Best Practice & Research Clinical Haematology 32 (2019) 3–12

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

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

Clinicopathological aspects of therapy-related acute myeloid leukemia and myelodysplastic syndrome

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ARTICLE INFO

Keywords:
Therapy-related myeloid neoplasm
t-AML
t-MDS
TP53
Clonal hematopoiesis

ABSTRACT

Therapy-related myeloid neoplasm (t-MN) is a rare but devastating consequence of chemotherapy and/or radiotherapy used for the treatment of solid cancers and various hematologic malignancies. Our current understanding of the etiology is that hematopoietic clones that are contemporaneous with the primary cancer and resistant to the cytotoxic exposure have the potential to undergo selective expansion and transformation to t-MN. Consequently, a large proportion of cases are associated with adverse risk factors, resulting in limited effective treatment options. Despite the emergence of some therapies with promising activity in t-MN, most effects are short-lived and allogeneic stem cell transplantation remains the only curative option for eligible patients. This review summarizes the current literature on t-AML and t-MDS, with the aim of providing practical recommendations on the clinical evaluation and management of these conditions.

1. Main text

1.1. Introduction

Therapy-related myeloid neoplasms (t-MN) encompass a spectrum of disorders including therapy-related acute myeloid leukemia (t-AML), therapy-related myelodysplastic syndrome (MDS), and t-MDS/myeloproliferative neoplasm (MPN) overlap syndrome. Although these terms are commonly used by default when there is a prior history of cytotoxic exposure for either malignant or non-malignant conditions, it is now recognized that t-MN usually arise from selection of a pre-existing clonal population that is characteristically chemoresistant and associated with a poor clinical prognosis. This review is directed at providing the practicing clinician with knowledge relevant to the recognition, diagnosis, risk assessment, therapy and potential preventative strategies in relation to patients with suspected t-MN. The reader is referred to other chapters within this special edition for in-depth analysis of many of the topics touched on herein.

1.2. When to suspect t-MN

t-MN should be considered in any patient with morphologic features of MDS or AML and a prior history of exposure to chemotherapy or radiotherapy. If the cytotoxic exposure was for a prior history of MDS, MPN or MDS/MPN, the term secondary AML (s-AML) is generally used, as the contribution of therapy is difficult to distinguish from the natural history of the preceding myeloid

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https://doi.org/10.1016/j.beha.2019.02.007
Received 19 January 2019; Received in revised form 11 February 2019; Accepted 15 February 2019

disease. If the patient has a history of prior cancer but no exposure to cytotoxic agents, the patient is denoted to have *de novo* AML (*dn*-AML). It is recommended that for t-MDS, t-AML or t-MDS/MPN, the cytogenetic abnormality be included in the diagnostic report, for example, "therapy-related AML with t (9; 11) (p22; q23)".

Although clinicians frequently use the term t-MN for patients with prior cytotoxic exposure, in many cases the risk association is tenuous. For example, the likelihood of t-MN resulting from localized therapeutic radiotherapy to a non-hematopoietic organ delivered three decades in the past is likely to be far less than accidental whole-body exposure to a radiation leak occurring 7 years ago. In all cases, clinicians consider the direct cause and effect attribution and provide an estimate of the probability of association.

1.3. Epidemiological aspects of t-MN

Multiple population-based AML registries have reported t-AML cases to account for < 1%–7.7% of all cases of AML [1–4]. Similarly, t-MDS accounts for approximately 10% of all MDS cases [5]. The median age of diagnosis is between 40 and 66 years [4,6]. An analysis of Surveillance Epidemiology and End Results (SEER) registry data has observed an increased incidence of t-MNs from 0.04 to 0.2 per 100,000 persons during two sequential periods (2001–2007 and 2008–2014) [6]. There are many factors that may have contributed to this apparent rise in t-MN. Confounding variables include increased cancer survivorship and surveillance for secondary cancers, an ageing population extending the time-dependent potential for t-MN to be diagnosed, changes in therapeutic regimens used for many cancers and increasing awareness of the terms t-MDS, t-AML and t-MN after their inclusion as an entity in the WHO classification in 2001.

1.4. Cytotoxic associations with t-MN

It is estimated that adults treated with chemotherapy and/or radiotherapy for cancer have a 4.7-fold risk of developing t-MN compared to the general population [4]. Among patients with t-MN, the commonest cancer sub-group receiving prior cytotoxic therapy was primary breast malignancy (up to 40% in some studies) followed by non-Hodgkin (NHL) or Hodgkin lymphoma (HL) (19–45% of cases) [1,3,4,6,7]. Despite the high proportion of t-MN among patients with a prior breast cancer, the estimated incidence of t-MN in this group is 1.44 t-MN cases per 1000-person-years (0.44 and 1.11 per 1000-person-years for t-AML and t-MDS respectively) after a mean follow up of 4 years [8].

The two main classes of chemotherapy implicated in leukemogenesis from epidemiological studies are alkylating agents and topoisomerase II (TPII) inhibitors [9]. Other chemotherapy agents including antimetabolites, platinum compounds and antitubulin agents (e.g. vincristine, docetaxel) have been associated with t-MN but to a lesser extent (Table 1). Thus far, targeted agents are not known to be associated with enhanced risk of t-MN.

Alkylating agents are responsible for the majority of t-MN cases and cause direct DNA damage through alkylation of DNA bases leading to inter- and intra-strand cross linking, abnormal base pairing and DNA double-strand breakage [10]. Melphalan, cyclophosphamide and chlorambucil account for 65% of cases [9]. The median latency is approximately 4–7 years, and the risk increases with age. There is often a preceding t-MDS phase prior to transformation to t-AML. There are distinct patterns of chromosomal alterations with deletions or loss of 7q or monosomy 7 being the most common finding, followed by abnormalities in chromosome 5 [11]. The latter group is also characteristically associated with complex karyotype and mutations in the *TP53* gene [12].

TPII inhibitors account for 20–30% of t-MN and are associated with a short median latency of 1–5 years, often presenting as overt AML without preceding MDS. The risk of t-MN secondary to TPII inhibitors is similar across all age groups. Historically, it has been assumed that TPII inhibitors interfere with DNA replication, leading to stabilization of double-stranded breaks, delay in DNA religation, increased occurrence of DNA repair errors and crossover recombination with another chromosome, predisposing to balanced chromosomal translocations [13]. The cytogenetic abnormalities often involve balanced translocation with 11q23, such as t (9; 11) (p21.3; q23.3), t (11; 19) (q23.3; p13.1), t (8; 21) (q22; q22.1), t (3; 21) (q26.2; q22.1), t (15; 17) (q24.1; q21.1) or inv (16) (p13.1q22).

For most types of solid tumors, the risk of t-MN appears to be rising following chemotherapy. A recent population-based SEER-Medicare cohort study of 700,612 adults with newly diagnosed and treated solid tumors between 2000 and 2013 identified 1,619 t-MN cases [14]. The risk of t-MN was increased from 1.5 to greater than 10-fold after chemotherapy for 22 of 23 tumor types, which persisted for at least 5 years after diagnosis. The highest incidence was in bone, testis and soft tissue cancer (standardized incidence ratio of 39.0, 12.3 and 10.4 respectively). In addition to the well-established t-MN risks in breast and brain cancers, this study confirmed the excess t-MN risk for gastrointestinal tract cancers (except colon cancer), larynx, bone, cervix, uterine corpus and vaginal/vulva cancers, purportedly related to the increased use of platinum-based treatment regimens.

For lymphoid malignancies, the risk of t-MN ranges from 0.8% at 30 years to 12% within 10 years of primary therapy [15–21]. The incidence was dependent on the age, lymphoma type, treatment modality, number of treatment lines and whether autologous stem cell transplantation (autoSCT) was performed. Among 3,412 NHL cases treated with cyclophosphamide-based therapy, cumulative cyclophosphamide doses exceeding 11,250 mg/m^2 were associated with increased t-MN (odds ratio 7.0) [21]. Among patients with HL, the risk of t-MN has changed over time due to variation in chemotherapy regimens. Two retrospective studies suggested higher rates of t-MN with the historical MOPP-like regimen (mechlorethamine, vincristine, procarbazine) as compared to ABVD (adriamycin, bleomycin, vinblastine, dacarbazine) [22,23]. More intensive HL therapy such as escalated BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisolone) may also result in a higher incidence of t-MN [16,24]. The German Hodgkin Study Group reported that ≥4 cycles of escalated BEACOPP to be associated with the highest risk for t-MN, compared to < 4 cycles or a non-BEACOPP regimen (1.7% vs 0.7% vs 0.3%, median follow-up of 6 years) [16].

Table 1
Considerations in the evaluation of patients with t-MN.

Factors	Comment
History	• History of exposure to chemotherapy and/or radiation therapy • If history of antecedent hematological disorder: o Prior *de novo* MDS or MDS/MPN (including prior cytotoxic therapy for these conditions) → diagnosis of AML-MRC [78] o If prior t-MDS, then subsequent development of AML should be designated as t-AML o Prior MPN should not be classified as t-MN as it is difficult to distinguish between disease evolution as part of natural history vs therapy-induced changes • Secondary AML (s-AML) is a non-WHO term that encompasses AML with prior MDS, MDS/MPN or MPN. Note: • It is imperative to obtain a detailed history of the cytotoxic exposure as the AML or MDS risk may vary extensively in accord with the nature and extent of the prior genotoxic insult • It is less certain whether cases with latencies > 10 years are attributable to prior cytotoxic therapies or represent a second *de novo* cancer • An AML case occurring many years after prior cytotoxic therapy for AML manifesting a distinct cytogenetic/molecular profile may represent transformation of an ancestral clone rather than relapsed or therapy-related AML
Predisposing factors: Chemotherapy	Alkylating agents (most common; ~65%) • Melphalan, chlorambucil, busulfan, carboplatin, cisplatin, dacarbazine, carmustine, lomustine, thiotepa • Higher cumulative doses of cyclophosphamide (exceeding 11250 mg/m^2 in one study) [21] Topoisomerase II inhibitors (~30%) • Epipodophyllotoxine: etoposide • Anthracyclines: doxorubicin, idarubicin, daunorubicin • Anthacenedione: mitoxantrone Others agents (~5%) • Antimetabolites: thiopurines (e.g. azathioprine), mycophenolate mofetil, fludarabine • Antitubulin agents: docetaxel, paclitaxel, vincristine, vinblastine • Platinum compounds: cisplatin, carboplatin Note: • Variations in multi-agent combinations, dose intensity, cumulative cytotoxic exposure and the addition of radiation therapy augment the risk of developing t-MN. However, quantitative risks associated with specific cytotoxic drugs are not available
Predisposing factors: Radiation therapy	• Therapeutic radiation o Total body irradiation o Localized radiation: large fields involving active bone marrow are often implicated. Impact of limited-field radiation in areas without active bone marrow is unclear • Accidental exposure (e.g. from diagnostic radiological procedures) are not strictly classified as t-MN according to WHO
Predisposing factors: Others	• Clonal hematopoiesis (CH) o Clonal selection of pre-existing CH present prior to diagnosis of primary malignancy, or o Appearance of CH after cytotoxic exposure • Autoimmune conditions requiring immunosuppressive therapy (azathioprine associated with 7-fold increase risk of t-MN [79]) • Aplastic anemia
Diagnosis	• Diagnosis regardless of bone marrow blast percentage: o t (15; 17) → t-APL with t (15; 17) o t (8; 21), t (16; 16), inv (16) → t-CBF AML with t (8; 21), t (16; 16), inv (16) • < 20% bone marrow blasts with myelodysplastic changes on morphology or MDS defining cytogenetic aberrations → t-MDS o 50% of t-MDS have < 5% bone marrow blasts • ≥20% bone marrow blasts →t-AML
Familial cancer history	• 17–21% of breast cancer patients who developed t-MN had germline mutations in cancer susceptibility genes e.g. *BRCA1, BRCA2, TP53, CHEK2, BARD1, PALB2* [40–42] • Consider screening if suggestive family history and offer genetic counselling
Genetic profiling	• Cytogenetics [78] o 10–15% have favorable risk fusion genes such as t (8; 21), t (15; 17) (q24.1; q21.1) or less commonly, inv (16) o 50% have adverse risk karyotype frequently involving abnormalities in chromosome 5 and/or 7, complex karyotype or balanced translocations involving chromosome 11q23. o Remaining cases have intermediate or normal karyotype • Molecular sequencing with targeted panels o *TP53* mutations (up to 37%) – strong association with monosomal and/or complex karyotype, del (5q) but can also occur independently o Although less frequent than *dn*-AML, targetable mutations (*IDH1, IDH2, FLT3*-ITD) should be identified given therapeutic implications
Treatment considerations	• Age of t-MN diagnosis • Remission status of primary cancer o Restaging assessments should be performed • Prior chemotherapy may impact t-MN treatment options o Anthracycline dose threshold exceeded? • Morbidities from prior cytotoxic agents

(*continued on next page*)

Table 1 (*continued*)

Factors	Comment
	o Cardiac, renal and liver function o ECOG ● Psychological state ● Determine fitness for therapy o Suitability for intensive vs non-intensive vs best supportive care o Eligibility for allogeneic stem cell transplantation

t-MN: therapy-related myeloid neoplasm, MDS: myelodysplastic syndrome, MPN: myeloproliferative neoplasm, AML-MRC: AML with myelodysplasia-related changes, *dn*-AML: *de novo* AML, ECOG: Eastern Cooperative Oncology Group.

AutoSCT has been identified as a significant risk factor for t-MN (especially t-MDS) ranging from 1% by 30 months to 24% by 43 months [20,25–27]. Risk factors include age ≥45 years at the time of transplant (HR 5.6, 95% CI 2.7–11.7), TBI conditioning (HR 4.0, 95% CI 1.4–11.6) and ≥3 prior lines of chemotherapy for NHL (HR 1.9, 95% CI 1.3–2.8). TBI-cyclophosphamide conditioning was associated with a t-MN rate of 12% at 6 years in 230 patients with NHL who underwent autoSCT at St Bartholomew's hospital [28]. After discontinuation of TBI conditioning, there was a significant decline in t-MN rates at that center.

1.5. Radiation and risk of therapy related neoplasm

t-MN due to ionizing radiation share similar clinicopathological features to alkylating agent associated t-MN, with a higher frequency of t-MDS [29]. t-MN can occur following radiotherapy or chemotherapy alone or after combination therapy [30]. However, instead of assuming that any prior cytotoxic insult is etiologically causative of t-MN, physicians should conceptually understand that each patient has a unique set of risks associated with a variety of mutagenic factors. Ionizing radiation is a known carcinogen linked to cancer development. The unit used to measure the amount of absorbed ionized radiation dose is the Gray (Gy), which is defined as the absorption of one joule of radiation energy per kilogram of matter. One Gy is equivalent to 1,000 milliSieverts (mSv), with a chest CT delivering 5–8 mSv and a whole body 18-FDG CT/PET delivering 13–32 mSv of radiation per scan. Epidemiological studies suggest that the excess relative risk of AML per Gy of exposure is 1.29 (90% CI –0.82 to 4.28) [31]. For acute whole body radiation exposures, online calculators are available to assess the probability of cancer causation (https://www.niosh-irep.com/irep_niosh/).

1.6. Susceptibility to t-MN related to cytotoxic induced expansion of pre-existing hematopoietic clones

Although cytotoxic drugs may exert DNA damage leading to genomic errors, this is unlikely to be the sole mechanism leading to evolution of t-MN. AML occurs as a consequence of multiple driver gene mutations converging within the same cell. Therefore, the current view of t-MN is that it results from the selection and expansion of pre-existing clonal hematopoietic stem cell populations, which have stochastically acquired mutations conferring increased levels of fitness and survival capability.

A landmark study used genome-wide sequencing approaches to show that the total number of somatic single-nucleotide variants and chemotherapy-related transversions were similar in t-AML and *dn*-AML, suggesting that chemotherapy did not cause extensive genome-wide DNA damage. Instead, small *TP53* mutant clones were detected years before the development of t-MN and even prior to any chemotherapy exposure, supporting the conclusion that t-MN is related to cytotoxic selection of pre-existing founding clones that are chemoresistant and preferentially expanded after treatment [32]. This is supported by a case-control study, which identified the presence of clonal hematopoiesis (CH) contemporaneous with the primary cancer in 71% patients, with *TP53* mutations present in 15–16% cases [33]. The cumulative incidence of t-MN was 30% among those with CH, compared to 7% if CH was not detected (p = 0.016). Another study in patients ≥70 years identified CH in 62% prior to t-MN diagnosis, with *TP53* mutation present in 37%

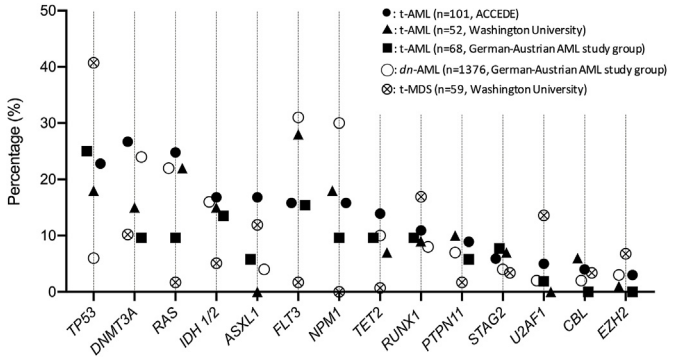

Fig. 1. Distribution of somatic mutations in t-MDS, t-AML and *dn*-AML in three patient datasets: ACCEDE trial (n = 101), Washington University (t-AML n = 52, t-MDS n = 59), German-Austrian AML Study Group (t-AML n = 68, *dn*-AML n = 1376) [32,37,77].

[34]. Not surprisingly, studies examining the mutation spectrum in t-MN have highlighted the frequent occurrence of *TP53* mutations, observed in up to 40% of t-AML and t-MDS cases. (Fig. 1). Please see the reviews elsewhere in this issue for analysis of clonal hematopoiesis, mutations in *p53* and germline polymorphisms contributing to t-MN development.

1.7. Evaluation of patients with t-MN

The development of unexplained cytopenias in a person with prior cytotoxic exposure warrants investigation for possible t-MN. The clinical and immunophenotypic presentation of t-MN is similar to *de novo* MDS and AML. The history is important and should include suggestions outlined in Table 1. Clinical evaluation should also include a detailed family history to identify familial cancer syndromes.

Karyotypic abnormalities are present in up to 95% of patients with t-MN [35,36]. Approximately 10–15% of t-AML have favorable risk fusion genes such as t (8; 21), t (15; 17) (q24.1; q21.1) or less commonly, inv (16). Half the cases with t-MNs have adverse risk karyotype, frequently involving abnormalities in chromosome 5 and/or 7, complex karyotype or balanced translocations involving chromosome 11q23. The remaining cases have intermediate risk or normal karyotype.

Molecular studies using whole genome and/or targeted sequencing approaches have demonstrated a heterogeneous mutational landscape (Fig. 1) [32,37]. In patients with t-AML, mutations can be grouped into three broad categories [37]. *TP53* mutation (23%) forms one group, with multiple studies confirming a higher rate of *TP53* mutation in t-MNs; ranging up to 37%, compared to 8–15% in *dn*-AML [32,37–39]. *TP53* mutations are strongly associated with monosomal and/or complex karyotype, del (5q) and typically a very poor prognosis [39]. The second group closely resembles *dn*-AML (47%) and the third has features reminiscent of s-AML (33%). The *dn*-AML-like group has a similar distribution of mutations affecting *NPM1, FLT3, DNMT3A, TET2, IDH1, IDH2* and *WT1,* whereas the s-AML-like group is characterized by mutations in *SRSF2, SF3B1, U2AF1, ZRSR2, ASXL1, EZH2, BCOR* and *STAG2. S*ome studies have reported an overall lower frequency of *FLT3* and *NPM1* mutations, likely due to the increased proportion of *TP53* mutant and s-AML-like cases.

1.8. Inherited genetic susceptibility

Several small studies focusing on breast cancer survivors found that 17–21% of patients with t-MN had germline mutations in inherited cancer susceptibility genes, often involving components of DNA damage response. Germline DNA from 47 breast cancer survivors identified mutations in *BRCA1* (6%), *BRCA2* (4%), *TP53* (6%), *CHEK2* (2%) and *PALB2* (2%) [40]. Similarly, germline *BRCA1, BRCA2, TP53* and *BARD1* mutations have been identified in 9 out of 53 (17%) patients with t-MN [41]. It was difficult to ascertain in these patients if the second malignancy was augmented by exposure to cytotoxic therapy or would have occurred regardless. Other studies have suggested the potential role of germline polymorphisms in genes encoding drug metabolizing enzymes (such as *GSTP1* [42], *NQ01* [43]), DNA damage pathways (such as *RAD51* [44], *XRCC1* [45]) or Fanconi anemia complementation group genes [46] in augmenting susceptibility of t-MN. Of note, patients who fulfill the criteria for myeloid neoplasm with germline predisposition should not be classified as t-MN.

1.9. Is there a role for CH screening during cancer survivorship?

Investigators at Memorial Sloan Kettering Cancer Center have performed targeted molecular sequencing of cancer-associated mutations on matched tumor sample and peripheral blood in 17,478 solid cancer patients [47]. NGS profiling of 341–410 cancer-associated genes identified somatic mutations representing CH in 25.1%, with the mutation variant detected in 77% at low level in the primary tumor [48]. CH was associated with tobacco use, higher WBC, monocytes, neutrophils, MCV and lower platelet counts. There was a higher proportion of CH involving mutations in DNA repair/cell cycle pathway (e.g. *TP53, PPM1D* and *CHEK2*) among those who received cytotoxic therapy compared to treatment naïve patients. *PPM1D* and *TP53* bearing clones increased in size over time with serial sampling.

For t-MN, it remains to be determined whether early detection of pathogenic clones prior to clinical presentation will alter treatment outcomes. Currently, few effective treatment options are available for these patients. Therefore, collection of prospective information on the evolution of CH detected in patients with solid cancers will help define patient subgroups at highest risk of developing t-MN. This will aid in the development of future risk-adapted interventional studies aimed at changing the natural history of this difficult myeloid subgroup [49]. The clinical efficacy and cost-effectiveness of such a screening strategy, however, remains unknown.

1.10. Prognosis and treatment

The management of t-MN is challenging. As a group, the median OS has been reported to be 7–10 months [14]. Two key factors influence the prognosis of t-MN; the underlying cytogenetic molecular abnormalities and patient fitness for therapy. The outcomes of t-MN are often poor, as a larger proportion of patients have adverse cytogenetic risk and/or *TP53* mutation. Other treatment considerations include impaired organ function from prior therapy-related complications, the need for ongoing immunosuppression in patients with solid organ transplantation, a history of aplastic anemia, the potential for recurrence of the primary neoplasm or disorder and the complexity associated with treating and controlling more than one active disease. Please see the accompanying reviews in this issue which comprehensively review induction therapy and the utility of allogeneic stem-cell transplantation.

Therapy-related acute promyelocytic leukemia (t-APL): Retrospective studies report variable outcomes in therapy-related versus *de novo* APL (*dn*-APL) treated with an ATRA-anthracycline backbone [50]. In a GIMEMA group study, complete remission (CR) rates (97% vs 93%) and 4-year OS (85 vs 78%) were similar for both t-APL (n = 51) and *dn*-APL (n = 641) [51]. However, the Mayo group report poorer outcomes for patients with t-APL in terms of a lower CR rate (64% vs 93%) and 4-year OS (51 vs 84%), compared to *dn*-APL [52]. The unfavorable outcomes were attributed to higher rates of early induction deaths (36%) in the t-APL group, compared to 7% among patients with *dn*-APL (p = 0.008).

The excellent outcomes with ATRA plus arsenic trioxide (ATO) in *dn*-APL were also apparent in two recent studies showing similar benefits in t-APL. In patients with t-APL, CR rates of 100% were achieved with ATRA + ATO (n = 24) vs 95% with ATRA + ATO + chemotherapy (n = 19) vs 78% for those who received ATRA + chemotherapy (n = 53) [53]. There were no early deaths recorded among patients treated with ATRA + ATO and with a median follow-up of 3.7 years, none of the ATO treated patients have relapsed. MD Anderson have also reported favorable remission rates (89% vs 70%) and median OS (not reached vs 161 weeks) in t-APL patients treated with ATRA + ATO (n = 19), compared to ATRA + chemotherapy (n = 10) [54].

For patients with standard risk t-APL (WBC $< 10 \times 10^9$/L), the chemotherapy-free ATRA and ATO approach is particularly attractive for patients who have previously received anthracyclines for treatment of their primary cancer. This option may help to limit the increased risk of cardiotoxicity from excessive cumulative exposure to anthracyclines. For patients with high risk t-APL (WBC $\geq 10 \times 10^9$/L) and excessive cumulative prior anthracycline exposure, combination of ATRA + ATO with gemtuzumab ozogamicin (GO) for t-APL represents a possible alternative to anthracyclines [55,56].

t-AML with t(8;21) and inv(16)/t(16;16): Although similarly high remission rates may be achieved, 2-year OS (100 vs 621 days) appear inferior for therapy-related, compared to *dn*-AML with core binding factor (CBF) abnormalities, with relapse rates up to 70% reported [57,58]. Therefore, for suitable patients with t-AML with t (8; 21) or inv (16)/t (16; 16) after standard intensive induction and consolidation chemotherapy and a matched sibling or unrelated hematopoietic stem cell donor, consideration should be given to an allogeneic stem cell transplant (alloSCT) in first remission. Although a survival benefit for CBF AML has been observed with the addition of GO to intensive induction and consolidation therapy, the benefit in t-AML with CBF remains to be determined [59]. Furthermore, caution should be exercised if an alloSCT is being considered due to the potential risk of veno-occlusive disease associated with GO. Among 139 AML cases with t (8; 21) that included 22 t-AML cases, the frequency of associated adverse risk mutations, such as c*KIT*D816 and *ASXL1* was similar between t-AML and *dn*-AML [60].

t-AML with NPM1 mutation: Patients with t-AML and *NPM1* mutation appear to have a distinct cytogenetic molecular profile compared to the other t-AML cases. Although *NPM1* mutations occur at a lower frequency (approximately 14%), these t-AML cases were associated with normal karyotype and *FLT3* mutation [61]. Furthermore, in one series, most cases had prior history of local radiotherapy or methotrexate-based therapy, whose association with t-AML remains doubtful. Therefore, in some cases, t-AML with *NPM1* mutation may actually represent *de novo NPM1*-mutated AML arising in patients with a prior history of therapy. Larger studies will be required to compare whether treatment outcomes differ between therapy-related and *de novo* cases. In the meantime, management and minimal residual disease monitoring of t-AML with *NPM1* mutation should follow practices outlined for *dn*-AML.

t-AML without favorable karyotype/genotype: Outcomes after intensive chemotherapy have been consistently inferior to *dn*-AML in t-AML cases lacking favorable genomic characteristics as outlined above. Population-based registries have reported a higher frequency of adverse karyotype, increased early mortality and lower median OS, especially in adults < 60 years in therapy-related versus *dn*-AML (Table 2) [2,3,7].

Non-intensive approaches: For patients deemed unfit for intensive therapy, hypomethylating agents (HMA) such as azacitidine or decitabine result in an overall response rate (ORR) ranging between 28 and 42% in retrospective studies [62,63]. A French study reviewed 54 t-MN cases (12 oligoblastic t-AML and 42 t-MDS) receiving compassionate access azacitidine [63]. Although the ORR was comparable to *de novo* MDS/AML patients treated on the same program (39 vs 45%), 2-year OS was significantly lower (14% vs 34%). On multivariate analysis, only a high IPSS score and complex karyotype retained significance. Another retrospective study reviewed azacitidine for t-AML (n = 16) and t-MDS (n = 34) across 10 Italian centers [62]. They reported an ORR of 42% including 20% CR after a median of 3 cycles. The median OS was 21 months, with better outcomes seen in those with < 20% bone marrow blasts and normal karyotype.

CPX-351 (Vyxeos): CPX-351 was approved by the U.S. Food and Drug Administration (FDA) in August 2017 for the treatment of

Table 2
Outcomes of intensively treated t-AML patients from population-based registries.

	Danish (2000–2013) [3]		Swedish (1997–2006) [2]		German (1993–2008) [7]	
	t-AML	*De novo*	t-AML	*De novo*	t-AML	*De novo*
Number	203	2249	259	2474	200	2653
Median age (range)	58 (22–76)[a]	48 (15–86)[a]	70 (NA)	70 (NA)	58 (19–79)	53 (16–85)
Adverse karyotype	40%	19%	46%	26%	39%	19%
Intensive treatment	50%	55%	56%	64%	100%	100%
Complete remission*	61%	75%	54%	72%	63%	67%
Overall survival	24%[a] (3y)	39%[a] (3y)	14 m[b] (median)	158 m[b] (median)	26% (4y)	38% (4y)

[a] Patients who received intensive treatment only.
[b] In age < 55y; NA: not available.

newly diagnosed t-AML and AML with myelodysplasia related changes (AML-MRC). The approval was based on a phase III study comparing CPX-351 against standard cytarabine plus daunorubicin chemotherapy in adults aged 60–75 years. The study included 63 patients with t-AML [64]. CPX-351 (100 mg/m^2 cytarabine + 44 mg/m^2 daunorubicin) was administered on days 1, 3, 5, followed by a second induction course on days 1 and 3 for those who did not achieve a hypoplastic bone marrow on day 14. Patients then received up to 2 cycles of post-remission CPX-351 (65 mg/m^2 cytarabine + 29 mg/m^2 daunorubicin). Standard chemotherapy comprised 7 + 3 induction followed by 1–2 cycles of 5 + 2 consolidation. The CR plus CR with incomplete count recovery (CRi) was 47% for CPX-351 (n = 30) vs 36% for 7 + 3 arm (n = 33). Median OS was longer for patients receiving CPX-351 (9.56 vs 5.95 months; p = 0.003). A key clinical question is whether CPX-351 will overcome the poor prognostic outcome associated with *TP53* mutation, which is prevalent in t-MN. In a retrospective multicenter study of 84 patients with molecular profiling treated with CPX-351, *TP53* mutations were identified in 18/84 (21.4% of patients) [65]. ORR with CPX-351 was achieved in 33% with *TP53* mutation, compared to 62% among patients who were *TP53* wild-type. Although OS was not significantly different, there was a trend to inferior survival if *TP53* mutations were present. Further studies will be necessary to confirm whether CPX-351 is superior to standard chemotherapy in patients with t-AML, especially patients with adverse risk and *TP53* mutation, for whom improved therapies are greatly needed.

t-MDS: A large retrospective study comparing 370 patients with t-MDS to 1,576 patients with *de novo* MDS, reported a median OS of 19 vs 46 months (p = 0.005) [66]. Although International Prognostic Scoring System (IPSS), revised IPSS (IPSS-R), WHO-based Prognostic Scoring System and MD Anderson Global Prognostic systems all have prognostic relevance to patients with t-MDS, outcomes were worse globally and within every prognostic subgroup compared to *de novo* MDS [66,67]. Patients with IPSS-R low and very low risk have median OS of 41 and 58 months, respectively. As treatment options for t-MDS remains very limited, alloSCT should be considered in suitable patients with intermediate and high-risk t-MDS.

Allogeneic stem cell transplantation: AlloSCT remains the only potentially curative option for patients with t-MN, given the suboptimal outcomes after intensive chemotherapy alone. Data regarding alloSCT outcomes are based on retrospective studies, with heterogeneous baseline variables making comparisons difficult. An Italian registry study (1999–2013) reported longer median OS in patients with t-MN receiving alloSCT (58.7 vs 12.1 months), compared to no transplant [68]. Another alloSCT study (1990–2004) reported a 5-year OS outcome of 22% among 868 patients with t-MN [69]. The European Group for Blood and Bone Marrow Transplantation group reported a 3-year OS of 35% for 429 patients with t-MN receiving an alloSCT between 1981 and 2006 [70]. Overall, the presence of adverse risk karyotype, presence of active disease pre-transplant, age > 35 years and poor performance status were recurrently associated with poorer outcomes. The optimal conditioning for patients with t-MN is not clear. Among 266 patients with MDS (67 t-MDS and 199 *de novo* MDS) treated between 2000 and 2014, 94% were transplanted using a reduced intensity conditioning approach [71]. Although adverse risk karyotype (61.2%) and *TP53* mutation (30%) were more prevalent in the t-MDS population, 5-year OS was similar to *de novo* MDS (50% vs 54%; p = 0.61), as was NRM (30% vs 27%; p = 0.48) after a median follow-up of 4.8 years.

1.11. Novel therapies

More effective treatment options are particularly needed for patients with t-MDS/AML and adverse cytogenetic risk and/or *TP53* mutation. Although numerous novel therapies are emerging for AML, none have been designed specifically for patients with t-MN. Information regarding potential new therapies are often derived from subset analyses of more inclusive AML trials.

HMA: Among patients with AML and *TP53* mutation, the median overall survival was 7.2 months for azacitidine vs 2.4 months for conventional care regimens (not significant) [72]. Therefore, for patients with t-AML and *TP53* mutation, azacitidine may be preferred over standard chemotherapy in older patients. A 10-day decitabine regimen was recently proposed as a useful regimen in patients with *TP53* mutant MDS and AML, based on the capacity of the treatment to suppress *TP53* mutant clones in the first 4 cycles of therapy and survival outcome that was comparable to patients with wild-type *TP53* [73]. More recently, however, a randomized study compared 5 vs 10-day decitabine in 71 patients with newly diagnosed AML [74]. In preliminary findings, no difference in CR/CRi or OS was observed between the two regimens. Among patients with *TP53* mutation, the median OS was 4.9 months in the 10-day arm vs 5.5 months in the 5-day arm. Responding patients had a ~50% reduction in the *TP53* variant allele frequency after the first cycle of therapy. Although decitabine may temporarily suppress *TP53* mutant clones, the clinical benefit appears short-lived.

HMA combination with venetoclax: The BCL-2 selective inhibitor venetoclax in combination with HMA or low dose cytarabine was recently approved by the FDA (21 Nov 2018) for the treatment of AML in adults aged ≥75 years, or unfit for intensive chemotherapy. Among patients with *TP53* mutation, CR/CRi rates of 60% have been reported, with the median CR/CRi duration of 5.6 months and median OS of 7.2 months [75]. Among patients with adverse risk karyotype, CR/CRi rates of 47% were achieved, with the median duration of CR/CRi at 6.7 months and median OS of 9.6 months. Specific outcomes for patients with t-AML have not been reported to date.

HMA combination with APR-246: A new molecule called APR-246 purportedly reactivates *TP53* by restoring the wild-type conformation in cancerous cells carrying mutant *TP53*. A phase 1b/2 trial combining APR-246 in combination with azacitidine is being conducted in patients with either MDS or oligoblastic AML and *TP53* mutation. In preliminary findings, five patients with t-MDS and 12 *de novo* patients (AML 3 and MDS 9), all with adverse karyotype, have been enrolled, with an ORR 100% reported. All 11 response evaluable patients have achieved either a CR (82%) or marrow CR (18%). With a median follow-up time of 7 months, the median OS has not been reached [76].

2. Summary

Therapy-related myeloid neoplasms are now recognized to be the consequence of clonal selection and transformation of pre-existing hematopoietic clones with a fitness advantage upon exposure to cytotoxic drugs and/or radiation therapy, usually for treatment of prior solid cancers. The incidence of t-MN is escalating, augmented by the increased incidence of solid cancer and clonal hematopoiesis, which are both strongly associated with rising age. The risk of t-MN will be further augmented by gains in survival among patients with breast cancer and lymphoma, the prior cancers most commonly found in association with t-MN. Effective therapy for t-MN remains limited, with poor outcomes linked to adverse risk genetic features and greater treatment-related toxicities due to morbidity from prior therapies. Although new therapies are emerging, no single treatment looks set to radically transform patient outcomes in the near future. Efforts to identify patients at risk for future development of t-MN will be an important objective for future research. Identification of clonal hematopoiesis at the time of primary cancer diagnosis may shape future attempts to monitor, risk-adapt treatment decisions and explore the potential for emerging therapies to suppress or eliminate high-risk clones prior to clinical progression.

Practice points

- Therapy-related myeloid neoplasms (t-MN) encompass a heterogeneous spectrum of disorders including t-AML, t-MDS and t-MDS/MPN, characterized by a high frequency of adverse risk features resulting in limited effective treatment options
- t-MN are now recognized to be the consequence of clonal selection and transformation of pre-existing hematopoietic clones with a fitness advantage upon exposure to cytotoxic chemotherapy and/or radiation therapy
- Current treatment of patients with t-MN should be tailored to the cytogenetic molecular risk profile, as well as patient fitness for therapy

Research agenda

- Further studies are required to determine if early detection of pathogenic hematopoietic clones prior to cytotoxic exposure can help define patient subgroups at highest t-MN risk and aid the development of a risk-adapted approach to prevent these patients from developing t-MN
- Given the markedly limited treatment options, novel therapies focusing on tackling t-MN are urgently needed

Conflicts of interest

All authors declare no conflict of interest.

Acknowledgments

AW receives funding support from National Health and Medical Research Council of Australia, the Medical Research Future Fund, Victorian Cancer Agency and the Leukemia Lymphoma Society Specialized Center of Research (SCOR).

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