Mediterranean Journal of Hematology and Infectious Diseases

Review Article

# Therapy-related Myeloid Neoplasms: Considerations for Patients' Clinical Evaluation

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**Competing interests:** The authors declare no conflict of Interest.

**Abstract. Therapy-related myeloid neoplasms (t-MNs) encompass a specific sub-group of myeloid malignancies arising after exposure to radio/cytotoxic agents for the treatment of unrelated diseases.**
**Such malignancies present unique features, including advanced age, high comorbidities burden, and unfavorable genetic profiles. All these features justify the need for a specific diagnostic work-up and dedicated treatment algorithms. However, as new classification systems recognize the unique clinical characteristics exhibited by t-MN patients, how to assess fitness status in this clinical setting is largely unexplored. Optimizing fitness assessment would be crucial in the management of t-MN patients, considering that factors usually contributing to a worse or better outcome (like age, comorbidities, and treatment history) are patient-specific.**
**In the absence of specific tools for fitness assessment in this peculiar category of AML, the aim of this review is to describe all those factors related to patient, treatment, and disease that allow planning treatments with an optimal risk/benefit ratio.**

**Keywords:** T-AML; T-MN; Clinical evaluation.

**Citation:** Palmieri R., Paterno G., Mallegni F., Frenza F., De Bernardis I., Moretti F., Meddi E., Del Principe M.I., Maurillo L., Venditti A., Buccisano F. Therapy-related Myeloid Neoplasms: considerations for patients' clinical evaluation. Mediterr J Hematol Infect Dis 2023, 15(1): e2023051, DOI: http://dx.doi.org/10.4084/MJHID.2023.051

**Published: September 1, 2023** **Received: July 18, 2023** **Accepted: August 11, 2023**



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**Introduction.** The specificity of myeloid neoplasms that arise following exposure to cytotoxic chemotherapy, ionizing radiotherapy, and/or immunosuppressive therapy for an unrelated antecedent disease is recognized as a specific sub-group, commonly referred to as therapy-related myeloid neoplasms (t-MNs).[1,2] Nevertheless, according to the recent version of World Health Organization (WHO) and International Consensus Classification (ICC) of myeloid neoplasms, characteristics related to patients and disease, rather than clinical history, seem to account for the differences observed between therapy-related and *de novo* neoplasms. As a result, both classifications now consider therapy-relatedness as a "disease qualifier" rather than a disease defining entity.[3,4]

The approach to this subgroup of acute myeloid leukemias (t-AML) and myelodysplastic syndromes (t-MDS) presents several challenges. In the large majority of cases, t-MNs typically present with unfavorable features, such as peripheral blood cytopenias and high-risk genetic and cytogenetic profile.[5] Furthermore, from a clinical point of view, the previous exposure to anticancer treatments may significantly affect fitness for antileukemic treatment. Consequently, even for young fit patients, 5-year overall survival hardly reaches 20-25%.[6] Taken together, all these features require a specific

diagnostic work-up and dedicated treatment algorithms.[7]

The purpose of this review is to explore the need of a specific approach to the fitness evaluation of t-AML patients and to pinpoint possible solutions to select treatments, included allogeneic stem cell transplantation (ASCT), with the optimal risk/benefit ratio.

**Current Status of t-MNs Classification.** Recently, the fifth version of the WHO Classification of Hematolymphoid Tumors has slightly modified the definition of t-MNs, speculating that pre-existing clonal hematopoiesis may play a role as a risk factor for the expansion of pre-existing (non-neoplastic) clones. This hypothesis is supported by the fact that only a minority of patients receiving mutagenic agents will develop t-MNs in their lifetime. As an additional point, most of such cases are associated with recurrent cytogenetic and molecular signatures, hinting that specific genetic lesions may emerge due to selection pressures of cytotoxic therapy agents in an altered bone marrow environment.[3] In line with this, the ICC of myeloid neoplasms and acute leukemias underlines that, although it remains important to recognize the therapy-relatedness of MNs, the first priority is to classify the disease according to its morphologic and genetic characteristics.[4]

Since its first recognition as a discrete entity, the criteria to be fulfilled for the definition of t-MNs have changed over time. Although prior exposure to radiotherapy or chemotherapy has always been considered a prerequisite for t-MN development, the list of "trigger drugs" and the latency between exposition to each treatment and disease manifestation have been periodically updated.[8,9,2] This evolution reflects not only the constant improvement in the understating of the mutagenic mechanisms of chemotherapy but also the need to include novel agents in the debate.

The main causative agents involved in the development of t-MNs include alkylating agents, ionizing radiations, and topoisomerase II inhibitors.[3] Patients previously exposed to alkylating agents or ionizing radiation tend to present with MDS after a median of 4-10 years from treatment exposure.[10,11] Many of these patients may eventually progress to AML, presenting with a loss of genetic materials (such as deletions involving chromosomes 5, 7, and 17), complex karyotype, and TP53 deletions.[12] The other way around, patients receiving topoisomerase II inhibitors develop t-MNs with a significantly shorter latency from exposure (1 to 5 years). Balanced chromosomal translocations, including t(16;16), t(8;21), t(9;22) and MLL involving chromosome band 11q23, are frequently observed in this second group.[13] In recent years, a third group of drugs targeting enzymes involved in DNA repair mechanisms (inhibitors of the enzyme poly ADP ribose polymerase, also called PARP inhibitors) were added to the list of agents with a documented influence on t-MN development.[14] Patients receiving PARP inhibitors are at higher risk of t-MNs with a two-year latency, especially when administered in association with alkylating agents.[15] Accordingly, exposure to such agents was added as a qualifying criterion for t-MNs in the latest WHO classification.[3]

Regarding t-MDS, despite the diagnosis and the consequent therapy being established following the same criteria adopted for their *de novo* counterpart, these diseases exhibit substantial genetic/cytogenetic and clinical differences. Accordingly, a future updated classification should consider this issue, possibly identifying t-MDS as a distinct sub-group.[16]

Although the majority of t-MNs are associated with high-risk defining genetic lesions (such as TP53 mutations), some cases may present with a *de novo* molecular signature, such as isolated NPM1 mutations, Acute Promyelocytic Leukemia, and core-binding factor leukemias.[17,18] Following the general rule according to which post-cytotoxic therapy designation is based on the medical history, these cases are currently classified as t-MNs. However, as t-MN patients characterized by these specific genetic/cytogenetic signatures seem to do well with conventional intensive chemotherapy, whether they should be considered or not as "low risk" (and treated accordingly) is still a matter of debate.[17-19]

**Specific Consideration for Fitness in t-AML Patients.** Clinical presentation of t-MNs can be extremely heterogeneous and heavily influenced by several factors that must be considered during treatment planning.[20] Patient-related characteristics, such as advanced age, lower performance status, a high number of concomitant comorbidities, and past medical history (including the type of antecedent cancer and treatment received) have historically qualified many t-MNs patients as "unfit" and therefore less likely to be included in curative-intended protocols.[21] The scenario is further complicated by the fact that more effective and better-tolerated treatment alternatives are limited and still under investigation.[22]

The price all patients pay when receiving chemo/radiotherapy is a reduction in the functional reserve of all organs and tissues involved (**Figure 1**).[23] These effects can be either acute and self-limiting or chronic and may worsen in the case of the administration of additional cytotoxic agents.[24] In this view, an accurate anamnesis is a fundamental step to calculate the total dose of drugs known to have a maximum cumulative dose. Anthracyclines, for instance, are antineoplastic agents with proven efficacy in a broad variety of neoplastic conditions (including breast, ovarian, bladder, and lung cancers, Wilms' tumor, both Hodgkin's and Non-Hodgkin's Lymphomas, acute leukemias) and whose administration has been associated with dose-dependent cardiotoxicity ($\geq$ 450 mg/m$^2$ over a lifetime).[25] Similarly, mitoxantrone at doses of more than

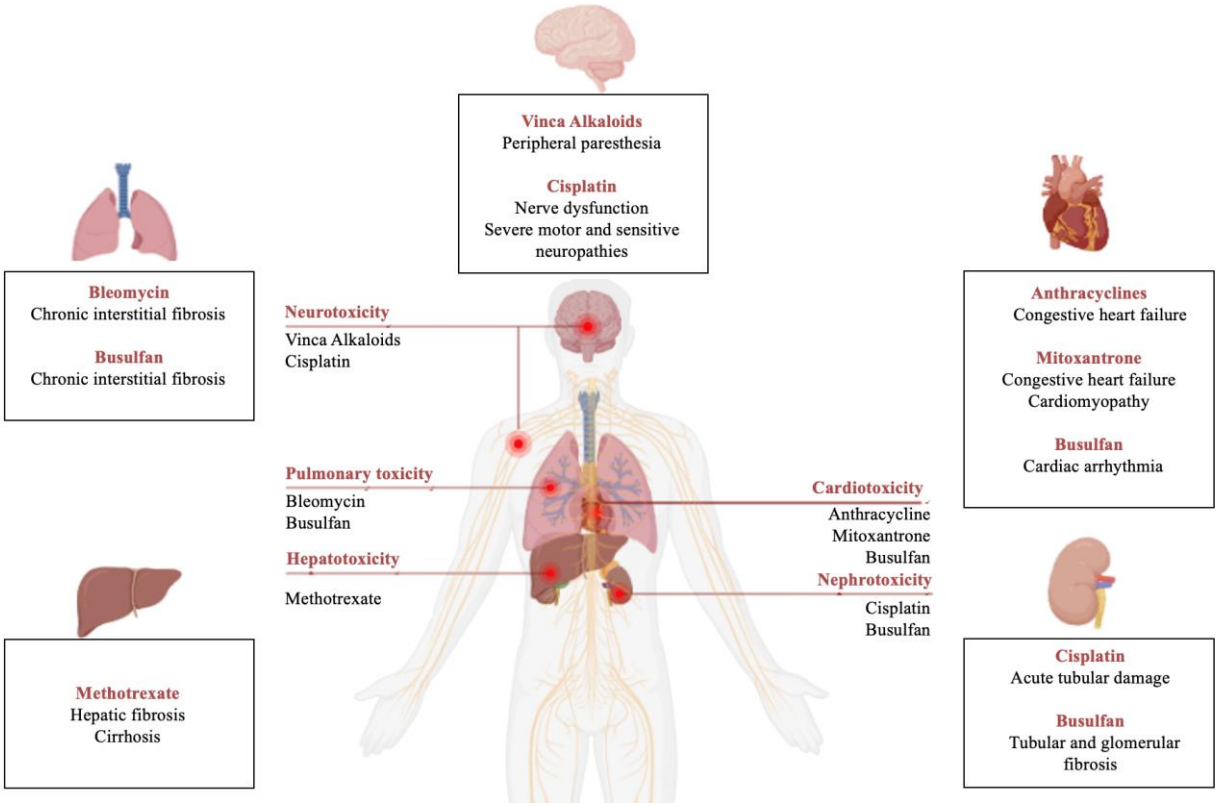


**Figure 1.** Organ-specific comorbidities induced by cytotoxic agents.

140 mg/m$^2$ can cause congestive heart failure and induce cardiomyopathy.[26] Older patients, especially those with concomitant cardiac comorbidities, are at higher risk of anthracyclines-induced cardiomyopathy even when not reaching the maximum cumulative dose. When performing pre-treatment cardiac testing, a decrease in left ventricular ejection fraction to less than 45% may suggest anthracycline-induced cardiotoxicity.[26] Therefore, in patients deemed at risk of developing acute cardiac complications on re-administration of anthracyclines, avoidance of such agents may be a reasonable precaution.

Along with cardiovascular toxicities, there are specific cytotoxic agents able to induce a dose-dependent irreversible pulmonary failure. Bleomycin is a drug used to treat several malignancies, including head-neck tumors, testicular and ovarian cancers, and lymphomas. Pulmonary diseases induced by such agent are generally observed around the maximum cumulative dose of 400-450 mg and mainly consist of chronic interstitial fibrosis.[27] In patients with t-MNs and prior exposure to such medication, periodical pulmonary function testing should be performed to treat those who develop pulmonary complications in a timely manner. As pulmonary abnormalities seem play a major role in the definition of fitness,[28] periodical pulmonary function testing could be an option in patients with t-MNs and prior exposure to Bleomycin. In case of pulmonary disfunction, such an approach could help treat those patients who develop pulmonary complications in a timely manner.

Several agents commonly adopted in a wide variety of tumors may have an influence on renal function. Among these, cisplatin and its derivates are used to treat different types of cancers, including testicular, ovarian, bladder, head-neck, lung, and cervical. A non-negligible proportion of patients (roughly 30%) receiving cisplatin will develop nephrotoxicity with a single dose of 2 mg/kg or 50-75 mg/m$^2$, especially when not adequately hydrated.[29] Acute kidney damage can present within a single day from a single dose of cisplatin, and patients may lose up to 12.5% of their renal function after receiving this medication.[30] Subjects previously exposed to cisplatin should be vigorously hydrated in conditions at high risk of acute tubular damage, such as hyper leucocytic onset, and to prevent tumor lysis syndrome in all cases.

Iatrogenic hepatic damage can be observed in patients submitted to specific agents for the treatment of both neoplastic and non-neoplastic conditions. Methotrexate is frequently prescribed at high doses in many cancers (such as non-Hodgkin's lymphomas) and at lower doses in autoimmune disorders (including systemic lupus erythematosus and rheumatoid arthritis). When administered in patients already taking putative hepatotoxic drugs or in those with other liver dysfunctions (alcohol liver disease or metabolic syndrome), methotrexate can cause hepatic fibrosis and cirrhosis.[31] Routine function testing, as well as periodic imaging, can be helpful in the identification of gross liver diseases. Furthermore, in patients with clinical and/or radiological evidence of chronic liver disease, transient

elastography may be an option to assess the severity of the hepatic dysfunction and to optimize (or even avoid) the use of hepatotoxic anti-cancer drugs.[32]

Neurotoxicity represents a common side-effect of many anti-cancer therapies. Vinca alkaloids and cisplatin can cause central, peripheral, and even autonomic nervous system toxicities. Usually starting as peripheral paresthesia, nerve dysfunction can progress up to severe motor and sensitive neuropathies.[33] Although uncommonly life-threatening, such conditions can have a relevant impact on daily activities and quality of life, hence deserving of proper management.

Whichever the cytotoxic agent delivered in the past, whether specific organ dysfunctions may be evident or not, extreme caution is needed when considering the eligibility/ineligibility of each patient with t-MNs to a given therapy. This may be particularly relevant when facing the opportunity to administer cytotoxic agents that have caused a significant reduction in organ functional reserve. An additional unmet need is represented by those patients who are diagnosed with concomitant t-MN and recurrent solid tumor. Since we still lack robust evidence on the actual feasibility of a simultaneous approach and how these patients may truly benefit from it, such circumstance commonly justifies referral to palliative care for most cases.[34]

An additional factor to be considered during treatment planning is the type of antecedent solid tumor. Although this information may not be crucial to decide treatment intensity, t-MNs following specific cancers (such as lymphoproliferative disorders) seem to be characterized by significantly shorter survival than others (such as breast cancers), whose outcome resembles that of de novo AML/MDS.[35,36]

Even though there are several validated scores for the definition of fitness/unfitness in patients with de novo myeloid neoplasms, all these tools fail to include information on how to modulate treatment intensity in t-MPs.[20] Consequently, fitness assessment in t-MNs patients mainly relies on a case-by-case evaluation that should take into account factors related to patient, treatment and disease. (**Figure 2**) In the absence of dedicated tools, further investigation is expected to address this issue, in the near future.

**Hematopoietic Stem Cell Transplantation in t-MNs.** The criteria to define the eligibility for hematopoietic stem cell transplantation (HCT) have been periodically updated. As a result of this constant improvement, more and more fit patients with blood cancers are referred to HCT every year. Patients with t-MNs represent the paradigm of high-risk diseases for whom HCT may represent the only chance for cure. Nevertheless, these patients are also at higher risk of experiencing HCT-related early and late complications. Although the long-term curative potential of HCT in such diseases is unquestioned, for some patients, the risks may outweigh the benefits. The evidence that even a remote history of an unspecified solid tumor may harm HCT long-term outcome has prompted the inclusion of the anamnestic criteria into scores commonly adopted to assess transplant eligibility.[37]

Chemo-radiotherapy that must be delivered as a pre-transplant conditioning regimen may have an additional

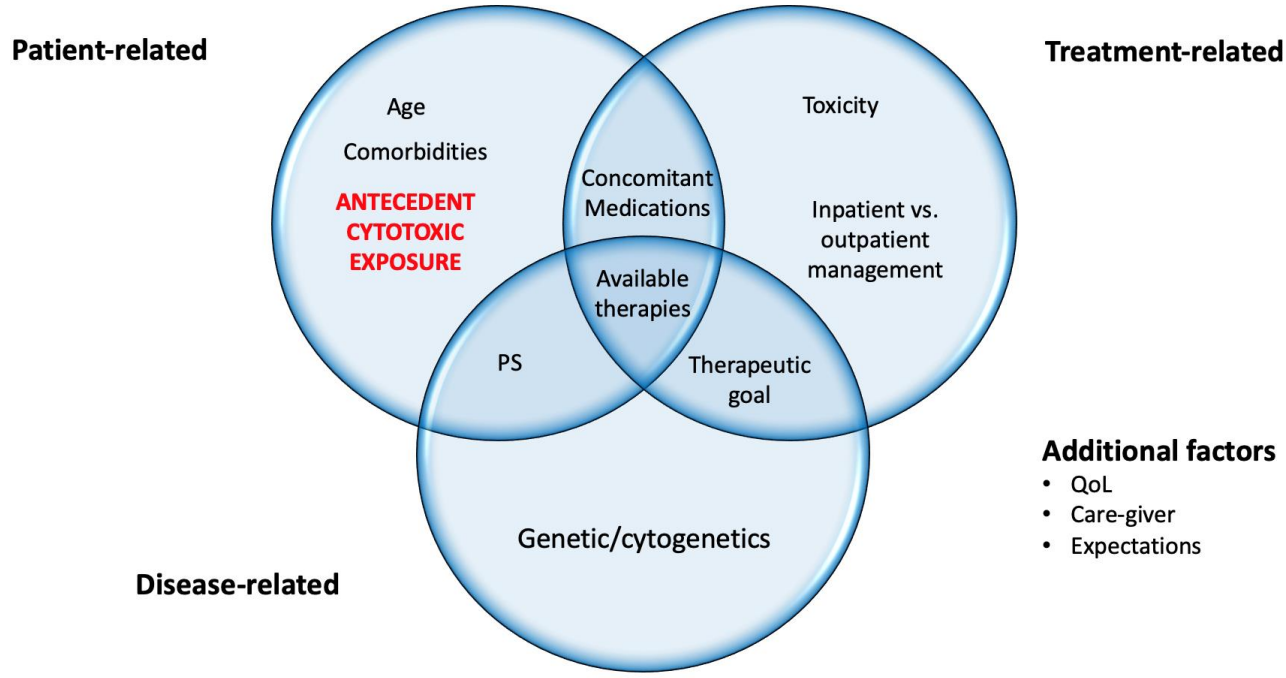


**Figure 2.** Patient, treatment, and disease-related factors with a possible influence of therapy selection in patients with t-MNs. *Abbreviations: PS, Performance Status; QoL, Quality of Life.*

impact on the residual functional reserve of specific organs and tissues. Agents like busulfan, which has historically represented the cornerstone of many conditioning regimens, can cause cardiac, renal, and pulmonary side effects shortly after infusion.[38] This evidence underlines the importance of modulating conditioning strategies in patients who already show signs or symptoms of organ insufficiencies before HCT. If possible, reduced-intensity conditioning (RIC) or non-myeloablative (NMA) regimens may be a reasonable option in this category.

In t-MN patients who are considered fit at the time of diagnosis, HCT is not always feasible.[21] Not uncommonly, the odds of exacerbating pre-existing organ frailties, even when delivering RIC or NMA, represent a significant contraindication to HCT. Unfortunately, this eventuality can't be predicted at the time of t-MN diagnosis and many patients witness the interruption of their curative program after developing severe side effects during induction or consolidation therapy. Such complications are almost always unforeseeable, with a dramatic impact not only on life expectancy but also on quality of life.[39]

Another issue to be considered during the pre-HCT workup is that immunosuppressive medications, usually administered as graft-versus-host disease prophylaxis, may increase the probability of relapse of pre-existing tumors.[40] In some institutions, potential transplant recipients who have a history of a solid tumor are considered eligible for HCT if the probability of recurrence of the solid tumor is estimated to be <20% over 5 years at the time of the pre-transplant evaluation.[40] These criteria were initially proposed for kidney transplant candidates but are applicable to HCT too. Although based on retrospective studies, the risk of solid tumor recurrence after HCT in patients with low localized (e.g., Stage I-II)/under control disease may justify transplant delivery. The risk of relapse in this setting is considerably outweighed by the benefit if we consider that a hematologic malignancy requiring HCT usually cannot wait for several months or years while being monitored for recurrent solid tumors.[40,41] As a possible solution for patients whose prior tumor is under control, a multi-disciplinary pre-transplant evaluation would afford more patients the option of HCT. Furthermore, a close collaboration between the cancer specialist and the transplant team would be essential to optimize the treatment strategy of those patients who experience a tumor relapse after HCT. Likewise, for patients at higher risk of solid tumor relapse, delivering adjuvant or even post-transplant maintenance therapy could represent an additional solution to reduce the risk of solid tumor recurrence, thus affording more patients the option of HCT.[42] In this view, how to update cancer specific HCT eligibility criteria and how to personalize post-transplant follow up in this group of patients represents an urgent need.

**Discussion.** The recent classifications consider therapy-relatedness as a qualifier of AML rather than a specific category of disease. Nevertheless, since t-MNs usually present with peculiar clinical and biological characteristics, dedicated therapeutic algorithms are necessary.

The available tools to assess eligibility for intensive or non-intensive therapies are not specifically designed for t-MNs. Anamnestic features and type of prior cytotoxic exposure are case-specific and may have determined long-term effects that deserve to be considered during treatment planning. In line with the change observed for classification systems, t-MN cases should not simply be identified as being "high-risk" patients and treated or not treated accordingly but deserve individualized pre-treatment evaluations.

In fact, some patients may present with multiple comorbidities or end-stage organ failures that may have been induced by prior cytotoxic agents. Alternatively, t-MNs may emerge while a patient is already receiving active treatment for the relapse of the antecedent neoplasm. Furthermore, the presence of t-MNs frequently excludes patients from innovative clinical trials.[42]

Defining fitness status in this clinical setting currently relies on the application of the same scores that have been designed and validated in patients with *de novo* myeloid neoplasms. Persevering with such an approach may fail to offer appropriate estimates of the applicability of emerging treatment strategies. In a future perspective, designing dedicated scores is warranted and may help optimize managing such "hard-to-treat" diseases.

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