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Review Article

A focused review of hematopoietic neoplasms occurring in the therapy-related setting

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Abstract: Hematological neoplasms developed in patients with a history of cytotoxic therapies comprise a group of diseases with a poor clinical outcome, and collectively categorized as "therapy-related myeloid neoplasms" (t-MN) in the 2008 World Health Organization (WHO) Classification. In recent years, numerous publications have emerged, and these studies have greatly expanded the scope of our understanding in this field. We here focused our review on several selected areas including secondary malignancies occurring in patients with autoimmune diseases; radiation therapy alone as a causative agent; the similarity and differences between therapy-related myelodysplastic syndromes (t-MDS) and acute myeloid leukemia (t-AML); clinical behavior and treatment outcome of t-AML patients with favorable cytogenetics; the incidence and clinical features of myelodysplastic/myeloproliferative neoplasms, as well as acute lymphoblastic leukemia and myeloproliferative neoplasms in patients with prior cytotoxic exposure. These recent studies have shown that therapy-related hematopoietic neoplasms are heterogeneous, and may manifest in various forms, more complex than we have recognized previously. Cytogenetic abnormalities and underlying mutations are likely to be the major factors dictating prognosis.

Keywords: Therapy-related myeloid neoplasm, autoimmune disease, myelodysplastic syndromes, acute myeloid leukemia, acute lymphoblastic leukemia, radiation, myelodysplastic/myeloproliferative neoplasm, myeloproliferative neoplasm

Introduction

Chemotherapeutic agents and ionizing radiation are well-recognized carcinogens, causing DNA damage through DNA double-strand breaks and loss of elements of the DNA mismatch repair system, resulting in consequent genomic instability [1, 2]. Hematopoietic neoplasms developed in patients who received chemotherapy/radiation for various malignancies or, rarely, for non-malignant diseases, have been recognized as late complications of cytotoxic therapy. This group of neoplasms carries high-risk karyotypes and confers to a poor prognosis in affected patients [3-5]. In the 2008 World Health Organization (WHO) Classification of Hematopoietic Neoplasms [6], the International Agency for Research on Cancer recognized the unique characteristics associated with these myeloid neoplasms and placed them under a separate category as therapy-related myeloid neoplasm (t-MN). t-MNs are often referred to therapy-related myelodysplastic syndromes (t-MDS) and therapy-related acute myeloid leukemia (t-AML). In recent years, great heterogeneity within t-MNs have been recognized; other forms of therapy-related hematopoietic neoplasms other than t-MDS and t-AML have been described, and more studies have looked into the role of causative agents in the pathogenesis of subsequent t-MNs. Here we review the recent studies in t-MN with specific focuses on above areas in order to expand our understanding and knowledge in this group of hematopoietic myeloid neoplasms.

Secondary malignancies in patients with autoimmune diseases

Recently, secondary myeloid neoplasms occurring in patients with autoimmune diseases (AD) have been increasingly recognized. A large population based study found that AD patients had significantly increased risk for AML and MDS [7], and this finding was subsequently confirmed by the study conducted by Kristinsson

and colleagues [8]. It has been known that AD and some MDS may be closely related in terms of pathogenesis, in which, increased release of inflammatory cytokines can trigger apoptosis of myeloid precursor cells with resultant cytopenias [9]. On the other hand, immunosuppressive therapy may be another contributing factor for development of secondary myeloid neoplasms. The treatment for AD includes non-steroid anti-inflammatory drugs (NSAID), corticosteroids, methotrexate, sulfasalazine, minocycline, azathioprine, cyclophosphamide and anti-tumor necrosis factor (TNF) agents. AD patients who received cyclophosphamide (an alkylating agent) or azathioprine (an antimetabolite) have shown significantly increased risk for hematological malignancies [10]. In general, chemotherapy agents implicated in t-MN can be categorized into different groups according to their mechanism of action. t-MN secondary to alkylating agents (such as melphalan, cyclophosphamide, cisplatin, dacarbazine and mitomycin D) is characterized by a latency of 3 to greater than 10 years, a preceding myelodysplastic phase, and deletions or loss of chromosomes 5 or 7 or both, often as part of complex karyotypes. Antimetabolites, such as fludarabine, azathioprine and 6-thioguanine, are also often used as immunosuppressant; and these agents could cause DNA double stand break and form highly mutagenic DNA bases similar to alkylating agents in theory. However, t-MN secondary to antimetabolite single-agent treatment is extremely uncommon [11-13], and the risk of t-MN only increases when antimetabolite is used in combination therapy with DNA-damaging agents, such as cyclophosphomide [13-16]. Mitoxantrone, a topoisomerase II inhibitor, has recently been reported to associate with secondary acute promyelocytic leukemia (APL) in patient with multiple sclerosis (MS) [17, 18]; and the susceptibility is likely linked to genetic variants in DNA repair and drug-metabolizing enzymes, such as *BRCA2, CXCCR5* and *CYP3A4,* that result in impaired detoxification of chemotherapy or inefficient repair of drug-induced genetic damage [19]. Interestingly, anti-TNF agents were recently reported to be associated with increased risk for myeloid neoplasms, and were labeled with "risk for malignancy" by the food and drug administration (FDA) [20]. It is noteworthy that AD patients who received immunosuppressive therapy other than cytotoxic agents and subsequently developed MDS/AML could be due to underlying genetic defects leading to increased susceptibility to MDS/AML [21]. Interestingly, a recent study by DiNardo C et al showed that the clinical course of AML occurring in AD patients was similar to de novo AML, better than t-AML; and the cytogenetic characteristics of AML developed in AD patients did not show frequent high-risk karyotypes like those seen in t-AML [22]. Nevertheless, when comes to label a case of MDS/AML occurring in patients with AD as "t-MDS/AML", the recommendation is to be extremely cautious when a direct causative relationship is difficult to prove; and to understand that AD patients often have increased inflammatory cytokines or may have genetic predisposition contributing to secondary malignancies [9].

Radiation as a causative agent for therapy-related myeloid neoplasms

The contribution of radiation (XRT) to carcinogenesis was recognized at the beginning of the twentieth century [23] with subsequent demonstration of a dose dependent relationship [24]. Exposure to ionizing radiation can cause DNA damages in a mechanism similar to alkylating agents; and radiation photon energy can also directly lead to DNA strand breakage. XRT is frequently used in conjunction with chemotherapy for cancer therapy, and only a few studies have specifically looked at the characteristics of myeloid neoplasms occurring after XRT alone [5, 25]. In addition, these published studies were conducted in patients treated with older XRT techniques, which often exposed large active hematopoietic marrow areas to XRT. In the past two decades, the field of radiation therapy has moved toward using more conformal treatment techniques that reduce the exposure of hematopoietic bone marrow [26, 27]. Recently, Nardi et al showed that t-MDS occurring in the modern radiation therapy era, if alone, was more close to de novo MDS/AML in cytogenetic characteristics and clinical behavior, and affected patients had better outcomes than patients with t-MDS secondary to chemotherapy [28]. Notably, a significant proportion of patients with t-MN post RXT alone had a normal karyotype in that series (43%). MDS post XRT alone had a low international prognostic score-revised (IPSS-R), likely attributing to a lower risk of karyotypic abnormalities seen in this group of patients [29]. It is likely

that in some patients, secondary MDS/AML occurring in patients treated with XRT could be coincidental, or simply reflect individual susceptibility to cancer. Radioiodine (I-131), a β emitter, induces chromosomal aberrations, theoretically, can lead to leukemogenesis. However, the occurrence of t-MDS/t-AML after radioiodine treatment for thyrotoxicosis and thyroid cancer has been considered to be rather uncommon, such cases had been reported only sporadically or often summarized under t-MDS/t-AML post radiation therapy [30, 31]. In a comprehensive review and meta-analysis of the currently available literature covering 16,502 patients with thyroid cancers, the relative risk for development of leukemia increased 2.5-fold in patients treated with radioiodine [31]. A more recent study indicated that MNs after radioiodine treatment was similar to other t-MN in terms of biological characteristics similar to those seen in patients with t-MN following other cytotoxic treatment modalities, associated with a low response rate to induction chemotherapy and a poor prognosis [32].

In summary, XRT alone has shown increased risk for secondary MDS/AML in general; however, in some patients, the causative relationship may not be so clear, especially in the era of modern XRT technology. It has been shown that in t-MDS/AML, the cytogenetic abnormalities determine the course of the resulting t-MN regardless of prior therapy [3]. Treatment recommendations should be based on performance status and karyotype regardless the type of prior therapy [3, 33].

Therapy-related myelodysplastic syndromes versus therapy-related acute myeloid leukemia

Therapy-related MDS and AML comprise the vast majority of t-MN cases. In the 2008 WHO classification, t-MDS and t-AML are not considered sufficiently distinctively different and classified together under t-MN [6]. However, recent studies showed that these two entities differed in molecular genetic features and clinical outcomes. A German group investigated the differences between t-AML and t-MDS in a large cohort of patients [34] and found that t-AML patients had a higher white blood cell count (WBC), lower hemoglobin and platelet level, more frequent aberrant karyotypes and a worse overall survival (OS) than patients with t-MDS. In our previous study of t-MDS and oligoblastic AML [29], patients with a low blast count had a significant superior survival than patients with a blast count of 10-30%, and the prognostic power of blast count was independent of other risk factors.

For cases first manifest with overt t-AML without a preceding MDS phase, there are some distinct features. Patients often had prior topoisomerase II inhibitor therapy, with a shorter latency period (usually 1-5 years), and many of them were associated with balanced recurrent chromosomal translocations that frequently involved 11q23 (*MLL*) or 21q22 (*RUNX1*) [6]. An earlier study from the University of Chicago showed that majority of t-AML in their study group had 11q23 re-arrangement and all of them received topoisomerase II inhibitor [35]. The Copenhagen study also found *MLL* abnormality being the most frequent cytogenetic finding in the t-AML group [36]. Recurrent translocations, such as t(8;21); t(15;17); inv(16), also can be seen in t-AML (see later discussion). t-AML with *MLL* gene rearrangement often presents as acute monoblastic or myelomonocytic leukemia. Additionally, dysplastic features in t-AML may not be apparent.

At the mutation level, t-MDS/AML showed a high frequency of *TP53* gene mutation [37], and the mutation profile, when compared to other published data on de novo MDS/AML [38-40], was different. Notably, t-AML showed a higher frequency of *FLT3* and *NRAS/KRAS* mutations than t-MDS [41]. These findings suggest that *TP53* mutation may be heavily involved in the early pathogenesis of myeloid neoplasms post cytotoxic exposure, but mutations in other genes likely provide the proliferative advantage in cases of t-AML.

In summary, although sharing some overlapping features, t-MDS and t-AML exhibit differences not only in clinical presentation and survivals but also in molecular cytogenetic characteristics. Instead of being lumped together under t-MN, different sub-categorization may provide meaningful information in risk-adapted therapeutic approaches.

Therapy-related acute myeloid leukemia with favorable cytogenetics

t-AML with recurrent favorable translocations had been characterized in the literature. An

earlier study identified 106 cases of acute promyelocytic leukemia (t-APL) in patients received prior cytoxic therapy over a period of 20 years from multiple European countries; and these t-APL cases showed similar characteristics as *de novo* APL, and patients had good response to all-trans-retinoic acid (ATRA) therapy [42]. Yin and colleagues [43] reported 17 cases of t-APL from one single institute; similarly, these t-APL patients had good response to ATRA therapy. In addition, their study also reported frequent dyserythropoiesis, dysmegakaryopoiesis, *FLT3* mutation (43%) and frequent additional cytogenetic abnormalities (60%) in t-APL. The interval from prior cytotoxic therapy to APL was 40 months (17-116 months). t-APL was preferentially associated with a prior exposure to DNA topoisomerase II inhibitors [44-46]. Ottone and colleagues [47] conducted genomic sequence analysis in 12 t-APL and revealed the presence of hotspots at the DNA level on both *RARA* and *PML* sites, which were likely to be the preferential sites of topoisomerase II mediated DNA cleavage in the presence of its inhibitor that led to rearrangement of *PML/RARA*.

Therapy-related AML with t(8;21)/*RUNX1-RUNX1T1* are uncommon. An earlier review article summarized 26 such cases published in literature and concluded that these patients had very similar hematological characteristics and treatment response as *de novo* AML with t(8;21) [48]. The 2002 international workshop studied 72 cases of t-AML with 21q22 (*RNUX1* or *AML1*) rearrangement, and found that 44 of these cases were t(8;21) [49]; and patients with t(8;21) rearrangement had more favorable outcome than patients with other rearrangements involving 21q22. t-AML with t(8;21) exhibited substantial morphological dysplasia in their patients' bone marrow [50]. We studied [51] 13 patients of t-AML with t(8;21) from one single institution and compared them to 38 patients with de novo AML with t(8;21). Eleven of the 13 patients in our study group received topoisomerase II inhibitor containing chemotherapy. We showed that patients with therapy-related t(8;21) AML were older, appeared to have a higher frequency of *KIT 816D* mutations, and an inferior overall survival than their de novo counterparts. Recently, high frequencies of additional cytogenetic and molecular lesions have been reported in AML with t(8;21)/*RUNX1-RUNX1* rearrangement [52]. Mutations involving the *RAS* pathway, *KIT* and *ASXL1* mutations were the most frequent; and mutations in *KIT D816* and *ASXL1* were associated with adverse outcomes. At the chromosomal level, -Y appeared to be associate with a good prognosis whereas +8 with an inferior prognosis. In this large series of t(8;21)/*RUNX1-RUNX1*, 22 patients were considered to have t-AML. These 22 patients showed no differences in secondary molecular genetic events from 117 de novo AML. However, similar to our series of patients, an inferior outcome was observed in patients with t-AML. The authors proposed that screening respective mutations should be included in all patients at diagnosis of AML with t(8;21)/*RUNX1-RUNX1T1*, regardless therapy-related or de novo, in order to improve risk stratification and probably further personalized therapies.

Cases of t-AML with inv(16) were also reported in the literature. The international workshop in Chicago showed that t-AML with inv(16) was often associated with prior therapy with topoisomerase II inhibitors [46]. Response rates to intensive chemotherapy in this study were comparable to those with de novo disease. inv(16) is characterized by a reciprocal rearrangement of the *CBFB* gene on 16q22 and *MYH11* on 16p13. *CBFB-MYH11* fusion transcripts are heterogeneous, dependent on the exons of the *CBFB* and *MYH11* genes that are fused. The German group study showed that t-AML with inv(16) was associated with rare fusion transcripts other than the typical fusion type commonly seen in *de novo* AML [53]. t-AML with inv(16) showed a significantly shorter event free survival than de novo AML; however, the presence of these rare fusion transcripts had no clear independent prognostic impact. In general, secondary chromosomal aberrations as well as gene mutations are very frequent in AML with inv(16), 80-90% patients with inv(16) AML have at least one mutation involving *NRAS, KRAS, KIT*, and *FLT* [54-56]. In the German-Austrian AML Study Group (AMLSG) study [54], 12/176 (7%) patients were considered to be therapy-related; and the secondary chromosomal abnormalities and mutations were not significantly different from de novo AML. However, a therapy-related history was an independent adverse prognostic factor in the multivariate analysis, along with *FLT3* mutations, trisomy 22, trisomy 8 and an old age.

In summary, t-AML with favorable cytogenetics shows good response to conventional intensive therapy, similar to their de novo counterpart. Therefore, these patents should be encouraged to participate in prospective clinical trials that are appropriately designed for de novo AML patients with similar cytogenetic abnormalities [57]. However, compared to de novo counterparts, t-AML with favorable cytogenetics is associated with an inferior survival in affected patients, which is not explained by additional molecular genetic alterations. Rather, the inferior outcome could possibly attribute to comorbidities or in some cases, the persistence of their primary malignancy [51, 58].

Therapy-related myelodysplastic/myeloproliferative neoplasms

Of t-MNs, in contrast to well-characterized t-AML and t-MDS, data on therapy-related myelodysplastic/myeloproliferative neoplasm (MDS/MPN) is limited. Chronic myelomonocytic leukemia (CMML) comprises the largest subset of the MDS/MPNs, characterized by persistent absolute monocytosis ($\geq 1 \times 10^9$/L) in peripheral blood. In the review of the earlier literature, only 11 cases of t-CMML with detailed clinical, pathological and cytogenetic characteristics had been reported [59-65], and of the other studies, t-CMML was lumped together with t-MDS/AML under t-MN [32, 66]. Recently, Takahashi and colleagues studied 39 (11%) t-CMML patients and compared them to 319 de novo CMML diagnosed and treated at one single institution over a 10-year period [67]. In this study, t-CMML occurred about 6 to 7 years after exposure to cytotoxic chemotherapy or ionizing radiation; was associated with higher-risk cytogenetic abnormalities. A therapy-related history was an adverse factor for prognosis, independent of other co-variants including cytogenetic abnormalities. Notably, 15 (38%) of these patients had radiation exposure only, most for prostate cancer.

Other forms of MDS/MPN, including MDS/NPN-unclassifiable (MDS/MPN-U), or atypical chronic myeloid leukemia (aCML), are very uncommon in general, and therapy-related cases were even rare. In the study of t-MN post radioiodine by Schroeder et al, 1 out of the 39 cases was classified as MDS/MPN-U [32]. Takeshita et al reported a case of therapy-related-aCML after achieving complete remission from APL; and the aCML quickly underwent clonal evolution and transformed to CD56-positive AML [68]. In this case, NUP98 was partially translocated to chromosome 7 in the phase of aCML. Recently, we studied a total of 69 cases of MDS/MPN-U other than refractory anemia with ring sideroblasts with marked thrombocytosis (RARS-T) and 65 cases of aCML, collected from 7 large medical centers [69]. Ten (8%) patients had a prior history of cytotoxic exposure, including 4 patients received both chemotherapy and XRT, one chemotherapy only, and 5 XRT only. Karyotypical abnormalities as well as the overall survivals were not different from patients with de novo MDS/MPN-U or aCML. However, due to a low incidence of such cases, and the inherent heterogeneity within these entities, an accurate comparison was difficult. Instead, the prognosis of these patients was largely decided by WBC, platelet counts, peripheral blood immature myeloid cells and LDH levels, similar to their de novo counterpart aCML and MDS/MPN-U.

Acute lymphoblastic leukemia occurring in patients with prior cytotoxic therapy

Although the majority of therapy-related acute leukemia are of myeloid lineage, since the early 1990s, therapy-related B-cell acute lymphoblastic leukemia (t-B-ALL) has been reported [70]. However, the relationship of these ALL with prior cytotoxic therapy had been largely debatable. The Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) Archive of Adult Acute Leukemia from 62 Hematologic Divisions [71] reported that 21 out of 901 (2.3%) adult ALL patients in archive had a prior history of cancer. Notably, ten of these 21 patients did not receive chemoradiotherapy but surgery only for cancer. The study raised the question if the secondary ALL was a direct result of prior cytotoxic therapy, or simply occurred as a random event, or was related to familial predisposition to cancer. In 2001, a review article by Andersen et al summarized 23 cases of B-ALL with balanced translocations involving 11q23 following cytotoxic therapy sporadically published in literature [72]; and they found that all patients received at least one prior topoisomerase II inhibitor containing cancer therapy regimen, the median latency period was 24 months. Sixteen of these patients had t(4;11)(q21;q23), and the rest had

other translocations involving 11q23 (*MLL*). Later, Ishizawa S et al [73] reported 6 cases of therapy-related B-ALL from one single institute, and found that all the cases had *MLL* rearrangement and 4 of them had t(4;11)(q21;q23). All 6 cases had a pro-B cell immunophenotype (CD10 negative). In 2012, Racke et al reported two cases of ALL occurring after chemotherapy, one following treatment for diffuse large B cell lymphoma and one for pleomorphic sarcoma, and both showed complex karyotypic abnormalities and distinct *MLL* amplification by fluorescence in situ hybridization (FISH) [74]. The recent study from our group [75] reviewed 457 B-ALL patients diagnosed and treated at our institute, 30 (6%) patients had a history of cytotoxic therapy. t(4;11)(q21;q23) was highly associated with a prior topoisomerase II inhibitor exposure; whereas, a hypodiploidy with loss of chromosomes 5, 7, 17 was highly related to prior alkylating agent with or without topoisomerase II inhibitor therapy. In contrast, the incidence of Philadelphia chromosome+ B-ALL and B-ALL with a normal karyotype showed no difference between patients with or without a history of cytotoxic therapy, and such cases might be merely coincidental or reflect individual genetic susceptibility to cancer. Overall, B-ALL patients with a prior history of cytotoxic therapy were older, had a lower complete remission rate to induction chemotherapy and had a shorter overall survival. However, unlike t-MDS/AML, a history of prior therapy was not an independent factor with respect to survival. Nevertheless, our data indicated that secondary precursor B-ALL could be stratified by the current precursor B-ALL risk stratification system similar to de novo precursor B-ALL, and cytogenetic risk appeared to be the most important factor in predicting survival.

T-cell acute lymphoblastic leukemia (T-ALL) occurring in patients with a history of cytoxic exposure has been rarely reported. A case of T-ALL with 11q23 translocation involving *MLL* gene was reported in a 14-year old boy 4 years following multi-agent chemotherapy and XRT for primary hepatocellular carcinoma[76]. Two cases of T-ALL [77, 78] arising in patients with APL treated with all-trans-retinoic acid (ATRA) and chemotherapy were reported. One T-ALL case had a normal karyotype and another case a complex karyotype, but both were negative for *PML-RARA* fusion. Another case of T-ALL [79] was reported in a 56-year-old woman 3 years following treatment for AML FAB-M2. The T-ALL had a karyotype of 46,XX,+1,t(6;14)(q23;q11),+i(7)(q10),add(17)(p11), different from that of the original AML. In these reports, possible causes including therapy-related reasons, genetic susceptibility to leukemia, and environmental exposure were discussed. Although this entity is presumably rare, the true frequency of T-ALL occurring following aggressive multiagent chemotherapy remains unknown, and it may only be ascertained by careful follow-up of cancer survivors.

Myeloproliferative neoplasms (MPN) occurring in patients with prior chemoradiation therapy

Myeloproliferative neoplasm (MPN) is a clonal stem cell neoplasm characterized by proliferations of one or more hematopoietic cell lineages. MPN has an incidence of 6-10/100,000 in the general population. Interestingly, MPNs, as a large group of hematopoietic stem cell neoplasms, had not been studied or reported in the therapy-related setting and the possible role of prior therapy in patients who subsequently developed MPN is not clear. Notably, MPN was reported in petroleum workers with Benzene exposure [80]; however, the incidence was much lower than MDS occurring in such setting. Also, in contrast to MDS, MPN showed no dose-response relationships with Benzene. We recently searched the database at our institution. Of about 4000 MPN patients diagnosed from 2005-2012, only 9 patients (0.2%) had a history of chemoradiaion therapy for prior malignancies. The median interval from cytotoxic exposure to onset of MPN was 37 months. The clinicopathological features of these 9 patients were typical of the respective subtype of MPN: 3 cases of chronic myelogenous leukemia (CML), 2 cases of polycythemia vera (PV), 1 case of essential thrombocythemia (ET), 1 case of primary myelofibrosis (PMF), and 2 cases of MPN-unclassifiable. Cytogenetic data showed that none of these 9 patients had 5q-/-5, 7q-/-7, inv(3), 11q23 (*MLL*) abnormalities or a complex karyotype. The outcomes and survivals of these 9 patients (all alive with a median follow-up of 32 months) were similar to their respective MPN subtype without cytotoxic exposure. In our review, several cases were initially diagnosed with MPN, but reclassified as MDS with fibrosis or MDS/MPN in the follow-up BM samples. Notably, a distinction between MDS, MDS/MPN and MPN can be difficult, either due to the pres-

ence of significant myelofibrosis that made it difficult to assess dysplasia, and/or a positive *JAK2 V617F* study [81]. *JAK2 V617F* mutations can be seen in a subset of MDS and MDS/MPN, especially in cases with significant myelofibrosis [69, 82]. It is likely that if t-MNs show proliferative features, they would more of combined MPN and MDS features rather than MPN alone. In aggregates, these findings indicate that true MPN may not occur as a consequence of prior cytotoxic exposure, rather more likely represents a coincidence or reflects individual genetic susceptibility to cancer.

Summary

In this article, we reviewed recent literatures in hematopoietic neoplasms in the therapy-related setting and focused our discussion on several selected areas. Autoimmune diseases (AD) have been suggested to be causative agents for t-MN. Indeed, in some AD patients, the secondary hematopoietic malignancies can be attributed to cytotoxic drugs given for AD; however, in some cases that patients have received immunosuppressant only, a direct causative relationship is difficult to prove, rather, a result of genetic predisposition and/or inflammatory cytokines contributing to secondary malignancies is plausible. XRT with modern technology as a direct causative agent for t-MN has been challenged; however, one cannot deny that XRT has no risk for t-MN. In t-MN developed post XRT alone, cytogenetic abnormalities rather than the history likely determine the course of disease. t-AML with favorable recurrent cytogenetic abnormalities show similar responses to conventional therapy as their de novo counterparts and patients should be encouraged to participate in clinical trials designed for de novo AML patients with similar cytogenetic abnormalities. t-MDS and t-AML are the most well-recognized t-MNs. While sharing great overlapping features, t-AML and t-MDS are distinct from each other in clinical, bone marrow histology, cytogenetic and molecular characteristics, and may deserve different subcategories. Acute lymphoblastic leukemia can occur in the therapy-related setting, mostly associated with *MLL* gene rearrangement or a hypodiploidy with -5, -7 and -17. Cases of Philadelphia chromosome-positive ALL or ALL with a normal karyotype occur with a similar incidence in patients with or without a history of cytotoxic therapy, likely not a direct result of prior cytotoxic therapy. Therapy-related chronic myelomonocytic leukemia (CMML) carries high-risk cytogenetic abnormalities and confers to an inferior outcome, as compared to its de novo counterpart. Other forms of MDS/MPN, due to their rare occurrence, the clinicopathological features remain to be defined. Myeloproliferative neoplasm (MPN) developed in the patients with prior cytotoxic exposures may not be therapy-related, rather a coincidence or due to individual genetic susceptibility to cancer. Overall, therapy-related hematopoietic neoplasms can present in forms other than well-recognized t-MDS and t-AML. Although an inferior outcome observed in this group of patients are likely to be multifactorial, cytogenetic abnormalities and underlying mutations likely determine the outcomes of affected patients.

Disclosure of conflict of interest

None.

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