Therapy-related Acute Myelogenous Leukemia and Myelodysplastic Syndrome

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Therapy-related acute myelogenous leukemia and myelodysplastic syndrome (t-AML/MDS) are increasing in prevalence with aging of the population and improved survival of patients treated with chemotherapy or radiotherapy for other malignancies. Research focused on the pathogenesis of t-AML/MDS will provide insight into the pathogenesis of de novo AML/MDS. Participation in clinical trials should be encouraged for this patient population because results with available treatment options are clearly suboptimal.

Introduction

Most cases of acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) develop de novo without exposure to prior chemo- or radiotherapy. The incidence of therapy-related AML (t-AML)/MDS increases with age. A subtle distinction between t-AML and secondary AML is that diagnosis of secondary AML encompasses both t-AML and AML that develops through a phase of antecedent hematologic disorder or MDS.

The relevance of ongoing research in t-AML/MDS is threefold: 1) The incidence is increasing because of the aging of the population, and patients receiving chemotherapy are living longer; 2) the clinical outcome in t-AML/MDS is poorer than in de novo AML/MDS; and 3) because de novo and t-AML share molecular and cytogenetic abnormalities, important insights into the pathogenesis of AML/MDS can be gained.

Incidence

Approximately 15% of patients [1] with AML and MDS will have a history of chemo- or radiotherapy and are thus designated as having therapy-related AML or MDS (t-AML/MDS). The actuarial risk of developing t-AML/MDS after chemotherapy is about 1% per year beginning 2 to 3 years after chemotherapy and lasting for 5 to 7 years [2–4]. The frequency of t-AML/MDS following therapies for common malignancies is summarized in Table 1. It is unclear whether t-AML/MDS developing after stem cell transplant is due to pretransplant chemotherapy or whether the preparative regimen for the transplant is responsible for the development of t-AML/MDS [5,6]. Type and duration of prior chemotherapy (particularly cumulative dose of alkylator therapy), age, and total body irradiation as part of preparative regimen, interact in development of t-AML/MDS after stem cell transplant [5,7]. Additionally, the natural history of some cancers may include development of AML/MDS with "cure" achieved by current therapies unmasking this natural history.

Clinically Relevant Subgroups

Two classes of etiologic agents are associated with t-AML/MDS-alkylating agents and topoisomerase II inhibitors. Clinical and biologic distinctions can be made between these two groups of t-AML. Alkylator-associated t-AML is usually preceded by MDS, develops after a latency of 2 to 7 years, increases in frequency with age, and is typically accompanied by deletions involving chromosomes 5 and 7. Topoisomerase II–associated t-AML, conversely, presents as AML with a short latency period without a clear age-related incidence and associated with balanced translocations, most commonly involving chromosome 11 (Table 2).

Pathogenesis

Alkylator associated

A wide variety of alkylating agents, including cyclophosphamide, melphalan, chlorambucil, and nitrosoureas, are implicated in t-AML/MDS [8–11]. Alkylating agents induce interstrand cross-linking of DNA, resulting in gene mutations and chromosomal damage. There are two subgroups of alkylator-associated t-AML. The first includes patients with chromosome 7 abnormalities without chromosome 5 abnormalities. The second includes patients with deletion or loss of the long arm of chromosome 5, with or without

Table 1. Characteristics of therapy-related acute myelogenous leukemia and myelodysplastic syndrome (alkylator versus topoisomerase inhibitor related)

Features	Alkylator related	Topoisomerase II inhibitor related
Latency period	2-8 years	1-2 years
Chromosomal abnormalities	Deletion/long arm deletion 5, 7	Band 11 q23,
Incidence of favorable cytogenetics: eg, inv 16, t(8;21), t(15;17)	Rare	More frequent in comparison
Preceding AHD/MDS	Frequent	Rare
Age association	Increases with age	No clear association

AHD—antecedent hematologic disorder; MDS—myelodysplastic syndrome.

Table 2. Occurrence of therapy-related acute myelogenous leukemia and myelodysplastic syndrome following common exposures

Disease	Exposure	Frequency, %
Non-Hodgkin lymphoma (reviewed in Hake et al. [5])	ASCT	3 to 13
Indolent lymphoma [44]	ASCT	3.8
Chronic lymphocytic leukemia [45]	ASCT	12.4
Hodgkin disease [4]	Chemotherapy ± radiation	9.9 +/- 2.9
Germ cell tumor [13]	Cisplatin, etoposide, bleomycin	4.7
Acute lymphoblastic leukemia	Combination chemotherapy	4.7
Breast cancer [46]	Mitoxantrone, cyclophosphamide, and 5-fluorouracil	2.9

ASCT—autologous stem cell transplant.

abnormalities of chromosome 7. The first subgroup has a relatively less complex cytogenetic pattern and, if associated with a sole abnormality involving chromosome 7, can survive longer with indolent MDS. The second subgroup has complex cytogenetics and poorer outcome.

Topoisomerase II inhibitor associated

Anthracyclines, epipodophyllotoxins, and mitoxantrone are a group of topoisomerase II inhibitors that have been implicated in leukemogenesis [3,12–14]. Topoisomerases play an important role in unwinding of supercoiled DNA to make it accessible to transcription factors. As part of this process, topoisomerase II, an ATP-dependent enzyme, causes double-stranded breaks, which are repaired by homologous realignment. Topoisomerase II inhibitors interfere with ligation of the breaks, leading to nonhomologous recombination and balanced translocations. The translocations seen in topoisomerase II inhibitor–associated t-AML involve sites for topoisomerase II–induced cleavage, thus linking topoisomerase II inhibitors with leukemogenesis. The *MLL* gene at chromosome band 11q23 is frequently rearranged in topoisomerase II inhibitor–related t-AML. A DNA cleavage site within the breakpoint cluster region (*bcr*) of the *MLL* gene is susceptible to double-stranded DNA breaks induced by topoisomerase II inhibitors [15–17]. *AML1/RUNX1*, *ETO*, and *PML* are some of the other genes involved in balanced translocations associated with t-AML, and topoisomerase II cleavage "hot spot" sites have been identified in all these genes [18,19].

Model for Leukemogenesis in t-AML/MDS

A coordinate interaction between a "proliferative signal" (eg, constitutive tyrosine kinase activation) and "differentiation block" (eg, inactivation of transcription factor) is thought to be required for AML pathogenesis [20••,21]. Based on clustering of cytogenetic abnormalities and point mutations, such "leukemogenic pathways" have been proposed for t-AML [22,23••]. For example, translocations involving chromosome band 11q23 that block transcription pathways (differentiation block) are often associated with mutations in *RAS/BRAF* [24] (proliferative signal). Similarly, silencing of negative cell cycle regulators such as p14(ARF), p15(INK4B), and p16(INK4A) by methylation (proliferative signal) is a common event in t-AML associated with translocations of *AML1*, *ETO*, *PML*, and *RARA* genes [23••,25] (differentiation block).

Mutations of *TP53* can also play a leukemogenic role in t-AML/MDS. Mutations in *TP53* have been associated with amplification and duplication of chromosome band 11q23 (in contrast with chromosome band 11q23 rearrangements), complex cytogenetic patterns including deletion of chromosome 5q, and prior alkylator exposure

[26,27]. *TP53* mutations are thought to play a central role in leukemogenesis in these cases because the genomic instability caused by such mutations sets a stage for loss, amplification, and duplication of genetic material.

Gene Polymorphisms and Risk of t-AML/MDS

Environmental toxins such as benzene have been linked to development of AML. Inherited variations in the toxin detoxification system may predispose patients with slow metabolism to leukemia. Slow metabolizers at the cytochrome p450 2D6 and 2C19 loci are at higher risk for developing t-AML [28]. In a similar vein, a polymorphism profile consisting of CYP1A1*2A, del{GSTT1}, and NADPH-quinone oxidoreductase (NQO1) NQO1*2 strongly modified the risk of t-AML/t-MDS [29]. Following chemotherapy exposure, patients with the NQO1-187Ser polymorphism have an increased risk of developing both clonal hemopoiesis and telomere shortening, which may partly explain the predisposition to t-AML in NQO1-187Ser null individuals [30].

Homeobox genes influence hematopoiesis, and DNA repair genes can modulate genotoxic damage. Polymorphisms of the human homeobox gene *HLX1* and of DNA repair genes involved in double-strand DNA break repair (eg, *RAD51* and *XRCC3*) can potentially influence mutations following environmental toxin or chemotherapy exposure and are associated with increased risk of both de novo and therapy-related AML [31,32].

Treatment for t-AML/MDS

One of the practical issues in making general recommendations regarding treatment of t-AML and MDS is that most studies combine t-AML/MDS and secondary AML developing after antecedent hematologic disorder or MDS. With induction regimens containing anthracycline (eg, idarubicin) and cytarabine, the early mortality averages 10% to 20% in patients with t-AML, and even though complete remissions are achieved the durations of such remissions are short [33]. The brevity of chemotherapy-maintained complete remissions has prompted use of stem cell transplant, which is often considered standard treatment of t-AML/MDS [34]. Comparisons of stem cell transplant (autologous or allogeneic) and chemotherapy without stem cell transplant in t-AML/MDS indicate that the outcomes with either option are uniformly poor; instead of comparison, the focus should be on designing studies to improve outcomes with both treatment options [6]. The dismal outcome with chemotherapy is not always uniform. A report from the EORTC/GIMEMA trials (European Organization for the Research and Treatment of Cancer/Gruppo Italiano Malattie e Matologiche dell'Adulto) indicated comparable outcomes between patients with de novo AML and t-AML with conventional chemotherapy [35]. One explanation for such comparable outcomes could be that because patients who received chemotherapy for prior malignancies are routinely followed by their physicians, emergences of t-AML/MDS are identified earlier and they have better performance status at diagnosis. Alternative induction therapies have been tried in order to take advantage of the modulation of intracellular levels of cytarabine by fludarabine. Regimens that combine fludarabine and cytarabine with or without granulocyte-stimulating factor and with or without idarubicin (FLAG, FLAG-Ida) produce reasonable complete remission rates in secondary/t-AML, but the superiority of such regimens over idarubicin and cytarabine has not been proven.

Multidrug Resistance and t-AML

Much, though not all, of the poor prognosis in t-AML/MDS reflects its association with "unfavorable" cytogenetic abnormalities. Among other poor prognosis features, t-AML is associated with high expression of P-glycoprotein and rhodamine efflux (indicative of drug resistance) [36,37]. Modulators of P-glycoprotein have been tested in clinical trials that include patients with secondary and t-AML without much success.

Outcomes in t-AML with Favorable Cytogenetics

The outcomes in patients with t-AML and favorable cytogenetics—eg, inv16, t(8;21) and t(15;17)—are significantly better than in their counterparts who do not have these cytogenetic abnormalities. Such outcomes are comparable to outcomes in patients with de novo AML and favorable cytogenetics [38,39]. t-AML associated with these balanced translocations occurs more frequently after exposure to topoisomerase II inhibitors [40].

Potential New Therapies

With suboptimal outcomes from standard chemotherapy and stem cell transplant, patients with t-AML/MDS should be enrolled in clinical trials. Because methylation of cell cycle regulators such as p14(ARF), p15(INK4B), and p16(INK4A) is common in t-AML, hypomethylating agents such as 5-azacytidine or decitabine have a potential role in the treatment of t-AML/MDS. Balanced translocations in t-AML/MDS can recruit histone deacetylases and nuclear corepressors, resulting in a block in transcription of genes important in hematopoietic cell differentiation. Such transcriptional repression is thought to be pathogenetically linked to core binding factor AML [41–43] [inv16 or t(8;21)]. Histone deacetylase inhibitors can reverse transcriptional inactivation through histone/protein deacetylation and can be incorporated into therapeutic trials for t-AML/MDS. More effective modulators of P-glycoprotein may overcome chemoresistance.

Conclusions

Treatment options for t-AML and MDS are far from optimal, and innovative therapies that take into account the pathogenesis of these diseases are needed. Unraveling of the pathogenesis of these diseases will help us understand the pathogenesis of de novo AML/MDS.

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