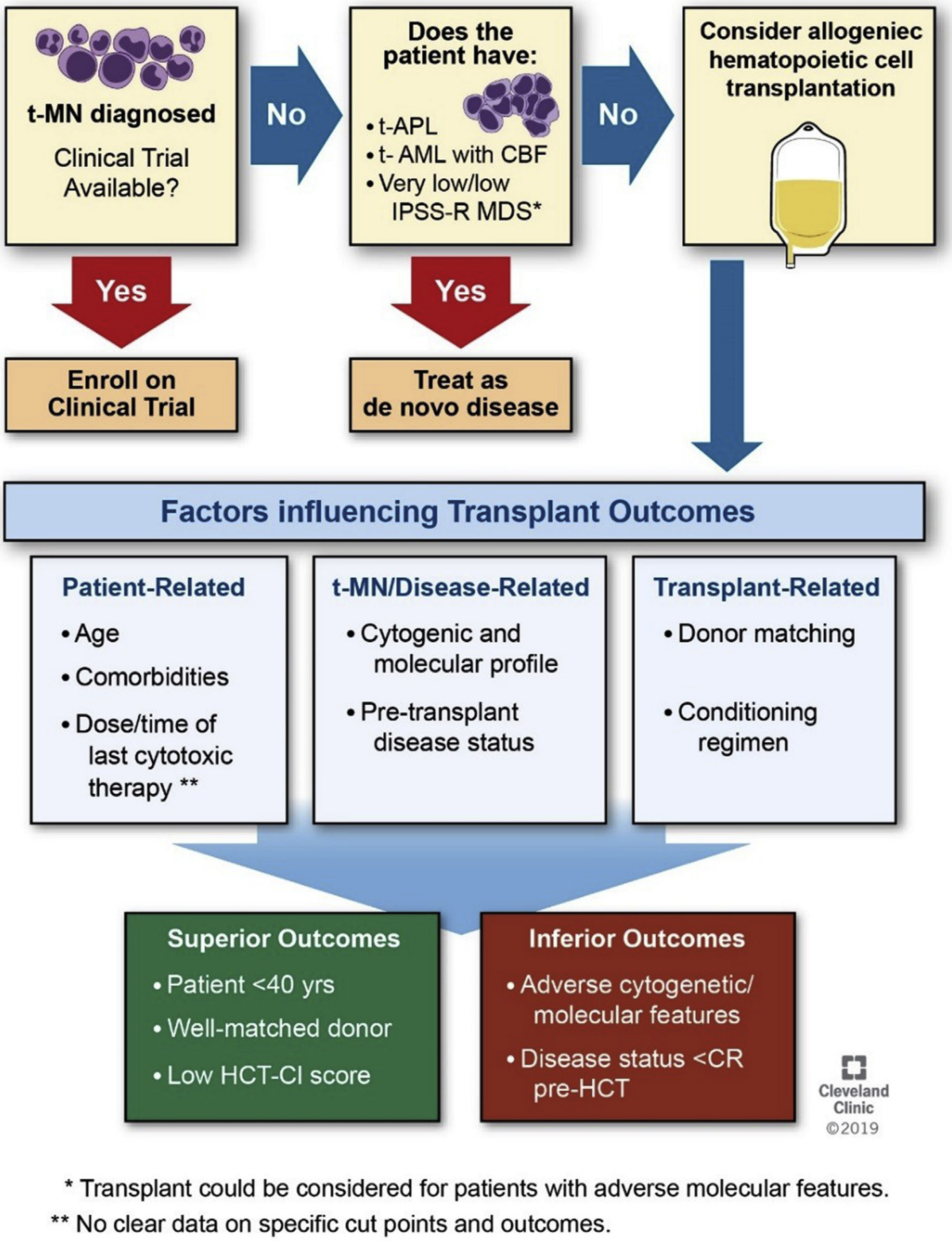

Fig. 1. Guide to t-MN Management and Factors Influencing Transplant Outcomes.

3.3. *T-AML with diploid karyotype and favorable molecular features*

In *de novo* AML, patients with normal karyotype constitute about 40–50% of patients and their outcomes are heterogeneous, largely due to the molecular heterogeneity of the disease. Molecularly favorable patients with *NPM1* mutation positive/FLT3-ITD negative AML are treated with consolidation chemotherapy and transplant is generally considered at disease relapse. Minimal/ measurable residual disease (MRD) testing for the *NPM1* mutation has been used to identify patients that may benefit from allo-HCT in first remission, as MRD positivity predicts for relapse [60]. Consensus guidelines by the European Leukemia Net (ELN) have go so far as to recommend MRD testing for patients with *NPM1*-mutated disease using quantitative RT-PCR [61]. The caveat here is that no randomized prospective trials have shown benefit of early intervention by proceeding to allogeneic transplant at the time of MRD positivity as opposed to clinical relapse. Additionally, several challenges remain in standardizing the method of MRD detection, threshold for positivity, and the ideal time points for testing, in addition to the utility of earlier intervention [62]. t-AML have lower frequency of *NPM1* mutations than *de novo* AML ($p < .0001$), however correcting for karyotype (i.e. comparing only those with diploid karyotype), the difference in occurrence of *NPM1* mutations is no longer there between the two etiologies [55]. This makes us wonder whether patients with cytogenetically normal t-AML with an *NPM1* mutation are truly therapy-related, and in turn, should be treated similarly to *de novo* AML, deferring transplant in first remission [63].

3.4. Induction regimens

While it is clear that being in remission prior to transplantation is key in optimizing post-transplant outcomes, the best method for getting to remission remains unclear. Few regimens have been prospectively compared to 7 + 3 in a randomized fashion. Non-transplant therapies are discussed elsewhere in this issue. One single center, single arm prospective trial investigating the remission induction rate of using high dose cytarabine at 3 g/m^2 followed by mitoxantrone at 30 mg/m^2 given for 2 doses on day 1 and 5 of induction chemotherapy showed a complete remission (CR) rate of 66% with a 30-day mortality of 9%. In the CR group, 62% of patients were able to undergo allo-HCT [64]. Thirteen patients underwent an allogeneic HCT in first remission, with the 1-year overall survival being 72% for those receiving an allo-HCT versus 17% for those who did not receive a transplant. Given the poor outcomes of patients in the non-transplant settings, we again emphasize consideration of allo-HCT for eligible patients.

A liposomal encapsulation of cytarabine and daunorubicin, also known as CPX-351, has now received regulatory approval for patients with newly diagnosed t-AML or AML with myelodysplasia-related changes (AML-MRC). This is based on a study that randomly assigned 309 patients to receive CPX-351 or standard induction chemotherapy (7 + 3), of those a total of 63 patients had t-AML (30 patients received CPX-351 and 33 received 7 + 3). Remission rates of this formulation were higher for CPX-351 when compared to standard 7 + 3 administration (CR rate 37.3% v 25.6% respectively; two-sided $p = .040$), additionally overall survival (OS) was prolonged by about 4 months using CPX-351 (median OS 9.56 vs 5.95 months for CPX-351 versus 7 + 3 respectively; hazard ratio 0.69; $p = .003$) [14]. Importantly, the outcomes post-transplant were quite remarkable and significantly better for patients receiving CPX-351 versus 7 + 3 in an exploratory landmark analysis (HR, 0.46; 95% CI, 0.24 to 0.89; one-sided $P = .009$) with a median survival (not reached compared for CPX-351 vs 10.25 for 7 + 3, $p = .009$) [14].

3.5. Outcomes of allogeneic hematopoietic cell transplantation (Allo-HCT)

As stated above, there are no prospective trials investigating transplant outcomes that enroll only patients with therapy-related myeloid neoplasms. This makes data-driven recommendations difficult and transplant physicians need to largely look at retrospective studies to derive outcome expectations to share with patients. Multiple retrospective studies analyzed the outcomes of patients with t-MN in the post-transplant setting, a selected group of larger studies and their outcomes are summarized in Table 1.

3.5.1. Factors impacting transplant outcomes

The majority of patients with t-MN have poor risk karyotypes and are appropriately referred for allogeneic HCT. Due to the unique aspects of this patient population, retrospective studies have looked into specific factors that affect transplant outcomes.

The largest cohort of t-MN patients undergoing allo-HCT was reported by the Center for International Blood and Marrow Transplant Research. A total of 868 patients with t-AML ($n = 545$) or t-MDS ($n = 323$) underwent allo-HCT. The majority of patients (77%) received a myeloablative regimen. The 1-year treatment-related mortality (TRM) and relapse rates were 41% and 27%, respectively, with a 1-year OS of 37%. However, at 5 years, TRM was 48% and the relapse rate was 31% resulting in an OS of 22%. This study identified a scoring system that predicts for worse outcomes. The risk factors include: (1) age older than 35 years; (2) poor-risk cytogenetics; (3) t-AML not in remission or advanced t-MDS; and (4) donor other than an HLA-identical sibling or a partially or well-matched unrelated donor. The 5-year OS dropped significantly for patients with increasing risk factors from 50% (0 risk factors) to 26% (1 risk factor) to 21% (2 risk factors) to 10% (3 risk factors) to 4% (4 risk factors). Thus, patients with 3 or 4 risk factors are not ideal candidates for allo-HCT due to their dismal outcomes (Fig. 1) [1].

Another cohort of 461 patients with t-MDS/t-AML reported by the European Group for Blood and Marrow Transplantation demonstrated a 3-year incidence of NRM of 37% and a relapse rate of 31%. Factors associated with relapse included depth of response at the time of transplant (i.e. less than 5% blasts) ($p = 0.002$), abnormal cytogenetics ($p = 0.005$), age ($p = 0.03$) and t-MDS ($p = 0.04$), while age was the only risk factor associated with higher NRM in a multivariate model. The 3-year overall survival was 35%. Survival was improved for patients with age less than 40 years and those with a normal karyotype [2]. Smaller datasets have shown similar post-transplant outcomes and have identified additional risk factors. In a study of 65 patients with t-MN, the 2-year overall survival (OS) was 34%. The 2-year OS in patients with monosomal karyotype (29%) was further reduced to 21%. Importantly, risk factors predicting for lower OS in a multivariate model were adverse risk cytogenetics (HR 2.7; 95% CI 1.02–7.2; $p = .02$) and unrelated donor (HR 2.7; 95% CI 1.5–5.0; $p = .0013$). Unrelated donor source was the only risk factor associated with an increase in 2-year non-relapse mortality of 60% versus 20% in the matched related cohort ($p = .0007$) [8]. In summary, patients deriving the most benefit of transplant are those who are younger, having the disease in complete remission (blasts < 5%) at the time of transplantation and having a well-matched donor (whether sibling or unrelated).

3.5.2. Effects of conditioning regimen on transplant outcomes

In a study of 257 patients with t-MDS/t-AML receiving a wide array of conditioning regimens, the 5-year relapse-free survival (RFS) was 43% (highest) and non-relapse mortality (NRM) was 28% (lowest) in patients conditioned with targeted busulfan/cyclophosphamide. Compared to patients with *de novo* disease (n = 339), transplant outcomes for t-MDS/t-AML were comparable without any significant differences using a multivariate model. The probability of relapse correlated with the disease stage (RA/RARS versus RAEB versus t-AML) and karyotype. Relapse rates were lower for patients receiving an unrelated donor transplant [3]. However, taking other study findings into account, no specific conditioning regimen was shown to be superior for patients with t-MN. Myeloablative conditioning (MAC) was shown to be superior to reduced intensity conditioning (RIC) in *de novo* MDS/AML in a randomized phase III clinical trial, relapse rates for MAC vs RIC were 13.5% vs 48.3%; respectively; $p < .001$, mandating early termination of the study. At 18 months, OS for patients in the RIC arm was 67.7% versus 77.5% for those in the MAC arm (difference, 9.8%; $P = .07$). Therefore, as data is lacking for t-MN, it may be reasonable to consider MAC in t-MN for patients who can tolerate it [65].

3.5.3. Should we transplant patients with adverse cytogenetics?

To further investigate the effects of cytogenetics on the outcomes of patients with t-MN vs *de novo* disease, a retrospective single-institution analysis of 556 patients (476 with *de novo*, 80 with t-MDS/t-AML) was completed. After patients were classified into 3 risk groups based on cytogenetics, risk group was found to be the predictor of overall survival. Importantly, this study demonstrated similar outcomes in patients with t-MN versus *de novo* disease after accounting for cytogenetics, whereby patients with a higher cytogenetic risk classification had a higher rate of relapse and decreased survival [66]. For patients with complex and higher risk cytogenetics, transplant remains the only potential curative option and should be highly considered.

3.5.4. Are there any long-term survivors with transplant?

In a German-Austrian cohort of over 2800 patients with AML, 200 of which had t-AML, allo-HCT in first remission was performed in 487 of 2064 (24%) patients ≤ 60 years, and in 30 of 789 (4%) patients > 60 years of age [34]. The 4-year OS in patients with t-AML receiving allogeneic HCT in first remission was 42.6%. The relapse rates after allo-HCT were similar in younger patients with t-AML, however, there was a higher cumulative incidence of death (35.8%, standard error 8.3%) as compared to that of *de novo* AML (17.2%, standard error 20%) $p = .006$. Conversely, in patients over the age of 60 years, there was increased incidence of relapse and not death in patients with t-AML as compared to *de novo* disease [34].

The longest duration of follow up outcomes for patients with t-MN in the post-transplant setting was reported in a study of 79 patients. The 10 year overall survival in this cohort of 79 patients was 24% with a stable rate of relapse of 42% between the 5–10 year mark [5,67]. These studies highlight the importance and efficacy of allogeneic HCT in patients with t-MN. The outcomes of t-AML are often inferior to *de novo* AML after transplantation (allo-HCT: *de novo* > therapy-related), however, it is also true that outcomes for t-AML are better with transplantation than non-transplant therapies (t-AML: allo-HCT ≫ non-HCT therapies).

3.5.4.1. Should we transplant patients with TP53 mutated disease?. The most common molecular abnormality in t-MN is by far is *TP53* – occurring in up to a third of patients – and when detected is associated with poor outcomes and shorter overall survival [68,69]. The role of high-dose chemotherapy and allo-HCT in patients with t-MN that harbor *TP53* mutations is an area of controversy and discussed here in more detail.

A study of 87 patients with MDS investigated 40 recurring somatic mutations in the pre-transplant setting. The most commonly detected mutations were in *ASXL1* (29%), *TP53* (21%), *DNMT3A* (18%), and *RUNX1* (16%). After adjustment for clinical variables associated with survival, mutations in *TP53, TET2 and DNMT3A* were associated with a shorter OS. Forty six percent of patient carried one of these mutations, and their presence resulted in shorted 3-year OS from 59% for patients without these mutations to 19% [70]. Thus patients with *TP53* mutations pose significant challenge for the optimal treatment and timing of allo-HCT. Another study investigating mutational profiles of 1514 patients with MDS using the CIBMTR database noted the presence of *TP53* mutations in 19% of patients. In multivariate analysis, *TP53* was independently associated with shorter OS (hazard ratio for death vs. no *TP53* mutation, 1.71; 95% CI, 1.45 to 2.02; $P < 0.001$) and shorter time to relapse (HR for relapse vs. no *TP53*, 2.03; 95% CI, 1.60 to 2.58; $P < 0.001$). The intensity of the conditioning regiment did not affect the outcomes or overcome the effect to *TP53* mutational status [71].

While the prior two studies investigated the effect of mutational status in the transplant setting, they were not specific for patients with t-MN. A single institutional report of a total of 266 patients; 67 with t-MDS and 199 patients with *de novo* MDS undergoing an allo-HCT showed the 5-year OS was not significantly different between the two cohorts (49.9% for t-MDS versus 53.9% for *de novo* MDS; $p = 0.61$). *TP53* mutations were detected in 30% of patients with t-MDS, and while the number of patients in this study was small, *TP53* mutational status did not affect OS or RFS [72,73]. Although, outcomes are worse with *TP53*-mutated MDS/AML as those compared to those with wild-type TP53, there are long-term disease-free survivors. Therefore, it is recommended to offer patients an allo-HCT for t-MN patients with *TP53* mutations.

4. Summary

Therapy-related myeloid neoplasms are diverse set of disorders grouped together by a common causative factor. Allogeneic hematopoietic cell transplantation remains the only potentially curative option for patients with t-MN. Patient characteristics such as older age and comorbidities, as well as certain disease characteristics such as complex karyotype and lack of remission are associated with poor post-transplant outcomes and negatively impacts the success of such an approach. Weighing the likelihood of success of allo-HCT against the toxicity is important to when discussing treatment options with our patients. For patients with a favorable AML karyotype, offering standard induction chemotherapy regimens similar to *de novo* AML may be appropriate while reserving transplant until the time of disease relapse. While t-MNs are more likely to harbor high-risk cytogenetic and molecular abnormalities, retrospective data suggest that allo-HCT should still be recommended despite the poor prognosis, and after accounting for these adverse markers, long-term disease-free survival may be on par with *de novo* disease.

Conflicts of interest

Y.F.M has no conflicts of interest to disclose. A.T.G has received consulting fees from Celgene, Apexx Oncology, CTI Biopharma, and Inctye; and research funding from Roche, Genentech, Incyte, Celgene, Imago Biosciences, Samus Therapeutics, and Gilead.

Practice points

- Older age, comorbidities, poor risk cytogenetic and molecular aberrations are important factors that impact consideration for allogeneic HCT and affect patient outcomes.
- Patients with core binding factor t-AML or t(15; 17) may be treated similarly to their *de novo* counterpart.
- Patients with poor risk cytogenetics or molecular features should be offered allogeneic hematopoietic transplantation (allo-HCT) in first remission, if eligible.
- t-MDS and t-MDS/MPN treatment remains challenging with low response rates to HMA and would favor enrollment on clinical trials, offering allo-HCT for those with higher molecular features or "higher-risk" disease per scoring systems.

References

[1] Litzow MR, Tarima S, Perez WS, Bolwell BJ, Cairo MS, Camitta BM, et al. Allogeneic transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia. Blood 2010;115(9):1850–7.
[2] Kroger N, Brand R, van Biezen A, Zander A, Dierlamm J, Niederwieser D, et al. Risk factors for therapy-related myelodysplastic syndrome and acute myeloid leukemia treated with allogeneic stem cell transplantation. Haematologica 2009;94(4):542–9.
[3] Chang C, Storer BE, Scott BL, Bryant EM, Shulman HM, Flowers ME, et al. Hematopoietic cell transplantation in patients with myelodysplastic syndrome or acute myeloid leukemia arising from myelodysplastic syndrome: similar outcomes in patients with de novo disease and disease following prior therapy or antecedent hematologic disorders. Blood 2007;110(4):1379–87.
[4] Witherspoon RP, Deeg HJ, Storer B, Anasetti C, Storb R, Appelbaum FR. Hematopoietic stem-cell transplantation for treatment-related leukemia or myelodysplasia. J Clin Oncol 2001;19(8):2134–41.
[5] Finke J, Schmoor C, Bertz H, Marks R, Wasch R, Zeiser R, et al. Long-term follow-up of therapy-related myelodysplasia and AML patients treated with allogeneic hematopoietic cell transplantation. Bone Marrow Transplant 2016;51(6):771–7.
[6] Yakoub-Agha I, de La Salmoniere P, Ribaud P, Sutton L, Wattel E, Kuentz M, et al. Allogeneic bone marrow transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia: a long-term study of 70 patients-report of the French society of bone marrow transplantation. J Clin Oncol 2000;18(5):963–71.
[7] de Witte T, Hermans J, Vossen J, Bacigalupo A, Meloni G, Jacobsen N, et al. Haematopoietic stem cell transplantation for patients with myelo-dysplastic syndromes and secondary acute myeloid leukaemias: a report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Br J Haematol 2000;110(3):620–30.
[8] Alam N, Atenafu EG, Kuruvilla J, Uhm J, Lipton JH, Messner HA, et al. Outcomes of patients with therapy-related AML/myelodysplastic syndrome (t-AML/MDS) following hematopoietic cell transplantation. Bone Marrow Transplant 2015;50(9):1180–6.
[9] Stone RM, Mandrekar SJ, Sanford BL, Laumann K, Geyer S, Bloomfield CD, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med 2017;377(5):454–64.
[10] Stein EM, DiNardo CD, Pollyea DA, Fathi AT, Roboz GJ, Altman JK, et al. Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. Blood 2017;130(6):722–31.
[11] DiNardo CD, Stein EM, de Botton S, Roboz GJ, Altman JK, Mims AS, et al. Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. N Engl J Med 2018;378(25):2386–98.
[12] Pratz K, Pollyea DA, Jonas BA, Pullarkat V, Wei A, Arellano M, et al. Safety and Efficacy of Venetoclax (ven) in Combination with Decitabine or Azacitidine in Treatment-Naive, Elderly Patients (≥65 Years) with Acute Myeloid Leukemia (Aml) Presented at EHA Learning Center; Jun 24, 2017. 181759Abstract: S472. 2017.
[13] Perl AE, Altman JK, Cortes J, Smith C, Litzow M, Baer MR, et al. Selective inhibition of FLT3 by gilteritinib in relapsed or refractory acute myeloid leukaemia: a multicentre, first-in-human, open-label, phase 1-2 study. Lancet Oncol 2017;18(8):1061–75.
[14] Lancet JE, Uy GL, Cortes JE, Newell LF, Lin TL, Ritchie EK, et al. CPX-351 (cytarabine and daunorubicin) liposome for injection versus conventional cytarabine plus daunorubicin in older patients with newly diagnosed secondary acute myeloid leukemia. J Clin Oncol 2018;36(26):2684–92.
[15] Cutler CS, Koreth J, Ritz J. Mechanistic approaches for the prevention and treatment of chronic GVHD. Blood 2017;129(1):22–9.
[16] Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114(5):937–51.
[17] Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127(20):2391–405.
[18] Granfeldt Ostgard LS, Medeiros BC, Sengelov H, Norgaard M, Andersen MK, Dufva IH, et al. Epidemiology and clinical significance of secondary and therapy-related acute myeloid leukemia: a national population-based cohort study. J Clin Oncol 2015;33(31):3641–9.
[19] Swerdlow S, Campo E, Harris N, Jaffe E, Pileri S, Stein H, et al. World Health Organization classification of tumours of haematopoietic and lymphoid tissues. WHO PRESSIARC; 2008.
[20] Smith MA, Rubinstein L, Ungerleider RS. Therapy-related acute myeloid leukemia following treatment with epipodophyllotoxins: estimating the risks. Med Pediatr Oncol 1994;23(2):86–98.
[21] Smith SM, Le Beau MM, Huo D, Karrison T, Sobecks RM, Anastasi J, et al. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. Blood 2003;102(1):43–52.
[22] Godley LA, Larson RA. Therapy-related myeloid leukemia. Semin Oncol 2008;35(4):418–29.

[23] Offman J, Opelz G, Doehler B, Cummins D, Halil O, Banner NR, et al. Defective DNA mismatch repair in acute myeloid leukemia/myelodysplastic syndrome after organ transplantation. Blood 2004;104(3):822–8.
[24] Wong TN, Ramsingh G, Young AL, Miller CA, Touma W, Welch JS, et al. Role of TP53 mutations in the origin and evolution of therapy-related acute myeloid leukaemia. Nature 2015;518(7540):552–5.
[25] Cleven AH, Nardi V, Ok CY, Goswami M, Dal Cin P, Zheng Z, et al. High p53 protein expression in therapy-related myeloid neoplasms is associated with adverse karyotype and poor outcome. Mod Pathol 2015;28(4):552–63.
[26] Heuser M. Therapy-related myeloid neoplasms: does knowing the origin help to guide treatment? Hematol Am Soc Hematol Educ Progr 2016;2016(1):24–32.
[27] Jaiswal S, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med 2014;371(26):2488–98.
[28] Genovese G, Kahler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med 2014;371(26):2477–87.
[29] Steensma DP. Predicting therapy-related myeloid neoplasms-and preventing them? Lancet Oncol 2017;18(1):11–3.
[30] Churpek JE, Larson RA. The evolving challenge of therapy-related myeloid neoplasms. Best Pract Res Clin Haematol 2013;26(4):309–17.
[31] Churpek JE, Marquez R, Neistadt B, Claussen K, Lee MK, Churpek MM, et al. Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop therapy-related leukemia. Cancer 2016;122(2):304–11.
[32] DiNardo CD, Bannon SA, Routbort M, Franklin A, Mork M, Armanios M, et al. Evaluation of patients and families with concern for predispositions to hematologic malignancies within the hereditary hematologic malignancy clinic (HHMC). Clin Lymphoma, Myeloma Leuk 2016;16(7). 417-28.e2.
[33] Churpek JE, Lorenz R, Nedumgottil S, Onel K, Olopade OI, Sorrell A, et al. Proposal for the clinical detection and management of patients and their family members with familial myelodysplastic syndrome/acute leukemia predisposition syndromes. Leuk Lymphoma 2013;54(1):28–35.
[34] Kayser S, Dohner K, Krauter J, Kohne CH, Horst HA, Held G, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 2011;117(7):2137–45.
[35] Kuzmanovic T, Patel BJ, Sanikommu SR, Nagata Y, Awada H, Hirsch CM, et al. Somatic mutations in therapy-related myeloid neoplasms are influenced by therapeutic modality and clonal hematopoiesis of indeterminate potential. Blood 2018;132(Suppl 1):3084.
[36] Lindsley RC, Mar BG, Mazzola E, Grauman PV, Shareef S, Allen SL, et al. Acute myeloid leukemia ontogeny is defined by distinct somatic mutations. Blood 2015;125(9):1367–76.
[37] Larson RA. Therapy-related myeloid neoplasms. Haematologica 2009;94(4):454–9.
[38] Morton LM, Gibson TM, Clarke CA, Lynch CF, Anderson LA, Pfeiffer R, et al. Risk of myeloid neoplasms after solid organ transplantation. Leukemia 2014;28:2317.
[39] Greenberg P, Cox C, LeBeau MM, Fenaux P, Morel P, Sanz G, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89(6):2079–88.
[40] Greenberg PL, Tuechler H, Schanz J, Sanz G, Garcia-Manero G, Sole F, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood 2012;120(12):2454–65.
[41] Kuendgen A, Tuechler H, Nomdedeu M, Garcia-Manero G, Komrokji RS, Sekeres MA, et al. An analysis of prognostic markers and the performance of scoring systems in 1837 patients with therapy-related myelodysplastic syndrome - a study of the international working group (IWG-PM) for myelodysplastic syndromes (MDS). Blood 2015;126(23):609.
[42] Koreth J, Pidala J, Perez WS, Deeg HJ, Garcia-Manero G, Malcovati L, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. J Clin Oncol 2013;31(21):2662–70.
[43] Ok CY, Hasserjian RP, Fox PS, Stingo F, Zuo Z, Young KH, et al. Application of the international prognostic scoring system-revised in therapy-related myelodysplastic syndromes and oligoblastic acute myeloid leukemia. Leukemia 2014;28(1):185–9.
[44] Dohner H, Estey E, Grimwade D, Amadori S, Appelbaum FR, Buchner T, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424–47.
[45] Klimek VM, Tray NJ. Therapy-related myeloid neoplasms: what's in a name? Curr Opin Hematol 2016;23(2):161–6.
[46] Andersen MK, Larson RA, Mauritzson N, Schnittger S, Jhanwar SC, Pedersen-Bjergaard J. Balanced chromosome abnormalities inv(16) and t(15;17) in therapy-related myelodysplastic syndromes and acute leukemia: report from an international workshop. Genes Chromosomes Cancer 2002;33(4):395–400.
[47] Aldoss I, Pullarkat V. Therapy-related acute myeloid leukemia with favorable cytogenetics: still favorable? Leuk Res 2012;36(12):1547–51.
[48] Dissing M, Le Beau MM, Pedersen-Bjergaard J. Inversion of chromosome 16 and uncommon rearrangements of the CBFB and MYH11 genes in therapy-related acute myeloid leukemia: rare events related to DNA-topoisomerase II inhibitors? J Clin Oncol 1998;16(5):1890–6.
[49] Quesnel B, Kantarjian H, Bjergaard JP, Brault P, Estey E, Lai JL, et al. Therapy-related acute myeloid leukemia with t(8;21), inv(16), and t(8;16): a report on 25 cases and review of the literature. J Clin Oncol 1993;11(12):2370–9.
[50] Borthakur G, Estey AE. Therapy-related acute myelogenous leukemia and myelodysplastic syndrome. Curr Oncol Rep 2007;9(5):373–7.
[51] Borthakur G, Lin E, Jain N, Estey EE, Cortes JE, O'Brien S, et al. Survival is poorer in patients with secondary core-binding factor acute myelogenous leukemia compared with de novo core-binding factor leukemia. Cancer 2009;115(14):3217–21.
[52] Sakugawa M, Kojima K, Kaneda K, Masuda K, Dansako H, Shinagawa K, et al. Therapy-related myelodysplastic syndrome/acute myeloid leukemia M2 and translocation (8;21). Ann Hematol 2001;80(12):763–6.
[53] Gustafson SA, Lin P, Chen SS, Chen L, Abruzzo LV, Luthra R, et al. Therapy-related acute myeloid leukemia with t(8;21) (q22;q22) shares many features with de novo acute myeloid leukemia with t(8;21)(q22;q22) but does not have a favorable outcome. Am J Clin Pathol 2009;131(5):647–55.
[54] Krauth MT, Eder C, Alpermann T, Bacher U, Nadarajah N, Kern W, et al. High number of additional genetic lesions in acute myeloid leukemia with t(8;21)/RUNX1-RUNX1T1: frequency and impact on clinical outcome. Leukemia 2014;28(7):1449–58.
[55] Kayser S, Dohner K, Krauter J, Kohne CH, Horst HA, Held G, et al. The impact of therapy-related acute myeloid leukemia (AML) on outcome in 2853 adult patients with newly diagnosed AML. Blood 2011;117(7):2137–45.
[56] Lo-Coco F, Avvisati G, Vignetti M, Thiede C, Orlando SM, Iacobelli S, et al. Retinoic acid and arsenic trioxide for acute promyelocytic leukemia. N Engl J Med 2013;369(2):111–21.
[57] Platzbecker U, Avvisati G, Cicconi L, Thiede C, Paoloni F, Vignetti M, et al. Improved outcomes with retinoic acid and arsenic trioxide compared with retinoic acid and chemotherapy in non-high-risk acute promyelocytic leukemia: final results of the randomized Italian-German APL0406 trial. J Clin Oncol 2017;35(6):605–12.
[58] Montesinos P, Gonzalez JD, Gonzalez J, Rayon C, de Lisa E, Amigo ML, et al. Therapy-related myeloid neoplasms in patients with acute promyelocytic leukemia treated with all-trans-retinoic Acid and anthracycline-based chemotherapy. J Clin Oncol 2010;28(24):3872–9.
[59] Dayyani F, Kantarjian H, O'Brien S, Pierce S, Jones D, Faderl S, et al. Outcome of therapy-related acute promyelocytic leukemia with or without arsenic trioxide as a component of frontline therapy. Cancer 2011;117(1):110–5.
[60] Ivey A, Hills RK, Simpson MA, Jovanovic JV, Gilkes A, Grech A, et al. Assessment of minimal residual disease in standard-risk AML. N Engl J Med 2016;374(5):422–33.
[61] Schuurhuis GJ, Heuser M, Freeman S, Bene MC, Buccisano F, Cloos J, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD working party. Blood 2018;131(12):1275–91.
[62] Forghieri F, Comoli P, Marasca R, Potenza L, Luppi M. Minimal/measurable residual disease monitoring in NPM1-mutated acute myeloid leukemia: a clinical viewpoint and perspectives. Int J Mol Sci 2018;19(11).
[63] Andersen MT, Andersen MK, Christiansen DH, Pedersen-Bjergaard J. NPM1 mutations in therapy-related acute myeloid leukemia with uncharacteristic features. Leukemia 2008;22(5):951–5.
[64] Godley LA, Njiaju UO, Green M, Weiner H, Lin S, Odenike O, et al. Treatment of therapy-related myeloid neoplasms with high-dose cytarabine/mitoxantrone followed by hematopoietic stem cell transplant. Leuk Lymphoma 2010;51(6):995–1006.

[65] Scott BL, Pasquini MC, Logan BR, Wu J, Devine SM, Porter DL, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol 2017;35(11):1154–61.
[66] Armand P, Kim HT, DeAngelo DJ, Ho VT, Cutler CS, Stone RM, et al. Impact of cytogenetics on outcome of de novo and therapy-related AML and MDS after allogeneic transplantation. Biol Blood Marrow Transplant 2007;13(6):655–64.
[67] Mukherjee S, Gerds AT. Long-term survival of patients with therapy-related myeloid neoplasms after allogeneic hematopoietic cell transplantation—more than just a myth. Bone Marrow Transplant 2016;51:763.
[68] Shih AH, Chung SS, Dolezal EK, Zhang SJ, Abdel-Wahab OI, Park CY, et al. Mutational analysis of therapy-related myelodysplastic syndromes and acute myelogenous leukemia. Haematologica 2013;98(6):908–12.
[69] Ok CY, Patel KP, Garcia-Manero G, Routbort MJ, Fu B, Tang G, et al. Mutational profiling of therapy-related myelodysplastic syndromes and acute myeloid leukemia by next generation sequencing, a comparison with de novo diseases. Leuk Res 2015;39(3):348–54.
[70] Bejar R, Stevenson KE, Caughey B, Lindsley RC, Mar BG, Stojanov P, et al. Somatic mutations predict poor outcome in patients with myelodysplastic syndrome after hematopoietic stem-cell transplantation. J Clin Oncol 2014;32(25):2691–8.
[71] Lindsley RC, Saber W, Mar BG, Redd R, Wang T, Haagenson MD, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med 2017;376(6):536–47.
[72] Aldoss I, Pham A, Li SM, Gendzekhadze K, Afkhami M, Telatar M, et al. Favorable impact of allogeneic stem cell transplantation in patients with therapy-related myelodysplasia regardless of TP53 mutational status. Haematologica 2017;102(12):2030–8.
[73] Cutler C. Transplantation for therapy-related, TP53-mutated myelodysplastic syndrome - not because we can, but because we should. Haematologica 2017;102(12):1970–1.