**Name of Journal: *World Journal of Stem Cells***

**ESPS Manuscript NO: 27389**

**Manuscript Type: Review**

**Therapy-related myeloid neoplasms - what have we learned so far?**

Zahid MF *et al.* Therapy-related myeloid neoplasms

**Mohammad Faizan Zahid, Aric Parnes, Bipin N Savani, Mark R Litzow, Shahrukh K Hashmi**

**Mohammad Faizan Zahid**, Medical College, Aga Khan University, Karachi 74800, Pakistan

**Aric Parnes**, Division of Hematology, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA 02115, United States

**Bipin N Savani,** Hematology and Stem Cell Transplantation Section, Division of Hematology/Oncology, Department of Medicine, Vanderbilt University Medical Center and Veterans Affairs Medical Center, Nashville, TN 37232, United States

**Mark R Litzow**, **Shahrukh K Hashmi**, Mayo Clinic Transplant Center, Blood and Marrow Transplant Program, Mayo Clinic, Rochester, MN 55905, United States

**Author contributions**: Zahid MF conceptualized the topic of the review; Zahid MF and Hashmi SK wrote the manuscript; Parnes A, Savani BN, Litzow MR and Hashmi SK critically revised the manuscript for important intellectual content; all authors approved the final version of the manuscript submitted.

**Conflict-of-interest** **statement:** The authors declared no conflict of interest.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Invited manuscript

**Correspondence to: Mohammad Faizan Zahid, MBBS,** Medical College, Aga Khan University, P.O. Box 3500, Stadium road, Karachi 74800, Pakistan. faizanzahid91@hotmail.com

**Telephone:** +92-323-4407740

**Received:** May 27, 2016

**Peer-review started:** May 28, 2016

**First decision:** July 6, 2016

**Revised:** July 21, 2016

**Accepted:** August 6, 2016

**Article in press:**

**Published online:**

**Abstract**

Therapy-related myeloid neoplasms are neoplastic processes arising as a result of chemotherapy, radiation therapy, or a combination of these modalities given for a primary condition. The disease biology varies based on the etiology and treatment modalities patients receive for their primary condition. Topoisomerase II inhibitor therapy results in balanced translocations. Alkylating agents, characteristically, give rise to more complex karyotypes and mutations in p53. Other etiologies include radiation therapy, high-dose chemotherapy with autologous stem cell transplantation and telomere dysfunction. Poor-risk cytogenetic abnormalities are more prevalent than they are in *de novo* leukemias and the prognosis of these patients is uniformly dismal. Outcome varies according to cytogenetic risk group. Treatment recommendations should be based on performance status and karyotype. An in-depth understanding of risk factors that lead to the development of therapy-related myeloid neoplasms would help developing risk-adapted treatment protocols and monitoring patients after treatment for the primary condition, translating in reduced incidence and early detection (and treatment).

**Key words:** Therapy-related myeloid neoplasms; Therapy-related myelodysplastic syndromes; Therapy-related acute myeloid leukemia; Ionizing radiation; Alkylating agents; Topoisomerase II inhibitors; Allogeneic hematopoietic stem cell transplantation

**© The Author(s) 2016.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Therapy-related myeloid neoplasms are becoming an increasing problem as the survival of cancer patients lengthens. The etiology has an important influence on the biological characteristics, time to onset and prognosis of the resultant disease. Although treatment of therapy-related myeloid neoplasms represents a substantial challenge due to prior treatment and comorbidities, cure is possible, especially with allogeneic stem cell transplantation, particularly in those with good-risk karyotype. Ultimately, individual assessment of risk factors may lead to developing risk-adapted therapies to reduce the incidence of this serious complication without affecting therapy for the underlying disorders.

Zahid MF, Parnes A, Savani BN, Litzow MR, Hashmi SK. Therapy-related myeloid neoplasms - what have we learned so far? *World J Stem Cells* 2016; In press

**INTRODUCTION AND EPIDEMIOLOGY**

Therapy-related myeloid neoplasms, which include both therapy-related myelodysplastic syndromes (t-MDS) and therapy-related acute myeloid leukemia (t-AML), are well-known sequelae of conventional anticancer chemotherapy and radiotherapy for solid tumors, such as ovarian cancer[1], breast cancer[2], testicular cancer[3] and various sarcomas[4], as well as hematologic malignancies[5-7]. Therapy-related myeloid neoplasms constitute approximately 10%-20% of all cases of AML and MDS[8], with incidence varying depending upon the underlying malignancy, type of cytotoxic agents (and/or radiotherapy), timing of administration and dosage of treatment modalities[9]. Therapy-related myeloid neoplasms can present at any age, but the median age at diagnosis is reported to be approximately 61 years in adults[10,11].

After conventional-dose anticancer chemoradiotherapy, the incidence of t-MDS/AML has been reported between 0.8%-6.3% at 20 years post-treatment, with a median time of 3-5 years from treatment to development of t-MDS/AML[12]. In contrast, the incidence of t-MDS/AML after high-dose chemotherapy and autologous hematopoietic stem cell transplant (auto-HSCT) ranges from 1.1%-24.3% at 5 years post-transplant with a median time to development of only 1-2 years post-transplant[12-16]. Use of etoposide (a topoisomerase II inhibitor) priming for stem-cell mobilization and total-body-irradiation (TBI) based conditioning regimens are particularly associated with t-MDS/AML after auto-HSCT[16,17].

According to the World Health Organization classification, therapy-related myeloid neoplasms are broadly categorized into two subtypes: (1) an alkylating agent/radiotherapy-related type; and (2) a topoisomerase II inhibitor-related type[18]. The development of t-MDS/AML after alkylating agents/radiotherapy usually occurs after a median latency of 4-7 years, with two-thirds of patients presenting with MDS and one-third presenting with AML[12,19]. There is prominence of peripheral cytopenias and dysplasia of multiple myeloid lineages with frequently observed abnormalities of chromosome 5 [-5/del(5q)] and chromosome 7 [-7/del(7q)][19,20]. Conversely, topoisomerase II inhibitor-related t-MDS/AML has a relatively shorter latency between exposure to drugs and onset (median of 2-3 years)[21]. Patients with this subtype often present with overt AML without features of preceding MDS. AML in this subtype shows monocytic predominance[21,22] with a high incidence of balanced translocations involving chromosomal segments 11q23, 17q21 and/or 21q22[21]. While the risk of developing t-MDS/AML after alkylating agents/radiotherapy rises with increasing age, the risk of the same after topoisomerase II inhibitors appears to remain constant across all age groups[18,23].

LEUKEMOGENESIS

Therapy-related myeloid neoplasms are clonal hematopoietic stem cell disorders that arise due to iatrogenic somatic mutations after treatment with cytotoxic chemotherapy/radiotherapy. These somatic mutations impart increased proliferative capacity and survival advantage in the affected hematopoietic progenitors[12].

Alkylating agents have established significant clinical applications in virtually all cancer types and were the first chemotherapeutic drugs to be associated with therapy-related myeloid neoplasms[24]. These drugs work by transferring alkyl groups to oxygen and nitrogen atoms on DNA bases, resulting in the formation of highly mutagenic DNA base lesions (such as O6-methylguanine and N3-methylcytosine) and inducing DNA damage[25]. Alkylated DNA-based lesions, specifically O6-methylguanine, cause mispairing during DNA replication, and while this replication error is efficiently repaired by mismatch-repair enzymes, alkylated bases cannot be cleaved by mismatch-repair enzymes, leading to mutagenicity, secondary DNA double-stranded breaks and eventual cytotoxicity[26,27]. Mono-functional alkylating agents, such as nitrosoureas, dacarbazine and temozolomide, have one active moiety and are able to induce such lesions. In contrast, bi-functional alkylators, such as cyclophosphamide, melphalan and chlorambucil, have two active moieties and are able to form crosslinks within and between DNA strands in addition to forming alkylated base lesions[28]. Inter-strand DNA crosslinks halt replication forks during DNA replication, resulting in the formation of double-stranded DNA breaks. These breaks can give rise to chromosomal translocations, insertions, inversions and loss-of-heterozygosity involving several vital cellular genes[29,30].

Drugs targeting DNA topoisomerases are also well-known to cause t-MDS/AML[31]. DNA topoisomerases mediate the unknotting and relaxing of DNA supercoils, thereby allowing DNA replication to occur. These enzymes accomplish this by creating transient single-stranded (DNA topoisomerase I) and double-stranded DNA breaks (DNA topoisomerase II). The release of topoisomerases from the DNA strands is followed by the re-ligating of these transient DNA breaks[32]. Topoisomerase II inhibitors, such as epipodophyllotoxins (etoposide and teniposide) and anthracyclines (daunorubicin, doxorubicin, *etc*.) prevent the release of topoisomerase II from cleaved DNA, preventing the re-ligation of strands and persistence of double-stranded breaks[26]. These DNA breaks are highly mutagenic and frequently result in translocations involving the genes *MLL* at 11q23, *RUNX1* at 21q22 and *RARA* at 17q21[33-35].

The substantial incidence of various leukemias and myeloid disorders in the survivors of the Hiroshima and Nagasaki nuclear attacks has established a firm causal relationship between ionizing radiation and hematologic malignancies[36-38]. Epidemiological data from several studies involving individuals receiving therapeutic radiation has corroborated its leukemogenicity[3,39-41]. Cellular exposure to ionizing radiations has multiple mechanisms of causing DNA damage and mutations. Energy in each individual photon of radiation is able to disrupt the sugar-phosphate backbone of the DNA molecule, leading to single- and double-strand breaks[28]. In addition to this direct effect, cellular exposure to ionizing radiations results in radiolysis of water molecules leading to the formation of reactive oxygen species (most notably hydrogen peroxide, superoxide and hydroxyl radicals)[42]. These highly reactive molecules are capable of oxidizing and deaminating DNA bases and disruption of the sugar-phosphate backbone. As discussed with alkylating agents and topoisomerase II inhibitors earlier in this section, double-stranded breaks are highly mutagenic and contribute to leukemogenesis in therapy-related myeloid neoplasms.

In the context of auto-HSCT, DNA damage is multifactorial, arising as a result of treatment with cytotoxic agents used in induction therapy prior to auto-HSCT, possibly from the transplant process itself (stem cell mobilization, stem cell collection and storage) and from the stress of engraftment and hematopoietic recovery during the post-transplant period[43-46], apart from the chemotherapy agents and TBI used in the conditioning regimen. It is probable that some progenitor cells persist within the patients despite pre-transplant conditioning and acquire mutations overtime, for example from injury caused by the conditioning regimen, leading to t-MDS/AML after auto-HSCT[16]. To scientifically ascertain this hypothesis, future studies may focus on genetically marking the autograft and performing assays of t-MDS/AML clones in patients who develop this complication post-transplant to ascertain whether progenitor cells persisting in the patient after pre-transplant conditioning give rise to t-MDS/AML or is it the rescuing hematopoietic progenitors that give rise to t-MDS/AML. Currently, the ongoing Center for International Blood and Marrow Transplant Research (CIBMTR) study LE14-01 is the largest retrospective study to date (to our knowledge) on t-MDS/AML after auto-HSCT[47]. The results of this study may provide deeper insight into t-MDS/AML in patients receiving auto-HSCT.

The *p53* gene plays a crucial role in DNA damage response pathways, DNA repair mechanisms, cell cycle control and apoptosis. Abnormalities affecting *p53* hinder the cell’s ability to repair damaged DNA and results in genomic instability and accumulation of various genetic lesions that contribute to leukemogenesis[12]. It is noteworthy that less than 10% of patients with *de novo* MDS and AML harbor *p53* mutations (with traditional techniques), whereas 27%-50% of patients with t-MDS/AML demonstrate *p53* mutations[48-50]. These are non-germline mutations that are often seen as a late adverse effect of therapy with alkylating agents and often occur simultaneously with chromosome 5 [-5/del(5q)] and chromosome 7 [-7/del(7q)] losses[12,50].

Telomeres are repeat sequences of non-coding DNA that flank the 3’ ends of linear chromosomes, permitting the replication of 3’ chromosomal ends and are vital for preventing dicentric fusion and chromosomal abnormalities[51]. Each mitotic division results in fractional loss of telomeric DNA, with cumulative telomeric loss leading to cellular senescence, a process by which normal cells lose their ability to divide after a specific number of cell divisions. In addition, loss of telomeric DNA also leads to genomic instability and somatic mutations[52,53]. Exposure to chemotherapeutic agents places proliferative stress on the bone marrow to allow for hematopoietic recovery after/in between cycles of chemotherapy[54]. The increased proliferative rates accelerate the loss of telomeric DNA, which would otherwise be conserved by the telomerase enzyme under physiologic conditions[52]. It is evident that telomere shortening is associated with the development of myeloid malignancies, such as MDS and AML, in both *de novo*[55] and therapy-related settings[43,56,57]. The nested case-control study by Chakraborty *et al*[57] showed that after auto-HSCT, those patients who developed t-MDS/AML showed a substantial increase in the rate of telomeric shortening after day +100 in comparison to the control group who did not develop t-MDSAML. Other studies[43,56] also demonstrated similar observations. These findings corroborate that increased telomeric loss and telomere dysfunction contributes to leukemogenesis and likely precedes the development of t-MDS/AML in premalignant cells.

**TREATMENT AND OUTCOMES**

***Conventional chemotherapy***

Intensive chemotherapy is one of the established therapeutic approaches to t-MDS/AML and its role has been investigated in earlier studies. In a retrospective study of 122 patients with t-MDS/AML at the MD Anderson Cancer Center, intensive chemotherapy with cytarabine yielded a complete remission (CR) rate of 37%[58]. In the same study, pooled data of 496 patients from 13 different studies revealed a cumulative CR rate of 27%[58]. No doubt, CRs have been achieved in this and other early studies on t-MDS/AML, but CR rates are lower and short-lived in comparison to *de novo* MDS/AML[11,59,60]. The fatal course of t-MDS/AML is due to profound and persistent cytopenias due to ineffective hematopoiesis regardless of the fraction of immature blasts accumulating in the bone marrow[61]. In contrast, a subsequent study reported a surprisingly high CR rate of 82% for t-MDS/AML treated with high-dose cytarabine + mitoxantrone[62].

For therapy-related acute promyelocytic leukemia (t-APML) and t-AML with good-risk cytogenetics, specifically inv(16) and t(8;21), induction chemotherapy is recommended, based on treatment guidelines for their *de novo* counterparts[28]. For t-APML, outcomes are encouraging with regimens containing all-*trans* retinoic acid, as evidenced by two large European studies[63,64]. One study reported a CR rate of 87%[64]. The other study reported a CR rate of 80% with actuarial survival of 59% at 8 years[63]. Since outcomes with non-transplant strategies are encouraging in t-APML, this allows patients to be spared from the toxicities associated with allogeneic hematopoietic stem cell transplant (allo-HSCT). However, recent evidence does not favor the same recommendations for t-AML with inv(16) and t(8;21) as these patients have shown shorter event-free and overall survival in comparison to patients with *de novo* AML exhibiting inv(16) and t(8;21)[65-67]. This suggests that these patients may also require allo-HSCT for a durable cure, as is the case with t-MDS/AML with intermediate- and poor-risk cytogenetics[12,61,68]. The general conclusion drawn from literature on the subject is that outcomes of t-MDS/AML treated with conventional chemotherapy are generally poor, with median survival as low as only 6 mo[12].

***Role of hypomethylating agents in therapy-related myeloid neoplasms***

With unimpressive survival rates for t-MDS/AML after allo-HSCT and even lower with conventional chemotherapy, exploration of alternative treatments and novel therapies is highly warranted to improve survival rates in this subset of patients. Azacitidine has shown promising efficacy in the treatment of high-risk MDS and AML[69,70] with a limited side effect profile and impressive tolerability, especially in patients with poor performance status and comorbidities[71]. Several recent retrospective studies suggested notable activity of azacitidine against t-MDS/AML, with overall response rates ranging from 39%-43% and median overall survival from 14.5-21 mo[72-74]. Azacitidine yielded the most benefit and better overall survival when used as first-line therapy[74] and detailed analysis of these studies showed similar outcomes between patients with *de novo* MDS/AML and those with t-MDS/AML[72,73]. A recent retrospective account of patients treated with azacitidine at the Memorial Sloan-Kettering Cancer Center and patients treated with decitabine in two industry-sponsored clinical trials (D0007 [75] and DACO-020[76]) was published by Klimek *et al*[77]. In a cohort of 42 patients with t-MDS, this account reported an overall response rate (CR + marrow CR + hematologic response) of 38%[77]. However, a multicenter retrospective case series published in 2015 reported relatively inferior outcomes compared to the aforementioned studies (overall survival: 9.6 mo; overall response rate: 35.7%)[78].

Prebet *et al*[79] recently reported results of the E1905 study, a phase II randomized trial comparing the effects of combination therapy with azacitidine and the histone deacetylase inhibitor, entinostat, against monotherapy with azacitidine. The results showed lower hematologic normalization rates (17% *vs* 46% in the monotherapy arm), shorter overall survival (6 mo *vs* 13 mo in the monotherapy arm) and increased toxicity in the combination arm, recommending against the use of the azacitidine/entinostat combination for t-MDS/AML[79]. A predecessor of the same study demonstrated pharmacologic antagonism of entinostat when added to azacitidine[80]. However, the same study showed that prolonged administration of azacitidine alone increased the rate of hematologic responses when compared to standard dosing, representing an area of future research interest[80].

***Allogeneic hematopoietic stem cell transplant***

The standard approach for most patients with t-MDS/AML is allo-HSCT, which has consistently been shown to be a potential curative option for t-MDS/AML[12,61,68]. Outcomes of patients with t-MDS/AML after allo-HSCT, albeit limited and mostly based on retrospective studies, are still uniformly poor due to the high-intensity and transplant-related complications associated with the procedure and the refractory nature of the disease. For example, an account of 13 patients receiving allo-HSCT for t-MDS/AML after auto-HSCT reported that all patients died of either transplant-related complications (11 patients) or relapse (2 patients) with a median overall survival of only 1.8 mo[81]. One study reporting outcomes of 461 patients estimated a 35% overall survival 3 years after allo-HSCT[82]. Another large study involving 306 patients reported a median survival of only 8-10 mo and a 5 year overall survival of less than 10%[35]. Other studies have also reported poor outcomes[68,83-86], with non-relapse mortality ranging between 54%-58%[86-88]. Since most clinical trials in the AML or MDS arena have usually excluded t-AML/MDS, to our knowledge, prospective phase III randomized data evaluating the role of allo-HSCT in t-MDS/AML is lacking.

Some studies have described notable influences of conditioning regimens on survival rates. In a large study by Witherspoon *et al*[88], the 5-year disease-free survival for patients receiving conditioning with busulfan (BU) targeted to 600-900 ng/mL steady-state plasma concentration with cyclophosphamide (CY) [(t-BU/CY)] was 30%, the highest in the patient cohort. Survival rates were significantly lower for other regimens (standard BU/CY: 19%; chemotherapy/TBI: 8%) in comparison to t-BU/CY (*P* = 0.006). In the same report, the 5-year cumulative non-relapse mortality was lowest for t-BU/CY (42%) *vs* that for standard BU/CY and chemotherapy/TBI regimens (52% and 58%, respectively); (*P* = 0.02)[88]. Subsequently, an even larger study (including 251 patients) also showed a greater 5-year disease-free survival for patients conditioned with t-BU/CY (BU targeted to 800-900 ng/mL steady-state plasma concentration) of 43% *vs* that for standard BU/CY, fludarabine (Flu)/BU, Flu/TBI and high-dose TBI/CY (28%, 24%, 23%, 18%, respectively); (*P* = 0.001)[87]. This study also showed the lowest 5-year cumulative non-relapse mortality for the t-BU/CY regimen (28%) *vs* high-dose TBI/CY, Flu/TBI and standard BU/CY (53%, 54% and 61%, respectively); (*P* < 0.001)[87].

***Factors affecting outcomes***

The dismal outlook of these patients is likely multifactorial, resulting from relapse-related and/or non-relapse-related mortality. The likelihood of relapse significantly correlates with disease stage. For example, a report from the Fred Hutchinson Cancer Research Center showed varying rates of relapse among their patient cohort (no relapses in the refractory anemia/refractory anemia with ringed sideroblasts group; 22% relapse in the refractory anemia with excess blasts group; and 36% relapse in the refractory anemia with excess blasts in transformation/AML group)[85]. Another study reported similar findings[88]. Likewise, disease karyotype also correlates with relapse rate. The impact of karyotype on outcomes in both *de novo* and t-MDS/AML were compared in large prospective studies which showed disease karyotype to be an independent prognostic factor in both groups, with poor-risk cytogenetic abnormalities more common in the t-MDS/AML group[84,89]. An optimized, 3-group cytogenetic classification proposed by Armand *et al*[90] was found to be the strongest predictor of overall survival in t-MDS/AML by its impact on relapse risk after allo-HSCT. Through this classification, cytogenetic abnormalities in these patients were divided into good-risk [normal, -5, (del)20q or -Y], poor-risk (chromosome 7 abnormalities, complex karyotype) and intermediate-risk (all others)[90]. Also, relapses are less likely with unrelated donor transplants, likely due to a more potent graft-versus-leukemia effect[12,91] and lower peripheral blood blast count (correlating with early-stage disease and low disease burden)[92].

Other outcome parameters after allo-HSCT have been scrutinized. Patient performance status strongly influences survival[79]. Treatment for the primary malignancy causes injury to various organ systems and depletion of normal hematopoietic progenitors, diminishing the patients’ ability to withstand the intensive nature and toxicities associated with allo-HSCT. In addition, damage to bone marrow stromal elements from prior therapy (especially radiotherapy) alters the bone marrow microenvironment, making hematopoietic regeneration difficult[61]. Younger patients (children, adolescents, young adults) have a better bone marrow reserve and better ability to withstand the toxicities associated with multiple treatments (both for the primary disease and allo-HSCT)[4], hence it would be expected that survival is better in this group in contrast to elderly. Since therapy-related myeloid neoplasms are relatively uncommon in young age groups[8,9], there is paucity of literature concerning the prognostic factors and survival in younger patients. This is a potential area of research interest. Future studies are warranted to ascertain if different prognostic factors confer survival advantage in younger patients with therapy-related myeloid neoplasms, or if the dismal outcomes in elderly are just a result of sheer fact of age.

Patients are also immunocompromised from prior treatment regimens and hence often acquire life-threatening infections, a well-known and feared cause of mortality after allo-HSCT. Additionally, relapse of the primary malignancy, especially metastatic cancer or disseminated lymphoma, carries its own risks of morbidity and mortality[61]. Also, the timing of allo-HSCT affects the outlook of patients, as a recent study demonstrated that those who received allo-HSCT later than 6 mo after diagnosis have inferior survival rates[93]. Thus it is imperative to refer a newly diagnosed case of t-MDS/AML to a transplant center early.

In addition to disease stage and karyotype, somatic mutations of specific genes may also have implications on prognostication. For example, frame shift mutations of the nucleophosmin gene (*NPM1*), internal tandem duplications of the *fms*-like tyrosine kinase 3 gene (*FLT3*) and double mutations in the *CEBPA* gene are now routinely assessed in the workup of AML patients and incorporated into therapeutic algorithms[94]. They have also been observed in t-MDS/AML[95,96]. While these (and perhaps other specific gene mutations) may have impact on t-MDS/AML prognosis, these mutations usually occur and have prognostic value in cases with normal cytogenetics[94], a karyotype which is relatively rare in t-MDS/AML, making their prognostic utility uncertain specifically for t-MDS/AML.

When taking only t-MDS into account, the International Prognostic Scoring System, a cornerstone in the prognostication of patients with MDS, has shown unsatisfactory ability to predict the outcome of patients after treatment[81]. Instead, an alternative prediction model utilizes the following four factors to gauge survival for patients with t-MDS and t-AML after allo-HSCT: (1) age greater than 35 years; (2) poor-risk cytogenetics; (3) advanced-stage t-MDS or t-AML not in CR after allo-HSCT; and (4) donor other than an HLA-identical sibling or a matched or partially-matched unrelated donor[68]. Five-year overall survival varies with the number of these factors present: none (50%), 1 (26%), 2 (21%), 3 (10%) and 4 (4%)[68]. Male sex has also been indicative of poor outcomes[86]. A proposed algorithmic approach to patients with therapy-related myeloid neoplasms is elaborated in Figure 1.

GAUGING THE RISK OF THERAPY-RELATED MYELOID NEOPLASMS

Keeping in mind the poor outcomes of t-MDS/AML, measures for early detection of this disorder would allow for timely and pre-emptive treatment approaches, such as reduced intensity conditioning allogeneic hematopoietic stem cell transplant (allo-HSCT). This approach would yield substantial advantages as opposed to waiting for the development of overt t-MDS/AML, when disease burden is higher and requires more intensive therapy which can have its own risks of morbidity and mortality[28]. In this section we will outline some methods for prediction and/or early detection of t-MDS/AML in patients at risk.

Metaphase cytogenetics and karyotyping analyze actively dividing cells, though the number of cells analyzed is limited (20-30 cells)[44]. It is worthy of note that patients developing t-MDS/AML, for example after auto-HSCT, may not show karyotypic abnormalities before the procedure. Conventional cytogenetics may lack sufficient sensitivity and specificity to efficiently recognize patients with increased predisposition to t-MDS/AML[16,44].

Interphase fluorescence *in situ* hybridization (FISH) offers several advantages over conventional cytogenetics, mainly the lack of need for cells to be actively dividing and the ability to analyze a greater number of cells (several hundreds)[44]. FISH is also able to detect abnormal clones prior to auto-HSCT. For example, in one report, FISH was able to detect clonal abnormalities in 9 out of 12 patients (75%) who later developed t-MDS/AML after auto-transplant[97]. In another study, FISH identified abnormal cell clones in 20 out of 20 patients who went on to develop t-MDS/AML[98]. Identification of clonal abnormalities in a high percentage of cells may indicate proliferative and survival advantages and foreshadows development of t-MDS/AML[44]. However, the locus specificity of FISH requires prior selection of multiple markers for adequate analysis and its labor- and time-intensive methodology are notable limitations[44].

Loss of heterozygosity (LOH) employs a polymerase chain reaction (PCR) analysis of a selected sample to detect loss of one allele at a specific locus and large chromosomal deletions. This technique is also labor and time intensive and is a population-based assay that requires prior selection of loci to be analyzed. In addition, its sensitivity is poor, unable to detect less than 20% cells for LOH of a selected locus[44]. Nevertheless, it may have impressive specificity, as a positive result suggests an abnormal cell clone. Thus, LOH may prove to be a viable “rule-in” test in this context and may be followed by more sensitive techniques, such as high-throughput analysis and next-generation sequencing[44,99]. However, prospective studies with large numbers of patient samples are needed to ascertain its validity as a predictor of t-MDS/AML.

Clonality assay based on X chromosome-inactivation at the human androgen receptor gene is another useful method. This is a PCR-based technique that does not require information about loci prior to analysis and detects abnormal clones with survival/proliferative advantage over normal polyclonal cells[44]. In a single center study by Mach-Pascual *et al*[100], monoclonal hematopoiesis, as indicated by X-inactivation-based clonality at the human androgen receptor locus, prior to auto-HSCT was predictive of the development of t-MDS/AML. Four out of 10 patients (40%) demonstrating monoclonal hematopoiesis before transplant subsequently developed t-MDS/AML *vs* only 2 out of 53 patients with polyclonal hematopoiesis (*P* = 0.004)[100]. However, this method is limited by the need for high numbers of monoclonal cells to be present for diagnosis (low sensitivity) and its applicability only to female patients[44]. Altered gene expression in CD34+ progenitors may also be used. A large study by Li *et al*[101] showed that a 38-gene panel analyzing gene expression in peripheral blood CD34+ progenitors showed remarkable ability to distinguish patients who would eventually develop t-MDS/AML from those who would not develop the complication after auto-HSCT. The implication of this study is that development of t-MDS/AML requires the acquisition of mutations in multiple genes as opposed to just one gene[44]. Additionally, due to different kinds and combinations of mutations, patients with this disorder show significant heterogeneity with multiple subtypes. Therefore, characterization of single gene mutations may not have a satisfactory predictive value in identifying patients prone to developing t-MDS/AML[12,28,44].

Significant advances have happened for identification of unique biomarkers associated with leukemias which is mainly driven by gene expression analysis and next generation sequencing (NGS), which have the potential to significantly improve the diagnostic and prognostic criteria. The utilization of a signature NGS panel for each disease (*e.g*., AML, ALL, MDS, *etc.*) is increasing worldwide[102,103]. In t-MDS/AML, the impact of NGS panel on long term outcomes are awaited. What we do know is some of clonal mutations with known association with leukemogenesis, *i.e.*, *TET2*, *DNMT3A*, and *ASXL1*[104,105], if found in a patient who is at risk of t-MDS/AML may predict a high likelihood of developing t-MDS/AML. Caution must be exercised with such an approach, as some cases of t-MDS/AML may have germline mutations in cancer susceptibility genes[106], thus a careful family history to discover cancer susceptibility is warranted in at-risk patients.

In summary, when a bone marrow biopsy is being obtained for work up for cytopenias in an at-risk patient (*e.g.*, cancer survivor who received chemotherapy or radiation), obtaining an NGS Panel specific for MDS and AML should be considered.

RISK REDUCTION STRATEGIES

Based on our knowledge of the risk factors and pathogenesis of t-MDS/AML, development of risk reduction strategies is a certain possibility. Standardized screening tests, including but not limited to the ones discussed in the previous section, may help identify patients at substantial risk. Accordingly, alterations of chemotherapeutic regimens and treatment modalities may be made under a risk-adapted model, thereby minimizing the risk of t-MDS/AML while providing adequate treatment to the underlying malignancy[12].

In the context of high-dose chemotherapy and auto-HSCT, modifications can be made to stem cell mobilization and harvesting and pre-transplant conditioning regimens, circumventing the use of alkylating agents, topoisomerase inhibitors and radiotherapy, to eliminate as many risk factors as possible. Specific FISH loci, such as 5q–, 7q–, +8, –11 and 20q–, may be screened preemptively to predict outcomes when any specific abnormalities in blood work are being worked up[44]. Alternatively, if the risk of t-MDS/AML is substantial (for example, in the case of hematologic malignancies evidence of cytogenetic or FISH abnormalities prior to transplant and high risk disease), these patients can be offered other therapeutic options, such as pre-emptive work up for allo-HSCT (HLA typing) and non-transplant modalities (emerging novel therapies and targeted agents).

**CONCLUSION**

There is much needed effort for further exploration and validation of biomarkers specifically for t-MDS/AML to develop a viable risk assessment tool for this subgroup of patients. When it comes to cancer survivorship, we urge the current professional societies, *e.g*., NCCN (National Comprehensive Cancer Network), ASCO (American Society of Clinical Oncology), and ESMO (European Society for Medical Oncology) to consider screening the at-risk population of cancer survivors for t-MDS/AML, at least with a complete blood count with peripheral smear annually, which is a relatively simple and economically feasible option for screening for t-MDS/AML.

Lastly, most of the large randomized studies in the arena of AML and MDS have traditionally excluded t-MDS/AML and thus prospective phase III data for t-MDS/AML with regards to outcomes is absent. It is imperative that the prospective clinical trials be conducted specifically for t-MDS/AML to delineate optimum treatment options. The cancer community has accomplished a lot in the past five decades in alleviating the burden of cancer by improvements in both radiation and chemotherapy fields, and currently efforts on personalized or individualized medicine are looking very promising for further improvements in decreasing cancer mortality. However, as the cancer survivors are living longer[107,108], the incidence of t-MDS/AML continues to increase and currently is one of the fastest growing cancers in the United States. Efforts must be made by clinicians and researchers globally for establishment of risk reduction strategies for this fatal cancer.

**REFERENCES**

1 **Travis LB**, Holowaty EJ, Bergfeldt K, Lynch CF, Kohler BA, Wiklund T, Curtis RE, Hall P, Andersson M, Pukkala E, Sturgeon J, Stovall M. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. *N Engl J Med* 1999; **340**: 351-357 [PMID: 9929525 DOI: 10.1056/NEJM199902043400504]

2 **Curtis RE**, Boice JD, Stovall M, Bernstein L, Greenberg RS, Flannery JT, Schwartz AG, Weyer P, Moloney WC, Hoover RN. Risk of leukemia after chemotherapy and radiation treatment for breast cancer. *N Engl J Med* 1992; **326**: 1745-1751 [PMID: 1594016 DOI: 10.1056/NEJM199206253262605]

3 **Travis LB**, Andersson M, Gospodarowicz M, van Leeuwen FE, Bergfeldt K, Lynch CF, Curtis RE, Kohler BA, Wiklund T, Storm H, Holowaty E, Hall P, Pukkala E, Sleijfer DT, Clarke EA, Boice JD, Stovall M, Gilbert E. Treatment-associated leukemia following testicular cancer. *J Natl Cancer Inst* 2000; **92**: 1165-1171 [PMID: 10904090 DOI: 10.1093/jnci/92.14.1165]

4 **Bhatia S**, Krailo MD, Chen Z, Burden L, Askin FB, Dickman PS, Grier HE, Link MP, Meyers PA, Perlman EJ, Rausen AR, Robison LL, Vietti TJ, Miser JS. Therapy-related myelodysplasia and acute myeloid leukemia after Ewing sarcoma and primitive neuroectodermal tumor of bone: A report from the Children's Oncology Group. *Blood* 2007; **109**: 46-51 [PMID: 16985182 DOI: 10.1182/blood-2006-01-023101]

5 **Boivin JF**, Hutchison GB, Zauber AG, Bernstein L, Davis FG, Michel RP, Zanke B, Tan CT, Fuller LM, Mauch P. Incidence of second cancers in patients treated for Hodgkin's disease. *J Natl Cancer Inst* 1995; **87**: 732-741 [PMID: 7563150 DOI: 10.1093/jnci/87.10.732]

6 **Neglia JP**, Meadows AT, Robison LL, Kim TH, Newton WA, Ruymann FB, Sather HN, Hammond GD. Second neoplasms after acute lymphoblastic leukemia in childhood. *N Engl J Med* 1991; **325**: 1330-1336 [PMID: 1922234 DOI: 10.1056/NEJM199111073251902]

7 **Travis LB**, Curtis RE, Glimelius B, Holowaty E, Van Leeuwen FE, Lynch CF, Adami J, Gospodarowicz M, Wacholder S, Inskip P. Second cancers among long-term survivors of non-Hodgkin's lymphoma. *J Natl Cancer Inst* 1993; **85**: 1932-1937 [PMID: 8230284 DOI: 10.1093/jnci/85.23.1932]

8 **Granfeldt Østgård LS**, Medeiros BC, Sengeløv H, Nørgaard M, Andersen MK, Dufva IH, Friis LS, Kjeldsen E, Marcher CW, Preiss B, Severinsen M, Nørgaard JM. Epidemiology and Clinical Significance of Secondary and Therapy-Related Acute Myeloid Leukemia: A National Population-Based Cohort Study. *J Clin Oncol* 2015; **33**: 3641-3649 [PMID: 26304885 DOI: 10.1200/JCO.2014.60.0890]

9 **Morton LM**, Dores GM, Tucker MA, Kim CJ, Onel K, Gilbert ES, Fraumeni JF, Curtis RE. Evolving risk of therapy-related acute myeloid leukemia following cancer chemotherapy among adults in the United States, 1975-2008. *Blood* 2013; **121**: 2996-3004 [PMID: 23412096 DOI: 10.1182/blood-2012-08-448068]

10 **Dores GM**, Devesa SS, Curtis RE, Linet MS, Morton LM. Acute leukemia incidence and patient survival among children and adults in the United States, 2001-2007. *Blood* 2012; **119**: 34-43 [PMID: 22086414 DOI: 10.1182/blood-2011-04-347872]

11 **Takeyama K**, Seto M, Uike N, Hamajima N, Ino T, Mikuni C, Kobayashi T, Maruta A, Muto Y, Maseki N, Sakamaki H, Saitoh H, Shimoyama M, Ueda R. Therapy-related leukemia and myelodysplastic syndrome: a large-scale Japanese study of clinical and cytogenetic features as well as prognostic factors. *Int J Hematol* 2000; **71**: 144-152 [PMID: 10745624]

12 **Bhatia S**. Therapy-related myelodysplasia and acute myeloid leukemia. *Semin Oncol* 2013; **40**: 666-675 [PMID: 24331189 DOI: 10.1053/j.seminoncol.2013.09.013]

13 **André M**, Henry-Amar M, Blaise D, Colombat P, Fleury J, Milpied N, Cahn JY, Pico JL, Bastion Y, Kuentz M, Nedellec G, Attal M, Fermé C, Gisselbrecht C. Treatment-related deaths and second cancer risk after autologous stem-cell transplantation for Hodgkin's disease. *Blood* 1998; **92**: 1933-1940 [PMID: 9731050]

14 **Govindarajan R**, Jagannath S, Flick JT, Vesole DH, Sawyer J, Barlogie B, Tricot G. Preceding standard therapy is the likely cause of MDS after autotransplants for multiple myeloma. *Br J Haematol* 1996; **95**: 349-353 [PMID: 8904891 DOI: 10.1046/j.1365-2141.1996.d01-1891.x]

15 **Howe R**, Micallef IN, Inwards DJ, Ansell SM, Dewald GW, Dispenzieri A, Gastineau DA, Gertz MA, Geyer SM, Hanson CA, Lacy MQ, Tefferi A, Litzow MR. Secondary myelodysplastic syndrome and acute myelogenous leukemia are significant complications following autologous stem cell transplantation for lymphoma. *Bone Marrow Transplant* 2003; **32**: 317-324 [PMID: 12858205 DOI: 10.1038/sj.bmt.1704124]

16 **Krishnan A**, Bhatia S, Slovak ML, Arber DA, Niland JC, Nademanee A, Fung H, Bhatia R, Kashyap A, Molina A, O'Donnell MR, Parker PA, Sniecinski I, Snyder DS, Spielberger R, Stein A, Forman SJ. Predictors of therapy-related leukemia and myelodysplasia following autologous transplantation for lymphoma: an assessment of risk factors. *Blood* 2000; **95**: 1588-1593 [PMID: 10688812]

17 **Milligan DW**, Ruiz De Elvira MC, Kolb HJ, Goldstone AH, Meloni G, Rohatiner AZ, Colombat P, Schmitz N. Secondary leukaemia and myelodysplasia after autografting for lymphoma: results from the EBMT. EBMT Lymphoma and Late Effects Working Parties. European Group for Blood and Marrow Transplantation. *Br J Haematol* 1999; **106**: 1020-1026 [PMID: 10520006 DOI: 10.1046/j.1365-2141.1999.01627.x]

18 **Vardiman JW**, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood* 2002; **100**: 2292-2302 [PMID: 12239137 DOI: 10.1182/blood-2002-04-1199]

19 **Karp JE**, Sarkodee-Adoo CB. Therapy-related acute leukemia. *Clin Lab Med* 2000; **20**: 71-81, ix [PMID: 10702897]

20 **Le Beau MM**, Albain KS, Larson RA, Vardiman JW, Davis EM, Blough RR, Golomb HM, Rowley JD. Clinical and cytogenetic correlations in 63 patients with therapy-related myelodysplastic syndromes and acute nonlymphocytic leukemia: further evidence for characteristic abnormalities of chromosomes no. 5 and 7. *J Clin Oncol* 1986; **4**: 325-345 [PMID: 3950675]

21 **Pedersen-Bjergaard J**, Philip P. Balanced translocations involving chromosome bands 11q23 and 21q22 are highly characteristic of myelodysplasia and leukemia following therapy with cytostatic agents targeting at DNA-topoisomerase II. *Blood* 1991; **78**: 1147-1148 [PMID: 1651134]

22 **Pedersen-Bjergaard J**, Andersen MK, Christiansen DH, Nerlov C. Genetic pathways in therapy-related myelodysplasia and acute myeloid leukemia. *Blood* 2002; **99**: 1909-1912 [PMID: 11877259 DOI: 10.1182/blood.V99.6.1909]

23 **Swerdlow SH**, Campo E, Harris NL. World Health Organization classification of tumours of haematopoietic and lymphoid tissues. IARC Press. Lyon, France, 2008

24 **Rowley JD**, Golomb HM, Vardiman JW. Nonrandom chromosome abnormalities in acute leukemia and dysmyelopoietic syndromes in patients with previously treated malignant disease. *Blood* 1981; **58**: 759-767 [PMID: 7272506]

25 **Drabløs F**, Feyzi E, Aas PA, Vaagbø CB, Kavli B, Bratlie MS, Peña-Diaz J, Otterlei M, Slupphaug G, Krokan HE. Alkylation damage in DNA and RNA--repair mechanisms and medical significance. *DNA Repair* (Amst) 2004; **3**: 1389-1407 [PMID: 15380096 DOI: 10.1016/j.dnarep.2004.05.004]

26 **Allan JM**, Travis LB. Mechanisms of therapy-related carcinogenesis. *Nat Rev Cancer* 2005; **5**: 943-955 [PMID: 16294218 DOI: 10.1038/nrc1749]

27 **Kaina B**, Christmann M, Naumann S, Roos WP. MGMT: key node in the battle against genotoxicity, carcinogenicity and apoptosis induced by alkylating agents. *DNA Repair* (Amst) 2007; **6**: 1079-1099 [PMID: 17485253 DOI: 10.1016/j.dnarep.2007.03.008]

28 **Sill H**, Olipitz W, Zebisch A, Schulz E, Wölfler A. Therapy-related myeloid neoplasms: pathobiology and clinical characteristics. *Br J Pharmacol* 2011; **162**: 792-805 [PMID: 21039422 DOI: 10.1111/j.1476-5381.2010.01100.x]

29 **Helleday T**, Petermann E, Lundin C, Hodgson B, Sharma RA. DNA repair pathways as targets for cancer therapy. *Nat Rev Cancer* 2008; **8**: 193-204 [PMID: 18256616 DOI: 10.1038/nrc2342]

30 **Richardson C**, Jasin M. Frequent chromosomal translocations induced by DNA double-strand breaks. *Nature* 2000; **405**: 697-700 [PMID: 10864328 DOI: 10.1038/35015097]

31 **Pedersen-Bjergaard J**, Daugaard G, Hansen SW, Philip P, Larsen SO, Rørth M. Increased risk of myelodysplasia and leukaemia after etoposide, cisplatin, and bleomycin for germ-cell tumours. *Lancet* 1991; **338**: 359-363 [PMID: 1713639 DOI: [10.1016/0140-6736(91)90490-G](http://dx.doi.org/10.1016/0140-6736%2891%2990490-G%22%20%5Ct%20%22_blank)]

32 **Nitiss JL**. Targeting DNA topoisomerase II in cancer chemotherapy. *Nat Rev Cancer* 2009; **9**: 338-350 [PMID: 19377506 DOI: 10.1038/nrc2607]

33 **Andersen MK**, Johansson B, Larsen SO, Pedersen-Bjergaard J. Chromosomal abnormalities in secondary MDS and AML. Relationship to drugs and radiation with specific emphasis on the balanced rearrangements. *Haematologica* 1998; **83**: 483-488 [PMID: 9676019]

34 **Pedersen-Bjergaard J**, Pedersen M, Roulston D, Philip P. Different genetic pathways in leukemogenesis for patients presenting with therapy-related myelodysplasia and therapy-related acute myeloid leukemia. *Blood* 1995; **86**: 3542-3552 [PMID: 7579462]

35 **Smith SM**, Le Beau MM, Huo D, Karrison T, Sobecks RM, Anastasi J, Vardiman JW, Rowley JD, Larson RA. Clinical-cytogenetic associations in 306 patients with therapy-related myelodysplasia and myeloid leukemia: the University of Chicago series. *Blood* 2003; **102**: 43-52 [PMID: 12623843 DOI: 10.1182/blood-2002-11-3343]

36 **Descatha A**, Jenabian A, Conso F, Ameille J. Occupational exposures and haematological malignancies: overview on human recent data. *Cancer Causes Control* 2005; **16**: 939-953 [PMID: 16132803 DOI: 10.1007/s10552-005-2301-3]

37 **Little JB**. Cellular, molecular, and carcinogenic effects of radiation. *Hematol Oncol Clin North Am* 1993; **7**: 337-352 [PMID: 8468269]

38 **Preston DL**, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T, Matsui T [corrected to Matsuo T]. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. *Radiat Res* 1994; **137**: S68-S97 [PMID: 8127953 DOI: [10.2307/3578893](http://dx.doi.org/10.2307/3578893%22%20%5Ct%20%22_blank)]

39 **Haddy N**, Le Deley MC, Samand A, Diallo I, Guérin S, Guibout C, Oberlin O, Hawkins M, Zucker JM, de Vathaire F. Role of radiotherapy and chemotherapy in the risk of secondary leukaemia after a solid tumour in childhood. *Eur J Cancer* 2006; **42**: 2757-2764 [PMID: 16965909 DOI: 10.1016/j.ejca.2006.05.034]

40 **Le Deley MC**, Suzan F, Cutuli B, Delaloge S, Shamsaldin A, Linassier C, Clisant S, de Vathaire F, Fenaux P, Hill C. Anthracyclines, mitoxantrone, radiotherapy, and granulocyte colony-stimulating factor: risk factors for leukemia and myelodysplastic syndrome after breast cancer. *J Clin Oncol* 2007; **25**: 292-300 [PMID: 17159192 DOI: 10.1200/JCO.2006.05.9048]

41 **Ojha RP**, Fischbach LA, Zhou Y, Felini MJ, Singh KP, Thertulien R. Acute myeloid leukemia incidence following radiation therapy for localized or locally advanced prostate adenocarcinoma. *Cancer Epidemiol* 2010; **34**: 274-278 [PMID: 20427255 DOI: 10.1016/j.canep.2010.04.003]

42 **Rassool FV**, Gaymes TJ, Omidvar N, Brady N, Beurlet S, Pla M, Reboul M, Lea N, Chomienne C, Thomas NS, Mufti GJ, Padua RA. Reactive oxygen species, DNA damage, and error-prone repair: a model for genomic instability with progression in myeloid leukemia? *Cancer Res* 2007; **67**: 8762-8771 [PMID: 17875717 DOI: 10.1158/0008-5472.CAN-06-4807]

43 **Bhatia R**, Van Heijzen K, Palmer A, Komiya A, Slovak ML, Chang KL, Fung H, Krishnan A, Molina A, Nademanee A, O'Donnell M, Popplewell L, Rodriguez R, Forman SJ, Bhatia S. Longitudinal assessment of hematopoietic abnormalities after autologous hematopoietic cell transplantation for lymphoma. *J Clin Oncol* 2005; **23**: 6699-6711 [PMID: 16170178 DOI: 10.1200/JCO.2005.10.330]

44 **Gilliland DG**, Gribben JG. Evaluation of the risk of therapy-related MDS/AML after autologous stem cell transplantation. *Biol Blood Marrow Transplant* 2002; **8**: 9-16 [PMID: 11846355 DOI: 10.1053/bbmt.2002.v8.pm11846355]

45 **Pedersen-Bjergaard J**, Andersen MK, Christiansen DH. Therapy-related acute myeloid leukemia and myelodysplasia after high-dose chemotherapy and autologous stem cell transplantation. *Blood* 2000; **95**: 3273-3279 [PMID: 10828005]

46 **Stone RM**. Myelodysplastic syndrome after autologous transplantation for lymphoma: the price of progress. *Blood* 1994; **83**: 3437-3440 [PMID: 8204870]

47 **CIBMTR**. Studies in progress: Risks and outcomes of therapy related myeloid neoplasms after autologous hematopoietic cell transplantation. Available from: URL: https://www.cibmtr.org/Studies/Observational/StudyLists/Pages/ObservationalStudy.aspx?OSID=a0JE000000cybOmMAI

48 **Ben-Yehuda D**, Krichevsky S, Caspi O, Rund D, Polliack A, Abeliovich D, Zelig O, Yahalom V, Paltiel O, Or R, Peretz T, Ben-Neriah S, Yehuda O, Rachmilewitz EA. Microsatellite instability and p53 mutations in therapy-related leukemia suggest mutator phenotype. *Blood* 1996; **88**: 4296-4303 [PMID: 8943866]

49 **Christiansen DH**, Andersen MK, Pedersen-Bjergaard J. Mutations with loss of heterozygosity of p53 are common in therapy-related myelodysplasia and acute myeloid leukemia after exposure to alkylating agents and significantly associated with deletion or loss of 5q, a complex karyotype, and a poor prognosis. *J Clin Oncol* 2001; **19**: 1405-1413 [PMID: 11230485]

50 **Horiike S**, Misawa S, Kaneko H, Sasai Y, Kobayashi M, Fujii H, Tanaka S, Yagita M, Abe T, Kashima K, Taniwaki M. Distinct genetic involvement of the TP53 gene in therapy-related leukemia and myelodysplasia with chromosomal losses of Nos 5 and/or 7 and its possible relationship to replication error phenotype. *Leukemia* 1999; **13**: 1235-1242 [PMID: 10450752 DOI: [10.1038/sj.leu.2401466](http://dx.doi.org/10.1038/sj.leu.2401466%22%20%5Ct%20%22_blank)]

51 **Blackburn EH**. Structure and function of telomeres. *Nature* 1991; **350**: 569-573 [PMID: 1708110 DOI: 10.1038/350569a0]

52 **Hackett JA**, Feldser DM, Greider CW. Telomere dysfunction increases mutation rate and genomic instability. *Cell* 2001; **106**: 275-286 [PMID: 11509177 DOI: 10.1016/S0092-8674(01)00457-3]

53 **Lange K**, Holm L, Vang Nielsen K, Hahn A, Hofmann W, Kreipe H, Schlegelberger B, Göhring G. Telomere shortening and chromosomal instability in myelodysplastic syndromes. *Genes Chromosomes Cancer* 2010; **49**: 260-269 [PMID: 19998444]

54 **Hake CR**, Graubert TA, Fenske TS. Does autologous transplantation directly increase the risk of secondary leukemia in lymphoma patients? *Bone Marrow Transplant* 2007; **39**: 59-70 [PMID: 17143301 DOI: 10.1038/sj.bmt.1705547]

55 **Ueda Y**, Calado RT, Norberg A, Kajigaya S, Roos G, Hellstrom-Lindberg E, Young NS. A mutation in the H/ACA box of telomerase RNA component gene (TERC) in a young patient with myelodysplastic syndrome. *BMC Med Genet* 2014; **15**: 68 [PMID: 24948335 DOI: 10.1186/1471-2350-15-68]

56 **Beauchamp-Nicoud A**, Feneux D, Bayle C, Bernheim A, Léonard C, Koscielny S, Tchernia G, Bourhis JH. Therapy-related myelodysplasia and/or acute myeloid leukaemia after autologous haematopoietic progenitor cell transplantation in a prospective single centre cohort of 221 patients. *Br J Haematol* 2003; **122**: 109-117 [PMID: 12823352 DOI: 10.1046/j.1365-2141.2003.04388.x]

57 **Chakraborty S**, Sun CL, Francisco L, Sabado M, Li L, Chang KL, Forman S, Bhatia S, Bhatia R. Accelerated telomere shortening precedes development of therapy-related myelodysplasia or acute myelogenous leukemia after autologous transplantation for lymphoma. *J Clin Oncol* 2009; **27**: 791-798 [PMID: 19124806 DOI: 10.1200/JCO.2008.17.1033]

58 **Kantarjian HM**, Estey EH, Keating MJ. Treatment of therapy-related leukemia and myelodysplastic syndrome. *Hematol Oncol Clin North Am* 1993; **7**: 81-107 [PMID: 7680643]

59 **Hoyle CF**, de Bastos M, Wheatley K, Sherrington PD, Fischer PJ, Rees JK, Gray R, Hayhoe FG. AML associated with previous cytotoxic therapy, MDS or myeloproliferative disorders: results from the MRC's 9th AML trial. *Br J Haematol* 1989; **72**: 45-53 [PMID: 2736242 DOI: 10.1111/j.1365-2141.1989.tb07650.x]

60 **Larson RA**, Wernli M, Le Beau MM, Daly KM, Pape LH, Rowley JD, Vardiman JW. Short remission durations in therapy-related leukemia despite cytogenetic complete responses to high-dose cytarabine. *Blood* 1988; **72**: 1333-1339 [PMID: 3167210]

61 **Godley LA**, Larson RA. Therapy-related myeloid leukemia. *Semin Oncol* 2008; **35**: 418-429 [PMID: 18692692 DOI: 10.1053/j.seminoncol.2008.04.012]

62 **Godley LA**, Njiaju UO, Green M, Weiner H, Lin S, Odenike O, Rich ES, Artz A, Van Besien K, Daugherty CK, Zhang Y, Le Beau MM, Stock W, Larson RA. Treatment of therapy-related myeloid neoplasms with high-dose cytarabine/mitoxantrone followed by hematopoietic stem cell transplant. *Leuk Lymphoma* 2010; **51**: 995-1006 [PMID: 20536346 DOI: 10.3109/10428191003763468]

63 **Beaumont M**, Sanz M, Carli PM, Maloisel F, Thomas X, Detourmignies L, Guerci A, Gratecos N, Rayon C, San Miguel J, Odriozola J, Cahn JY, Huguet F, Vekhof A, Stamatoulas A, Dombret H, Capote F, Esteve J, Stoppa AM, Fenaux P. Therapy-related acute promyelocytic leukemia. *J Clin Oncol* 2003; **21**: 2123-2137 [PMID: 12775738 DOI: 10.1200/JCO.2003.09.072]

64 **Pagana L**, Pulsoni A, Tosti ME, Avvisati G, Mele L, Mele M, Martino B, Visani G, Cerri R, Di Bona E, Invernizzi R, Nosari A, Clavio M, Allione B, Coser P, Candoni A, Levis A, Camera A, Melillo L, Leone G, Mandelli F. Clinical and biological features of acute myeloid leukaemia occurring as second malignancy: GIMEMA archive of adult acute leukaemia. *Br J Haematol* 2001; **112**: 109-117 [PMID: 11225603 DOI: 10.1046/j.1365-2141.2001.02527.x]

65 **Borthakur G**, Lin E, Jain N, Estey EE, Cortes JE, O'Brien S, Faderl S, Ravandi F, Pierce S, Kantarjian H. Survival is poorer in patients with secondary core-binding factor acute myelogenous leukemia compared with de novo core-binding factor leukemia. *Cancer* 2009; **115**: 3217-3221 [PMID: 19441109 DOI: 10.1002/cncr.24367]

66 **Gustafson SA**, Lin P, Chen SS, Chen L, Abruzzo LV, Luthra R, Medeiros LJ, Wang SA. 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**: 647-655 [PMID: 19369623 DOI: 10.1309/AJCP5ETHDXO6NCGZ]

67 **Schnittger S**, Bacher U, Haferlach C, Kern W, Haferlach T. Rare CBFB-MYH11 fusion transcripts in AML with inv(16)/t(16; 16) are associated with therapy-related AML M4eo, atypical cytomorphology, atypical immunophenotype, atypical additional chromosomal rearrangements and low white blood cell count: a study on 162 patients. *Leukemia* 2007; **21**: 725-731 [PMID: 17287858 DOI: 10.1038/sj.leu.2404531]

68 **Litzow MR**, Tarima S, Pérez WS, Bolwell BJ, Cairo MS, Camitta BM, Cutler CS, de Lima M, Dipersio JF, Gale RP, Keating A, Lazarus HM, Luger S, Marks DI, Maziarz RT, McCarthy PL, Pasquini MC, Phillips GL, Rizzo JD, Sierra J, Tallman MS, Weisdorf DJ. Allogeneic transplantation for therapy-related myelodysplastic syndrome and acute myeloid leukemia. *Blood* 2010; **115**: 1850-1857 [PMID: 20032503 DOI: 10.1182/blood-2009-10-249128]

69 **Fenaux P**, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, Sanz G, List AF, Gore S, Seymour JF, Dombret H, Backstrom J, Zimmerman L, McKenzie D, Beach CL, Silverman LR. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. *J Clin Oncol* 2010; **28**: 562-569 [PMID: 20026804 DOI: 10.1200/JCO.2009.23.8329]

70 **Fenaux P**, Mufti GJ, Hellstrom-Lindberg E, Santini V, Finelli C, Giagounidis A, Schoch R, Gattermann N, Sanz G, List A, Gore SD, Seymour JF, Bennett JM, Byrd J, Backstrom J, Zimmerman L, McKenzie D, Beach C, Silverman LR. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; **10**: 223-232 [PMID: 19230772 DOI: 10.1016/S1470-2045(09)70003-8]

71 **Garcia-Manero G**, Huang X, Cabrero M, DiNardo CD, Pemmaraju N, Daver NG, Borthakur G, Wierda WG, Kadia T, Alvarado Y, Cortes JE. A bayesian phase II randomized trial of azacitidine versus Azacitidine Vorinostat in patients with newly diagnosed AML or high-risk MDS with poor performance status, organ dysfunction, or other comorbidities. *Blood* 2014; **124**: 3277

72 **Bally C**, Thépot S, Quesnel B, Vey N, Dreyfus F, Fadlallah J, Turlure P, de Botton S, Dartigeas C, de Renzis B, Itzykson R, Fenaux P, Adès L. Azacitidine in the treatment of therapy related myelodysplastic syndrome and acute myeloid leukemia (tMDS/AML): a report on 54 patients by the Groupe Francophone Des Myelodysplasies (GFM). *Leuk Res* 2013; **37**: 637-640 [PMID: 23499498 DOI: 10.1016/j.leukres.2013.02.014]

73 **Duong VH**, Lancet JE, Alrawi E, Al-Ali NH, Perkins J, Field T, Epling-Burnette PK, Zhang L, List AF, Komrokji RS. Outcome of azacitidine treatment in patients with therapy-related myeloid neoplasms with assessment of prognostic risk stratification models. *Leuk Res* 2013; **37**: 510-515 [PMID: 23332452 DOI: 10.1016/j.leukres.2012.12.012]

74 **Fianchi L**, Criscuolo M, Lunghi M, Gaidano G, Breccia M, Levis A, Finelli C, Santini V, Musto P, Oliva EN, Leoni P, Aloe Spiriti A, D'Alò F, Hohaus S, Pagano L, Leone G, Voso MT. Outcome of therapy-related myeloid neoplasms treated with azacitidine. *J Hematol Oncol* 2012; **5**: 44 [PMID: 22853048 DOI: 10.1186/1756-8722-5-44]

75 **Kantarjian H**, Issa JP, Rosenfeld CS, Bennett JM, Albitar M, DiPersio J, Klimek V, Slack J, de Castro C, Ravandi F, Helmer R, Shen L, Nimer SD, Leavitt R, Raza A, Saba H. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer* 2006; **106**: 1794-1803 [PMID: 16532500 DOI: 10.1002/cncr.21792]

76 **Steensma DP**, Baer MR, Slack JL, Buckstein R, Godley LA, Garcia-Manero G, Albitar M, Larsen JS, Arora S, Cullen MT, Kantarjian H. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. *J Clin Oncol* 2009; **27**: 3842-3848 [PMID: 19528372 DOI: 10.1200/JCO.2008.19.6550]

77 **Klimek VM**, Dolezal EK, Tees MT, Devlin SM, Stein K, Romero A, Nimer SD. Efficacy of hypomethylating agents in therapy-related myelodysplastic syndromes. *Leuk Res* 2012; **36**: 1093-1097 [PMID: 22608310 DOI: 10.1016/j.leukres.2012.04.025]

78 **Minoia C**, Sgherza N, Loseto G, Greco G, Buquicchio C, Merchionne F, Toldo C, Galise I, Melpignano A, Tarantini G, Pavone V, Guarini A. Azacitidine in the front-line treatment of therapy-related myeloid neoplasms: a multicenter case series. *Anticancer Res* 2015; **35**: 461-466 [PMID: 25550588]

79 **Prebet T**, Sun Z, Ketterling RP, Zeidan A, Greenberg P, Herman J, Juckett M, Smith MR, Malick L, Paietta E, Czader M, Figueroa M, Gabrilove J, Erba HP, Tallman MS, Litzow M, Gore SD. Azacitidine with or without Entinostat for the treatment of therapy-related myeloid neoplasm: further results of the E1905 North American Leukemia Intergroup study. *Br J Haematol* 2016; **172**: 384-391 [PMID: 26577691 DOI: 10.1111/bjh.13832]

80 **Prebet T**, Sun Z, Figueroa ME, Ketterling R, Melnick A, Greenberg PL, Herman J, Juckett M, Smith MR, Malick L, Paietta E, Czader M, Litzow M, Gabrilove J, Erba HP, Gore SD, Tallman MS. Prolonged administration of azacitidine with or without entinostat for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: results of the US Leukemia Intergroup trial E1905. *J Clin Oncol* 2014; **32**: 1242-1248 [PMID: 24663049 DOI: 10.1200/JCO.2013.50.3102]

81 **Friedberg JW**, Neuberg D, Stone RM, Alyea E, Jallow H, LaCasce A, Mauch PM, Gribben JG, Ritz J, Nadler LM, Soiffer RJ, Freedman AS. Outcome in patients with myelodysplastic syndrome after autologous bone marrow transplantation for non-Hodgkin's lymphoma. *J Clin Oncol* 1999; **17**: 3128-3135 [PMID: 10506609]

82 **Kröger N**, Brand R, van Biezen A, Zander A, Dierlamm J, Niederwieser D, Devergie A, Ruutu T, Cornish J, Ljungman P, Gratwohl A, Cordonnier C, Beelen D, Deconinck E, Symeonidis A, de Witte T. Risk factors for therapy-related myelodysplastic syndrome and acute myeloid leukemia treated with allogeneic stem cell transplantation. *Haematologica* 2009; **94**: 542-549 [PMID: 19278968 DOI: 10.3324/haematol.2008.000927]

83 **Mauritzson N**, Albin M, Rylander L, Billström R, Ahlgren T, Mikoczy Z, Björk J, Strömberg U, Nilsson PG, Mitelman F, Hagmar L, Johansson B. Pooled analysis of clinical and cytogenetic features in treatment-related and de novo adult acute myeloid leukemia and myelodysplastic syndromes based on a consecutive series of 761 patients analyzed 1976-1993 and on 5098 unselected cases reported in the literature 1974-2001. *Leukemia* 2002; **16**: 2366-2378 [PMID: 12454741 DOI: [10.1038/sj.leu.2402713](http://dx.doi.org/10.1038/sj.leu.2402713%22%20%5Ct%20%22_blank)]

84 **Schoch C**, Kern W, Schnittger S, Hiddemann W, Haferlach T. Karyotype is an independent prognostic parameter in therapy-related acute myeloid leukemia (t-AML): an analysis of 93 patients with t-AML in comparison to 1091 patients with de novo AML. *Leukemia* 2004; **18**: 120-125 [PMID: 14586477 DOI: 10.1038/sj.leu.2403187]

85 **Witherspoon RP**, Deeg HJ. Allogeneic bone marrow transplantation for secondary leukemia or myelodysplasia. *Haematologica* 1999; **84**: 1085-1087 [PMID: 10586209]

86 **Yakoub-Agha I**, de La Salmonière P, Ribaud P, Sutton L, Wattel E, Kuentz M, Jouet JP, Marit G, Milpied N, Deconinck E, Gratecos N, Leporrier M, Chabbert I, Caillot D, Damaj G, Dauriac C, Dreyfus F, François S, Molina L, Tanguy ML, Chevret S, Gluckman E. 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**: 963-971 [PMID: 10694545]

87 **Chang C**, Storer BE, Scott BL, Bryant EM, Shulman HM, Flowers ME, Sandmaier BM, Witherspoon RP, Nash RA, Sanders JE, Bedalov A, Hansen JA, Clurman BE, Storb R, Appelbaum FR, Deeg HJ. 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**: 1379-1387 [PMID: 17488876 DOI: 10.1182/blood-2007-02-076307]

88 **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**: 2134-2141 [PMID: 11304765]

89 **Kern W**, Haferlach T, Schnittger S, Hiddemann W, Schoch C. Prognosis in therapy-related acute myeloid leukemia and impact of karyotype. *J Clin Oncol* 2004; **22**: 2510-2511 [PMID: 15197216 DOI: 10.1200/JCO.2004.99.301]

90 **Armand P**, Kim HT, DeAngelo DJ, Ho VT, Cutler CS, Stone RM, Ritz J, Alyea EP, Antin JH, Soiffer RJ. Impact of cytogenetics on outcome of de novo and therapy-related AML and MDS after allogeneic transplantation. *Biol Blood Marrow Transplant* 2007; **13**: 655-664 [PMID: 17531775 DOI: 10.1016/j.bbmt.2007.01.079]

91 **Zahid MF**, Rizzieri DA. Haploidentical Hematopoietic Stem Cell Transplantation: Expanding the Horizon for Hematologic Disorders. *Adv Hematol* 2016; **2016**: 1423493 [PMID: 26949395 DOI: 10.1155/2016/1423493]

92 **Anderson JE**, Gooley TA, Schoch G, Anasetti C, Bensinger WI, Clift RA, Hansen JA, Sanders JE, Storb R, Appelbaum FR. Stem cell transplantation for secondary acute myeloid leukemia: evaluation of transplantation as initial therapy or following induction chemotherapy. *Blood* 1997; **89**: 2578-2585 [PMID: 9116305]

93 **Spina F**, Alessandrino PE, Milani R, Bonifazi F, Bernardi M, Luksch R, Fagioli F, Formica C, Farina L. Allogeneic stem cell transplantation in therapy-related acute myeloid leukemia and myelodysplastic syndromes: impact of patient characteristics and timing of transplant. *Leuk Lymphoma* 2012; **53**: 96-102 [PMID: 21740299 DOI: 10.3109/10428194.2011.603445]

94 **Döhner H**, Estey EH, Amadori S, Appelbaum FR, Büchner T, Burnett AK, Dombret H, Fenaux P, Grimwade D, Larson RA, Lo-Coco F, Naoe T, Niederwieser D, Ossenkoppele GJ, Sanz MA, Sierra J, Tallman MS, Löwenberg B, Bloomfield CD. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood* 2010; **115**: 453-474 [PMID: 19880497 DOI: 10.1182/blood-2009-07-235358]

95 **Andersen MT**, Andersen MK, Christiansen DH, Pedersen-Bjergaard J. NPM1 mutations in therapy-related acute myeloid leukemia with uncharacteristic features. *Leukemia* 2008; **22**: 951-955 [PMID: 18273044 DOI: 10.1038/leu.2008.17]

96 **Au WY**, Fung AT, Ma ES, Liang RH, Kwong YL. Low frequency of FLT3 gene internal tandem duplication and activating loop mutation in therapy-related acute myelocyticleukemia and myelodysplastic syndrome. *Cancer Genet Cytogenet* 2004; **149**: 169-172 [PMID: 15036894 DOI: 10.1016/j.cancergencyto.2003.07.007]

97 **Abruzzese E**, Buss D, Rainer R, Pettenati MJ, Rao PN. Progression of a myelodysplastic syndrome to pre-B acute lymphoblastic leukemia: a case report and cell lineage study. *Ann Hematol* 1996; **73**: 35-38 [PMID: 8695722 DOI: [10.1007/s002770050197](http://dx.doi.org/10.1007/s002770050197%22%20%5Ct%20%22_blank)]

98 **Lillington DM**, Micallef IN, Carpenter E, Neat MJ, Amess JA, Matthews J, Foot NJ, Young BD, Lister TA, Rohatiner AZ. Detection of chromosome abnormalities pre-high-dose treatment in patients developing therapy-related myelodysplasia and secondary acute myelogenous leukemia after treatment for non-Hodgkin's lymphoma. *J Clin Oncol* 2001; **19**: 2472-2481 [PMID: 11331326]

99 **Kohlmann A**, Bacher U, Schnittger S, Haferlach T. Perspective on how to approach molecular diagnostics in acute myeloid leukemia and myelodysplastic syndromes in the era of next-generation sequencing. *Leuk Lymphoma* 2014; **55**: 1725-1734 [PMID: 24144312 DOI: 10.3109/10428194.2013.856427]

100 **Mach-Pascual S**, Legare RD, Lu D, Kroon M, Neuberg D, Tantravahi R, Stone RM, Freedman AS, Nadler LM, Gribben JG, Gilliland DG. Predictive value of clonality assays in patients with non-Hodgkin's lymphoma undergoing autologous bone marrow transplant: a single institution study. *Blood* 1998; **91**: 4496-4503 [PMID: 9616144]

101 **Li L**, Li M, Sun C, Francisco L, Chakraborty S, Sabado M, McDonald T, Gyorffy J, Chang K, Wang S, Fan W, Li J, Zhao LP, Radich J, Forman S, Bhatia S, Bhatia R. Altered hematopoietic cell gene expression precedes development of therapy-related myelodysplasia/acute myeloid leukemia and identifies patients at risk. *Cancer Cell* 2011; **20**: 591-605 [PMID: 22094254 DOI: 10.1016/j.ccr.2011.09.011]

102 **Braggio E**, Egan JB, Fonseca R, Stewart AK. Lessons from next-generation sequencing analysis in hematological malignancies. *Blood Cancer J* 2013; **3**: e127 [PMID: 23872706 DOI: 10.1038/bcj.2013.26]

103 **Klco JM**, Miller CA, Griffith M, Petti A, Spencer DH, Ketkar-Kulkarni S, Wartman LD, Christopher M, Lamprecht TL, Helton NM, Duncavage EJ, Payton JE, Baty J, Heath SE, Griffith OL, Shen D, Hundal J, Chang GS, Fulton R, O'Laughlin M, Fronick C, Magrini V, Demeter RT, Larson DE, Kulkarni S, Ozenberger BA, Welch JS, Walter MJ, Graubert TA, Westervelt P, Radich JP, Link DC, Mardis ER, DiPersio JF, Wilson RK, Ley TJ. Association Between Mutation Clearance After Induction Therapy and Outcomes in Acute Myeloid Leukemia. *JAMA* 2015; **314**: 811-822 [PMID: 26305651 DOI: 10.1001/jama.2015.9643]

104 **Genovese G**, Kähler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoum SF, Chambert K, Mick E, Neale BM, Fromer M, Purcell SM, Svantesson O, Landén M, Höglund M, Lehmann S, Gabriel SB, Moran JL, Lander ES, Sullivan PF, Sklar P, Grönberg H, Hultman CM, McCarroll SA. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med* 2014; **371**: 2477-2487 [PMID: 25426838 DOI: 10.1056/NEJMoa1409405]

105 **Jaiswal S**, Fontanillas P, Flannick J, Manning A, Grauman PV, Mar BG, Lindsley RC, Mermel CH, Burtt N, Chavez A, Higgins JM, Moltchanov V, Kuo FC, Kluk MJ, Henderson B, Kinnunen L, Koistinen HA, Ladenvall C, Getz G, Correa A, Banahan BF, Gabriel S, Kathiresan S, Stringham HM, McCarthy MI, Boehnke M, Tuomilehto J, Haiman C, Groop L, Atzmon G, Wilson JG, Neuberg D, Altshuler D, Ebert BL. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med* 2014; **371**: 2488-2498 [PMID: 25426837 DOI: 10.1056/NEJMoa1408617]

106 **Churpek JE**, Marquez R, Neistadt B, Claussen K, Lee MK, Churpek MM, Huo D, Weiner H, Bannerjee M, Godley LA, Le Beau MM, Pritchard CC, Walsh T, King MC, Olopade OI, Larson RA. Inherited mutations in cancer susceptibility genes are common among survivors of breast cancer who develop therapy-related leukemia. *Cancer* 2016; **122**: 304-311 [PMID: 26641009 DOI: 10.1002/cncr.29615]

107 **de Moor JS**, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, Forsythe L, Scoppa S, Hachey M, Rowland JH. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomarkers Prev* 2013; **22**: 561-570 [PMID: 23535024 DOI: 10.1158/1055-9965.EPI-12-1356]

108 **Herrmann C**, Cerny T, Savidan A, Vounatsou P, Konzelmann I, Bouchardy C, Frick H, Ess S. Cancer survivors in Switzerland: a rapidly growing population to care for. *BMC Cancer* 2013; **13**: 287 [PMID: 23764068 DOI: 10.1186/1471-2407-13-287]

109 **Oken MM**, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, Carbone PP. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; **5**: 649-655 [PMID: 7165009]

110 **Sorror ML**. How I assess comorbidities before hematopoietic cell transplantation. *Blood* 2013; **121**: 2854-2863 [PMID: 23355537 DOI: 10.1182/blood-2012-09-455063]

**P-Reviewer:** Guo ZS, Moschovi MA **S-Editor:** Ji FF **L-Editor: E-Editor:**



**Figure 1 Algorithmic approach to patients with therapy-related myeloid neoplasms.** 1Oken *et al*[109]; 2Sorror[110]; 3Litzow *et al*[68]. ECOG: Eastern Cooperative Oncology Group; APL: Acute promyelocytic leukemia; ATRA: All-*trans* retinoic acid; HiDAC: High-dose cytarabine; HCT-CI: Hematopoietic cell transplant-co-morbidity index.