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

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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 into reduced incidence, early detection and timely treatment.

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

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Core tip: Therapy-related myeloid neoplasms are becom-
ing 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.

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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 sequela 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, and 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[21,22].

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[22].

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[24]. 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[25,26]. 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[26]. 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 topoisomerase enzymes 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 topoisomerase II) DNA breaks. The release of topoisomerases from the DNA strands is followed by the re-ligating of these transient DNA breaks[28]. 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[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 study LE14-01 is the largest retrospective study to date (to the best of 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, whereas 27%-50% of patients with t-MDS/AML demonstrate p53 mutations[46-50]. 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[53,56,57]. 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-MDS/AML. Other studies[56,58] 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 these rates are lower and short-lived in comparison to de novo MDS/
AML. The fatal course of t-MDS/AML is due to profound and persistent cytophenias due to ineffective hematopoiesis regardless of the fraction of immature blasts accumulating in the bone marrow. In contrast, a subsequent study reported a surprisingly high CR rate of 82% for t-MDS/AML treated with high-dose cytarabine + mitoxantrone.

For therapy-related acute promyelocytic leukemia (t-APL) and t-AML with good-risk cytogenetics, specifically inv(16) and t(8;21), induction chemotherapy is recommended, similar to the treatment guidelines for their de novo counterparts. For t-APL, outcomes are encouraging with regimens containing all-trans retinoic acid, as evidenced by two large European studies. One study reported a CR rate of 87%. The other study reported a CR rate of 80% with actuarial survival of 59% at 8 years. Since outcomes with non-transplant strategies are encouraging in t-APL, 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). 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. 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.

Role of hypomethylating agents in therapy-related myeloid neoplasms

With suboptimal 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 in this subset of patients. Azacitidine has shown promising efficacy in the treatment of high-risk MDS and AML with a limited side effect profile and impressive tolerability, especially in patients with poor performance status and comorbidities. 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. Azacitidine yielded the most benefit and better overall survival when used as first-line therapy. Detailed analysis of these studies showed similar outcomes between patients with de novo MDS/AML and those with t-MDS/AML. 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 and DACE-020) was published by Klimek et al. In a cohort of 42 patients with t-MDS, this account reported an overall response rate (CR + marrow CR + hematologic response) of 38%. 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%).

Prebet et al. 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. A predecessor of the same study demonstrated pharmacologic antagonism of entinostat when added to azacitidine. 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.

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. 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. One study reporting outcomes of 461 patients estimated a 35% overall survival 3 years after allo-HSCT. 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%. Other studies have also reported poor outcomes, with non-relapse mortality ranging between 54%-58%. 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., 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/
RELATED MYELOID NEOPLASMS

Gauging the risk of therapy-related myeloid neoplasms

Keeping in mind the poor outcomes of t-MDS/AML, mea-
sures for early detection of this disorder would allow for timely and pre-emptive treatment approaches, such as reduced intensity conditioning 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. 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). 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.

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). 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-HSCT. In another study, FISH identified abnormal cell clones in 20 out of 20 patients who went on to develop t-MDS/AML.

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.

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. 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 (NGS).

However, prospective studies with large numbers of patients are needed to validate the clinical utility of these methods.
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 normal 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 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., National Comprehensive Cancer Network, American Society of Clinical Oncology, and 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 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 current 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 worldwide. 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, Andersson M, Pukkala E, Stovall M. Risk of leukemia after platinum-based chemotherapy for ovarian cancer. N Engl J Med 1993; 328: 140: 351-357 [PMID: 9929525 DOI: 10.1056/NEJM199204034005045]

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, Stellner DT, Clarke EA, Boice JD, Stovall M, Gilbert E. Treatment-associated leukemia following testicular cancer. J Natl Cancer Inst 2000; 92: 1165-1171 [PMID: 10904060 DOI: 10.1093/jnci/92.14.1165]

4 Bhatia S, Kraal MD, Chen Z, Burden L, Askin FB, Dickman PS, Grier HE, Link MP, Meyers PA, Perlman EJ, Rauser 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-2006-01-233011]

5 Boivin JF, Hutchison GB, Zaufer 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, Ruyman FB, Sather HN, Hammond GD. Second neoplasms after acute lymphoblastic leukemia in childhood. N Engl J Med 1991; 325: 1330-1336 [PMID: 1922224 DOI: 10.1056/NEJM199111073251902]

7 Travis LB, Curtis RE, Glimeilus B, Holowaty E, Van Leeuwen FE, Lynch CF, Adamu J, Gospodarowicz M, Wacholder S, Inskip P. Second cancer risk after autologous stem cell transplantation for multiple myeloma. Br J Haematol 1996; 95: 349-353 [PMID: 8904891 DOI: 10.1046/j.1365-2141.1996.801-1891.x]

8 Howe R, McAlifee IN, Inwards DJ, Ansell SM, Demadow GW, Consienzer 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]

9 Krishnan A, Bhatia S, Slovak ML, Arber DA, Nadelman IC, Fung H, Bhatia R, Kashyap A, Molina A, O’ Donnell MR, Parker PA, Sniecinski I, Snyder DS, Spielberg 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]

10 Milligan DW, Ruiz De Elvira MC, Kolb JJ, Goldstone AH, Meloni G, Rohlattin AZ, Colombo 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]

11 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]

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

13 Le Beau MM, Albin 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]

14 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]

15 Pedersen-Bjergaard J, Andersson 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]

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

17 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]

18 Drablus F, Feyzi E, Aas PA, Vaagbo 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]

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

20 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]

21 Sili H, Olipitz W, Zebisch A, Schulz E, Wöfler 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]

22 Helldeay 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]

Richardson C, Jasin M. Frequent chromosomal translocations induced by DNA double-strand breaks. Nature 2000; 405: 697-700 [PMID: 10864329 DOI: 10.1038/35015097]

Pedersen-Bjergaard J, Daugaard G, Hansen SW, Philip P, Larsen SO, Rørth M. Increased risk of myelodysplasia and leukemias after etoposide, cisplatin, and bleomycin for germ-cell tumours. Lancet 1991; 338: 359-363 [PMID: 1713639 DOI: 10.1016/0140-6736(91)90490-G]

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

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]

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]

Smith SM, Le Beau MM, Hau 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 leukaemia: the University of Chicago series. Blood 2003; 102: 43-52 [PMID: 12623843 DOI: 10.1182/blood-2002-11-3343]

Descatha A, Jenabian A, Confo 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/s10552-005-0230-3]

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

Preston DL, Kusumi S, Tomonaga M, Izumi S, Ron E, Kuramoto A, Kamada N, Dohy H, Matsuo T, Matsui T [corrected to Matsuo A], Kamada N. Cancer incidence in atomic bomb survivors. Part III. Leukemia, lymphoma and multiple myeloma, 1950-1987. Radiat Res 1994; 137: 568-S97 [PMID: 8127953 DOI: 10.2307/3578893]

Haddy N, Le Deley MC, Saramand A, Dhalio I, Guirin 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: 2577-2564 [PMID: 16965909 DOI: 10.1016/ejca.2006.05.034]

Le Deley MC, Suzan F, Cutuli B, Delaplace S, Shamsaldin A, Linassier C, Clisant S, de Vathaire F, Fenaux P, Hill C. Anthracylean, 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.2006.09.0408]

Ojha RP, Fischbach LA, Zhou Y, Felini MJ, Singh KP, Thertulien M, Ojha RP, Fischbach LA, Zhou Y, Felini MJ, Singh KP, Thertulien M, Ojha RP, Fischbach LA, Zhou Y, Felini MJ, Singh KP, Thertulien M, Ojha RP, Fischbach LA, Zhou Y, Felini MJ, Singh KP, Thertulien M. Occupational exposures to cytotoxic therapy, MDS or myeloproliferative disorders: results from a single centre cohort of 221 patients. Br J Haematol 2003; 120: 109-117 [PMID: 12823352 DOI: 10.1046/j.1365-2411.2003.03438.x]

Chakraborty S, Sun CL, Francisco L, Sabado M, Li L, Chang KL, Horiike S, Horiike S, Horiike S, Horiike S, Horiike S, Horiike S, Horiike S, Horiike S. Survival of 5q, a complex karyotype, and a poor prognosis. J Clin Oncol 2001; 19: 1405-1413 [PMID: 11230485]

Horiike S, Misawa S, Kaneko H, Sasaki Y, Kobayashi M, Fuji 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]

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

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]

Langé K, Holm L, Nang Nielsen K, Hahn A, Hoffmann W, Kreipe H, Schlegelberger B, Göring H. Telomere shortening and chromosomal instability in myelodysplastic syndromes. Genes Chromosomes Cancer 2010; 49: 260-269 [PMID: 19998444]

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

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 gene (TERC) is a germline in a young patient with myelodysplastic syndrome. BMC Med Genet 2014; 15: 68 [PMID: 24948335 DOI: 10.1186/1471-2350-15-68]

Beauchamp-Nicoud A, Feneux D, Bayle C, Bernheim A, Léonard C, Koscielny S, Tchernia G, Bourhis JH. Therapy-related myeloid and myeloproliferative disorders after autologous hematopoietic cell transplantation in a prospective single centre cohort of 221 patients. Br J Haematol 2003; 120: 109-117 [PMID: 12823352 DOI: 10.1046/j.1365-2411.2003.03438.x]
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: 18092692 DOI: 10.1053/j.seminoncol.2008.04.002]
62 Godley LA, Nijjua 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: 20536646 DOI: 10.1080/10428194.2010.537453]
63 Beaumont M, Sanz M, Carli PM, Maloisel F, Thomas X, Detournay M, Guerri A, Griticos N, Rayon C, San Miguel J, Ondrizuola J, Cahn JY, Huguet F, Velkhao A, Stamatoulas A, Dombrret 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, Palusini A, Tosti ME, Avvisati G, Mele L, Mele M, Martinò B, Visani G, Cerri R, Di Bona E, Invernozi R, Nosari A, Clavio M, Allione B, Coser P, Canioni A, Levis A, Camera A, Mellilo L, Leone G, Mandelli F. Clinical and biological features of acute myeloid leukemia occurring as second malignancy: GIMEMA archive of adult acute leukaemia. Br J Haematol 2001; 112: 109-117 [PMID: 11225603 DOI: 10.1046/j.1365-2451.2001.02527.x]
65 Borthakur G, Lin E, Jain N, Estey EE, Cortes JE, O’Brien S, Fader S, Ravandi F, Pierce S, Kantarjian H. Survival is poorer in patients with secondary core-ribinding factor acute myelogenous leukemia compared with de novo core-ribinding factor leukemia. Cancer 2009; 115: 3217-3221 [PMID: 19441109 DOI: 10.1002/cancer.23457]
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/AJCP5ETHDXO6NGCZ]
67 Schnitter S, Bacher U, Haferlach C, Kern W, Haferlach T. Rare CBFB-MYH11 fusion transcripts in AML with inv(16)/t(16; 16) share many features with de novo acute myeloid leukemia with t(8; 21) (q22; q22) but does not have a favorable outcome. Myelodysplasia-related changes: results of the US Leukemia Intergroup study. J Clin Oncol 2009; 27: 3842-3848 [PMID: 19528372 DOI: 10.1200/JCO.2008.19.6550]
68 Litzow MR, Tarima S, Pérez WS, Cairo MS, Camitta BM, Cutler CS, de Lima M, Dipersio JF, Gale RP, Keating A, Lazarus HM, Luerssens J, Marks DJ, 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: 1880-1887 [PMID: 20002503 DOI: 10.1182/blood-2009-10-249128]
69 Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Gattermann N, Germing U, Lennon C, List AF, Gore SD, Tallman MS, Stock W, Larson RA. Therapy-related myeloid neoplasm: further results of the E1905 North American Leukemia Intergroup study. Haematologica 2016; 101: 1177-1185 [PMID: 26922325 DOI: 10.1182/hematol.2015.08.04614]
70 Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Finelli C, Giagounidis A, Schoch R, Gattermann N, Sanz M, List AF, Gore SD, Seymour JF, Bennett JM, Byrd J, Backstrom J, Zimmerman H, Detourmignies L, Guerci A, Gratecos N, Rayon C, San Miguel J, Ondricek J, Cahn JY, Huguet F, Velkhao A, Stamatoulas A, Dombrret 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]
71 Garcia-Manero G, Huang X, Cabrero M, DiNardo CD, Pavone V, Guarnier A, Azacitidine in the front-line treatment of therapy-related myeloid neoplasms: a multicenter case series. Anticancer Res 2015; 35: 461-466 [PMID: 25550588]
72 Prebet T, Sun Z, Ketterling RP, Zeidan A, Greenberg P, Herman J, Juckett M, Smith MR, Malicke L, Paietta E, Czader M, Figueroa M, Gabrilove J, Erba HP, Tallman MS, Litzow M, Gore SD. Azacitidine with or without Ensitinet for the treatment of therapy-related myelodysplastic syndrome: further results of the E1905 North American Leukemia Intergroup study. Br J Haematol 2016; 172: 384-391 [PMID: 26577691 DOI: 10.1111/bjh.13832]
73 Prebet T, Sun Z, Figueroa ME, Ketterling R, Melnick A, Greenberg PL, Herman J, Juckett M, Smith MR, Malicke L, Paietta E, Czader M, Litzow M, Gabrilove J, Erba HP, Gore SD, Tallman MS. Prolonged administration of azacitidine with or without ensitinet 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]
74 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: 10566609]
75 Kröger N, Brand R, van Biezen A, Zanetta 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: 19278951 DOI: 10.3324/haematol.2009.009227]
leukemia with uncharacteristic features. Leukemia 2008; 22: 951-955 [PMID: 18273044 DOI: 10.1038/leu.2008.17]
96 Au WY, Fung AF, Ma ES, Liang RH, Wong YL. Low frequency of FLT3 gene internal tandem duplication and activating loop mutation in therapy-related myeloid neoplasms. Cancer Genet Cytogenet 2004; 149: 169-172 [PMID: 15036894 DOI: 10.1016/j.cancergeneto.2003.07.007]
97 Abuzzahab 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]
98 Lillington DM, Micallef IN, Carpenter E, Neat MJ, Amess JA, Matthews I, Foot NJ, Young BD, Lister TA, Rottonari 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, Schnittert 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: 24413432 DOI: 10.1080/10428193.2013.856427]
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, Gyoryffy J, Chang K, Wang S, Fan W, Li J, Zhao LP, Radich J, Forman S, Bhata S, Bhata 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 Kclo 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, Grubert TA, Westervelt P, Radich JP, Link DC, Mardis ER, O’Connor 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, Kahler AK, Handsaker RE, Lindberg J, Rose SA, Bakhoun SF, Chambert K, Mick E, Neale BM, Fromer M, Purcell SM, Savontaus O, Landen M, Hoglund M, Lehmann S, Gabriel SB, Moran JL, Lander ES, Sullivan PF, Sklar P, Grönhäg 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 F, Flannick J, Manning A, Grauman PV, Mar BG, Lindsley RC, Merril CH, Burt N, Chavez A, Higgins JM, Molchanov V, Kuo FC, Kluk MJ, Henderson B, Kinnunen L, Koistinen HA, Ladenvall C, Gietz G, Correa A, Banahan BF, Gabriël S, Kathiresan S, Stringham HM, McCarthy MJ, Boehnke M, Tsoni Melito J, Haiman C, Grigoryev I, Wilson RK, Ley TJ. Association between next-generation sequencing and cancer risk. Blood Cancer J 2014; 4: 449-459 [PMID: 25426837 DOI: 10.1056/NEJMoa1408617]
106 Churpek JE, Marquez R, Neistadt B, Claussen K, Lee MK, Churpek MM, Hao D, Weiner H, Bannejee 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, Eas 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]
