Therapy-related leukemia and myelodysplasia: susceptibility and incidence

Giuseppe Leone, Livio Pagano, Dina Ben-Yehuda, Maria Teresa Voso

From Istituto di Ematologia, Università Cattolica S. Cuore, Rome, Italy (GP, LP, MTV); Department of Hematology, Hadassah University Hospital, Jerusalem, Israel (DB-Y).

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Correspondence:
Giuseppe Leone, Istituto di Ematologia, Universita' Cattolica S. Cuore, L. go A. Gemelli, 1, 00168 Rome, Italy.
E-mail: gleone@rm.unicatt.it

ABSTRACT

Therapy-related myelodysplastic syndrome/acute myeloid leukemia (t-MDS/AML) is an increasingly recognized treatment complication in patients treated with radiotherapy or chemotherapy for previous hematologic malignancies or solid tumors. Distinct clinical entities have been described according to the primary treatment, corresponding to defined genetic lesions. Chromosome 7 and/or 5 losses or deletions are typical of alkylating agent-induced AML, while development of t-AML with balanced translocations involving chromosome bands 11q23 and 21q22 has been related to previous therapy with drugs targeting DNA-topoisomerase II. In addition, anti-metabolites, and in particular the immunosuppressant azathioprine, have been shown to induce defective DNA-mismatch repair. This could promote survival of misrepaired cells giving rise to the leukemic clone. Individual predisposing factors, including polymorphisms in detoxification and DNA repair enzymes have been identified. Their combination may significantly increase the risk of t-MDS/AML. Among patients with hematologic malignancies, long-term survivors of Hodgkin's lymphoma are exposed to an increased risk of t-MDS/AML, particularly when receiving MOPP-based, and escalated BEACOPP regimens, and when alkylators are combined with radiotherapy. Patients with Hodgkin's and non-Hodgkin's lymphoma are at highest risk when total body irradiation followed by autologous stem cell transplantation is used as rescue or consolidation therapy. The addition of granulocyte-colony-stimulating factor and radiotherapy plays a significant role in t-AML following treatment of children with acute lymphoblastic leukemia. In non-hematologic malignancies, treatment for breast cancer and germ-cell tumors has been associated with a 1-5% lifetime risk of both lymphoid as well as myeloid leukemia. In all cases the risk of t-MDS/AML drops sharply by 10 years after treatment.

Key words: susceptibility, therapy-related, AML, MDS.

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Most cancers result from the interaction of genetics and environment. Established genetic factors alone explain approximately 5% of all cancers, the remainder can be attributed to environmental carcinogens, tobacco smoke, dietary costituents, pollutants, drugs, radiation, and infectious agents that act in conjunction with both genetic and acquired susceptibility.[1] Yet, the role of exogenous factors is not always so evident. Apart from radiotherapy and chemotherapy, which are recognized as the most frequent causes of secondary malignant neoplasms, therapy-related acute myeloid leukemia (t-AML) and myelodysplastic syndromes (t-MDS) account for 10-20% of all cases of AML.[2] In the GIMEMA registry, the incidence of AML occurring as a second malignancy was about 5%, but this registry includes only patients in whom treatment is feasible.[3] The high incidence of t-AML has been attributed to the increasing use of cytotoxic drugs causing DNA damage, and to the longer survival of many treated patients. Yet, only a minimal proportion of subjects exposed present with a secondary leukemia, indicating that an important role is played by the susceptibility of hematopoietic progenitor cells to inductive agents[1,4] (Figure 1).

Drugs and radiation inducing secondary leukemia

Therapy-related MDS/AML include leukemias following radiotherapy and chemotherapy. Leukemias following accidental exposure to ionizing radiation and benzol are

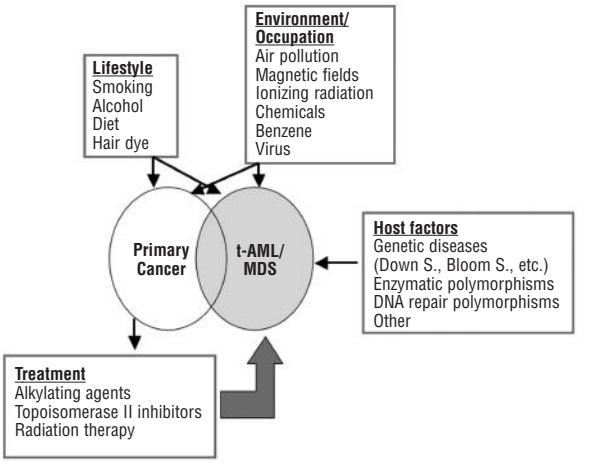

Figure 1. Risk factors for therapy-related AML/MDS.

considered strictly related to t-MDS/AML. Although an increased risk of AML has been observed after radiotherapy or chemotherapy alone, chemotherapy generally confers a greater risk and limited field radiation in the therapeutic dose range is associated with very little or no increased risk of leukemia.[4] The majority of secondary leukemias resulting from the use of cytotoxic drugs can be divided into two well-defined groups (Table 1) depending on whether the patient has received alkylating agents (melphalan, cyclophosphamide, nitrogen mustard, etc.)[5,6] or drugs binding to the enzyme DNA-topoisomerase (etoposide, doxorubicin, daunorubicin, mitoxantrone, etc.).[5-7] Less frequently, therapy-related leukemias have been described following the use of antimetabolites, such as fluorouracil, methotrexate, 6-mercaptopurine, and fludarabine, etc.[5] Leukemias following ionizing radiation do not have a unique pattern, but can be frequently likened to leukemias following treatment with alkylating agents.[8]

The combination of chemotherapy and radiotherapy definitively increases the risk of secondary leukemia, which is also influenced by the dose and the schedules of the drug administration.

Topoisomerase II inhibitors

Commonly used topoisomerase inhibitors bind to the enzyme/DNA complex at the strand cleavage stage of the topoisomerase reaction interacting with topoisomerase I or II. Drugs that interact with topoisomerase II include intercalating agents (e.g. doxorubicin) and non-intercalating epipodophyllotoxins (e.g. etoposide and teniposide). The only topoisomerase I inhibitor currently used in clinical trials is topotecan, while the intercalator actinomycin D interacts with both topoisomerase I and II.

Topoisomerase II inhibitors block the enzymatic reaction through re-ligation and enzyme release, leaving the DNA with a permanent strand break. Multiple DNA-strand breaks lead to cell death and apoptosis. Topoisomerase I inhibitors induce a replication block. There is evidence that both the antineoplastic and the leukemogenic effect are due to chromosomal breakages which are resolved by chromosomal translocation and cause leukemic transformation.[7]

The risk of t-AML after epipophyllotoxins averages from 2 to 12%.[7] Several regimen-related factors, such as schedule and concurrent use of asparaginase and G-CSF, are very important in determining the relative risk, while the role of cumulative doses is equivocal.[37-40] Exposure to topoisomerase II poisons such as etoposide, is predominantly associated with translocations of the *MLL* gene on chromosome band 11q23. *MLL* is a critical transcriptional regulator, and the several translocation types involving *MLL* suggest that its gain of function contributes to the critical leukemogenic lesions. In a culture system of primary human hematopoietic CD34$^+$ cells, alterations of the *MLL* region were observed at a readily detectable frequency in etoposide-treated cells.[40] Illegitimate repair events after minimal repair included *MLL* tandem duplications and translocations, with few deletions or insertions.[41] *MLL* gene abnormalities were mainly reciprocal translocations (84%), with as many as 40 different partner genes including t(9;11), t(19;11) and t(4;11).[42] Around 5 to 10% of *MLL* -associated leukemias are therapy-related. Younger age and a non-specific topoisomerase II inhibitor seem to predispose to t-MDS and t-AML with translocations involving *MLL*.[42] *MLL* rearrangements initiate within undifferentiated hematopoietic stem cell as suggested by gene expression profiling,[41] and can induce both lymphoid as well myeloid leukemia. Moreover it is notheworthy the partner gene of *MLL* is generally chromosome 4 in therapy-related ALL and chromosome 9 in AML, particularly t-AML.[42,43] Other less frequent genetic alterations are t(8;21), t(3;21), t(16;21), t(17;21), inv(16), t(8;16), t(15;17) and t(9;22)(42-45). Translocations (8;21) and t(15;17) are more frequent after antracyclines (44-45) . By analogy to *MLL*, the transcription factor *AML1* (*CBFA2*), located at the 21q22 chromosome band, is involved in balanced translocations with different partner chromosomes in epipodophyllotoxin-related leukemias.[46] Translocation breakpoints in cases of acute promyelocytic leukemia (APL) with t(15;17) were tightly clustered in a 8-bp region within intron 6 of *PML*.[47] In functional assays, this *hot spot* and the corresponding RAR· breakpoint were common sites of mitoxantrone-induced cleavage by topoisomerase II. Etoposide and doxorubicin also induced cleavage by topoisomerase II at the translocation breakpoints in APL arising after exposure to these agents. Homologous sequences in *PML* and *RARα* suggested the occurrence of DNA repair by means of the non-homologous end-joining pathway.[47] Despite these specific molecular abnormalities, the clinical outcome of secondary APL is not different from that of *de novo* APL.[48]

Susceptibility to t-MDS/AML

Predisposition to t-MDS/AML has been an area of great interest in recent years. Understanding individual suscep-

tibility factors can not only help to identify patients at risk in order to tailor therapy, but also to clarify the biological processes leading to leukemogenesis. The interaction between the genotoxic effects of chemotherapy or ionizing radiation and the *host* is influenced, among others, by genetic polymorphisms in drug metabolism and DNA repair processes, which may increase individual susceptibility to these agents.

Polymorphisms of detoxification enzymes

Drug or xenobiotic metabolizing enzymes (DME) play central roles in the metabolism, biotransformation, and detoxification of xenobiotics and foreign compounds. They generally protect against the potential harmful insults from the environment and also influence the metabolism of drugs. Table 2 shows the role of different classes of metabolizing enzymes in the detoxification of anti-cancer drugs. DME are expressed by various tissues and include phase I and phase II enzymes which are abundantly present under basal conditions or increased/induced after exposure to xenobiotics.[9] These enzymes display a high degree of polymorphism in the general population. Phase I DME primarily consist of the cytochrome P450 (CYP) superfamily, which is found in abundance in the liver, gastrointestinal tract, lung and kidneys, and consists of families and subfamilies classified based on their amino acid sequence identities or similarities.

The phase II drug metabolizing or conjugating enzymes consist of many superfamilies of enzymes, including sulfotransferases, glucuronosyltransferases, NAD(P)H:quinone oxidoreductase (NQO), epoxide hydrolases (EPH), glutathione S-transferases (GST) and N-acetyltransferases (NAT). Conjugation by phase II DME increases hydrophilicity and enhances excretion in the bile and/or the urine, and consequently affects detoxification and ultimately elimination of many drugs and xenobiotics that contain hydroxyl (OH) functional groups present either on the parent molecules and/or after biotransformation by the phase I enzymes. Under certain situations, conjugation with phase II enzymes can result in activated metabolites and increased toxicity. For instance, reactive electrophiles are typically conjugated with glutathione (GSH) by various GST, and have been implicated in the formation of reactive intermediates, in particular when GSH levels in the cells are attenuated, resulting in toxicological effects.[55]

Epipodophyllotoxins, etoposide and teniposide, as well as cyclophosphamide, ifosphamide, vinblastine, and vindesine are substrates for metabolism by CYP3A, the most abundant component of the CYP system in the human liver.[10] A variant in the 5' promoter region of the *CYP3A4* gene (CYP3A4-V) affects production of the epipodophyllotoxin catechol metabolite, which is the precursor of the potentially DNA-damaging quinine.[11] Felix *et al.* showed that 19 of 99 cases of *de novo* leukemias (19%) and only one of 30 treatment-related leukemias (3%) carried the *CYP3A4-V* (p=0.026), and that the variant was absent in patients with *MLL* gene translocation.[12] These data were confirmed by Rund *et al.* in adults,[13] but not in t-AML developing in children previously treated for ALL.[14] Individuals with the *CYP3A4*-wild type genotype may have increased production of potentially DNA-damaging reactive intermediates and are at increased risk for t-AML.

Benzene represents a model for secondary carcinogenesis, in particular, due to its toxic effects on blood and bone marrow. Benzene is metabolized by the phase I hepatic enzyme *CYP2E1* to benzene oxide, which spontaneously forms phenol and is further metabolized by *CYP2E1* to hydroquinone. Hydroquinone and related hydroxyl-metabolites are potent hematotoxins and genotoxins that can be converted by NAD(P)H:quinone oxidoreductase (NQO1) to less toxic hydroxyl-metabolites. Defects in the NQO1 pathway also cause accelerated telomere shortening and a switch to clonal hematopoiesis due to oxidative stress which induces release of oxygen-free radicals.[15] Looking at toxicity following benzene exposure in workers over a 16-month period, Lan *et al.*[16] found that total blood counts and colony formation from myeloid progenitor cells significantly declined with increasing benzene exposure. Hematologic impairment was significantly associated with single-nucleotide polymorphisms, the *MPO* –463GG (p=0.04) and *NQO1* 465CT (p=0.014), in particular when combined. Accordingly, Larson *et al.*[17] showed that the frequency of *NQO1* heterozygous was higher among leukemia patients than expected in the general population, and homozygotes mutants accounted for 4% of patients with primary AML, and 11% of those with t-AML. This proportion further increased when looking at patients with chromosome 5 or 7 abnormalities, alone or combined, or when looking at patients treated with alkylating agents for their primary tumor. A model for carcinogenesis due to a NQO1 defect is that of infant t-ALL, which is supposed to arise *in utero* and to be influenced by maternal exposure to carcinogens. In these children, a higher frequency of *MLL* translocations and of *NQO1* C609T polymorphism was reported.[18]

Many cytostatic drugs, such as adriamycin, BCNU, bleomycin, chlorambucil, cisplatin, etoposide, melphalan, mitomycin C, mitoxantrone, vincristine and cyclophosphamide, are inactivated by GST. Several GST are polymorphically expressed; in particular the *GSTP1* gene has a variant allele, with a substitution of isoleucine to valine at amino acid codon 105 (Ile105Val), which occurs at a frequency of about 30% in Caucasian populations and is associated with decreased activity of the enzyme.[19] In central Europe, *GSTM1* is homozygously deleted in about 50% of Caucasian individuals and *GSTT1* in 20%. Individuals with a *GSTM1* and/or *GSTT1* or *NAT* polymorphism show greater DNA damage following exposure to carcinogens, as determined by sister chromatid exchange (SCE) and formation of DNA-adducts.[20] The impact of GST enzymes in modulating the effects of chemotherapy has been further confirmed by the greater toxicity and reduced survival after chemotherapy for AML in children with *GSTT1* deletion, compared with children

with at least one *GSTT1* allele.[21] Sasai *et al*. reported an increased risk of t-AML in Japanese with the *GSTT1* null genotype.[22] In a retrospective study, 213 patients with AML and 128 with MDS, 44 of which were therapy-related, were compared to 239 healthy individuals. A significant (p=0.0003) over-representation of combined deletions of GSTM1 and GSTT1 was found in t-MDS/AML secondary to chemotherapy- and/or radiotherapy for breast cancer (55% for the double null genotype versus 8.8% in the control group).[23] In our series of patients, we did not find any difference in the prevalence of *GSTM1* and/or *GSTT1* deletions between patients with *de novo* or t-AML.[24]

Allan *et al*.,[25] examining 89 t-AML, 420 *de novo* AML, and 1022 matched controls, found that *GSTM1* or *GSTT1* deletions were not specifically associated with susceptibility to t-AML, while individuals with at least one *GSTP1* codon 105 Val allele were significantly over-represented in t-AML cases (OR 1.81). In particular, the highest t-AML risk was present in patients with *GSTP1* codon 105Val allele with prior exposure to chemotherapy (OR, 2.66), particularly to known *GSTP1* substrates (OR, 4.34), and not among t-AML patients with prior exposure to radiotherapy alone.

DNA repair polymorphisms

Another mechanism of secondary leukemogenesis are DNA-repair defects. Double-strand breaks in DNA are the most important class of DNA damage because they lead either to cell death or loss of genetic material resulting in chromosomal aberrations or to translocations. Too little repair leads to the acquisition and persistence of mutations, whereas elevated levels of repair can inhibit the apoptotic pathway and enable a cell with damaged DNA to attempt repair, potentially mis-repair, and survive. Double-strand breaks are predominantly repaired in mammalian cells by homologous recombination or non-homologous end-joining.

One of the central proteins in the homologous recombination repair pathway is RAD51 which binds to DNA and promotes ATP-dependent homologous pairing and strand transfer reactions. RAD51 interacts with BRCA1 and BRCA2 and is essential to the viability and genetic stability of the cell: knock-out models in mice are embryonically lethal, probably due to an accumulation of chromosomal breaks.[26] The *RAD51* gene has a G/C polymorphism at position –135 in the 5' untranslated region (*RAD51*-G135C) .

The XRCC3 protein also functions in the double-strand break repair pathway and directly interacts with and stabilizes RAD51. A polymorphism at codon 241 in the *XRCC3* gene results in a Thr-to-Met amino acid substitution and this variant allele has been associated with higher levels of DNA adducts, compared with the wild-type gene. In 51 t-AML patients, the frequency of the *RAD51-G135C* polymorphism was significantly higher than in normal controls, matched for ethnicity and age, translating in a 2.66-fold increased risk of t-AML.[27] The risk of the development of AML was found to be significantly increased when both variant *RAD51*-135C and *XRCC3*-241Met alleles were present [odds ratio (OR), 3.77; 95% confidence interval (CI), 1.39-10.24], and the risk of t-AML development was even higher (OR, 8.11; 95% CI, 2.22-29.68).[27]

DNA mismatch repair is also important for correcting replicative errors that escape DNA polymerase proofreading. In humans, the MutS· complex (composed of MSH2 and MSH6) and the MutSα complex (MSH2 and MSH3) recognize and bind to single base mismatches and insertion/deletion loops in DNA. Subsequent recruitment of MutLα (MLH1 and PMS2) facilitates degradation and resynthesis of the mispaired region in the newly synthesized daughter strand. Although defects in any of the proteins can impair the DNA mismatch repair system, the process is most greatly affected by abnormal MSH2 or MLH1 function.[27] Worrillow *et al*. determined the distribution of microsatellite instability by examining three quasi-monomorphic mononucleotide markers (BAT16, BAT25, and BAT26). In a case-control series of 420 patients with *de novo* AML, 91 with t-AML and 837 matched unaffected controls,[29] MSI was low in *de novo* AML (0–30% of cases), while it was detected in 13 of 34 (38%) of t-AML cases. In 12 of 13 MSI-positive t-AML, allelic shortening was found at BAT25. These data were consistent with those of other reports[13] on MSI in 30–60% of t-AML and t-MDS. Offman *et al*. identified MSI in t-AML, which was associated with mutations of *Caspase*-5, *FANCD2* and *NF1*.[30]

One tempting hypothesis is that reactive species escaping detoxification mechanisms or produced in excess due to drug metabolizing enzymes polymorphisms, damage DNA which is inefficiently repaired due to defective DNA-repair. This hypothesis is supported by the significantly higher number of t-AML patients carrying a combined detoxification/DNA repair defect, such as the combination of *GSTM1*-deleted genotype with the double *RAD51*-G135C/ *XRCC3*-241Met, which is associated with a 15-fold increased risk of developing t-AML.[27]

Finally, genetic heterogeneity in drug metabolizing enzymes may influence treatment response. It has been shown that etoposide clearance is influenced in children with ALL by polymorphisms in *CYP3A5*, *GSTP1*, and *MDR1* and that prednisone strongly induces etoposide disposition.[31]

Epidemiology of t-MDS/AML

The 2005 annual combined report from the American Cancer Society, NCI, CDC and NAACCR showed that the overall cancer death rates decreased by 1.1% from 1993 through 2002 in the United States.[32] On the basis of these data, there is an increasing number of cured patients at risk of developing t-AML or t-MDS. Prior radiochemotherapies play the major role in the onset of secondary leukemias. However, it has been observed that 20-30% of acute leukemias, occurring as second malignancy, developed in the absence of previous chemo-radiotherapy suggesting that besides a proven leukemogenic mechanisms

Table 1. Anti-cancer agents and detoxification/DNA repair.

Class		*GST*	*CYP*	*DNA repair*
Alkylating agents	Mechlorethamine Cyclophosphamide Melphalan Busulphan BCNU, CCNU	GSTT1 GSTM1 GSTP1	CYP2B6 CYP2C19 CYP3A4	MGMT BER (RAD51 XRCC3)
Topoisomerase I inhibitors	Topotecan Irinotecan		CYP3A	NHEJ
Topoisomerase II inhibitors	Mitoxantrone Daunorubicin Doxorubicin Etoposide Teniposide	(GSTP1)	CYP1B1 CYP3A4	NHEJ (RAD51 XRCC3)
Ionizing radiation				(RAD51 XRCC3)

of chemotherapy and ionizing radiations, common genetic and environmental factors could favor the onset of multiple neoplastic diseases.[1, 3] The more frequent primary malignancies are lymphomas and breast cancer in adults, ALL and central nervous system tumors in children.[3,33,34]

This review focuses on relevant articles published in journals covered by MedLine between 2001 and 2006.

Hematologic diseases

In patients with Hodgkin's lymphoma (HL), the risk of t-MDS/AML has been reported to be 10 to 80-fold higher than in the general population, with 10-year cumulative incidence rates ranging between 1% and 10%, depending upon the study population size, the duration of follow-up, and the type of therapy administered[35-37] (Table 3). Several studies have proven that alkylators play the major role in inducing t-AML and t-MDS. Furthermore, combinations of alkylators and radiotherapy cause a higher risk of leukemia than either treatment alone.[35-37]

Recently the incidence of t-MDS/AML was evaluated in two large series considering HL patients with a prolonged follow-up.[36,37] Delwail *et al*. analyzed 462 patients treated with ABVD and 373 with MOPP, followed by high-dose irradiation, between 1972 and 1998.[36] Thirteen patients developed a secondary leukemia: 11 t-AML and two t-ALL, both with a 11q23 translocation, with an overall incidence of 1.5%. The 15-year risk was 2.4% for the whole patient group, with a significant difference between those that received the ABVD (1.3%, 0.7% considering t-AML only) and MOPP regimens (3.4%). The German Hodgkin's Lymphoma Study Group reported on 5411 patients treated between 1981 and 1998 with different schedules (ABVD, 304 patients; COPP-ABVD-based, 3330; BEACOPP, 960; radiotherapy alone: 677).[37] They registered 36 t-AML and 10 t-MDS, with an overall incidence of 0.85%. A significantly increased risk ($46/10^5$ patient-years) was associated with the escalated-BEACOPP regimen. Moreover it is noteworthy that a very large study on 1-year Hodgkin's lymphoma survivors (n=35511), identified within 14 population-based cancer registries in Nordic countries and North America from January 1, 1970, through December 31, 2001, revealed that the excess absolute risk of t-MDS/AML declined significantly after 1984 (7.0 to 4.2 and 16.4 to 9.9-fold in the <35 and ≥35 age groups, respectively), which may be associated with reduced use of MOPP therapy.[38]

Patients with non Hodgkin's lymphoma (NHL), whether aggressive or indolent, are at risk of second malignancies including t-MDS/AML. Despite differences in methods used to identify cases, and to estimate the cumulative incidence over time (actuarial v cumulative calculations), up to 10% of NHL patients treated with either conventional-dose chemotherapy or high-dose therapy and autologous stem-cell transplantation may develop t-MDS/AML within the 10 years following primary therapy.[39]

In a recent British study, 123 second malignancies were reported in 2456 NHL patients (5%), treated between 1973 and 2000.[40] The main malignancies were lung, colorectal and breast cancer, but 17 acute leukemias (9 AML) were also documented, with a relative risk of 10.5. A significantly increased risk of leukemia was confined to patients who had received chemotherapy, with or without radiotherapy. No cases of leukemia were observed in patients treated with radiotherapy alone. The relative risk of leukemia in the patients who were treated with CHOP was 14.2 (95%CI, 6.8 to 26.2), and that for patients treated with chlorambucil was 19.2 (95% CI, 9.6 to 34.3). The risk seemed to be equivalent in aggressive and indolent NHL.

The GELA group analyzed 2837 patients with aggressive NHL treated with the ACVBD (adriamycin, bleomycin, vindesine, cyclophasphamide and prednisone) regimen between 1984 and 1998.[41] Eighty-one secondary malignancies were collected, 17 hematologic (7 AML, 4 MDS, 1 CMML), with a statistically increased risk of t-MDS/AML (SIR 5.65, $p<0.006$ and SIR 19.9, $p<0.001$ respectively). In 202 patients with indolent lymphomas treated with fludarabine, dexamethasone, novantrone ± rituximab, eight cases (4%) of t-MDS/AML were reported by a study conducted at the M.D. Anderson.[32] The addition of monoclonal antibodies conjugated to I^{131} did not seem to increase the incidence of t-MDS/AML. Bennett *et al*., reported 35 t-MDS/AML cases (3.5%) in NHL patients treated with I^{131} tositumomab, at a median follow-up of 6 years.[43] High-dose radio-chemotherapy followed by autologous stem cell transplantation (ASCT) is being increasingly used as salvage therapy in patients with Hodgkin's disease and NHL. By analyzing 2739 patients (955 HD and 1784 NHL) treated between 1989 and 2005, 56 t-MDS/AML were identified, corresponding to a 7-year risk of 3.7% (3.3% for HD and 3.9% for NHL).[44] A randomized study on patients with indolent lymphoma was performed by the German Low-Grade Lymphoma Study Group:[13] 440 patients were randomly assigned after a cyclophosphamide, doxorubicin, vincristine, and pred-

nisone–like induction therapy, to myeloablative radio-chemotherapy, followed by ASCT or interferon treatment. After a median follow-up of 44 months, 431 patients were assessable. Five of 195 patients developed a secondary hematologic malignancy after ASCT; two of these malignancies were AML. Accordingly, the estimated 5-year risk for secondary hematologic neoplasia after ASCT was 3.8%. In contrast, in the interferon arm, the 5-year risk of hematologic neoplasia was 0.0% (p=0.0248). This randomized trial demonstrated an increased risk of secondary hematologic malignancies after myeloablative radio-chemotherapy and ASCT compared with conventional chemotherapy. However, as ASCT significantly improves progression-free survival, it is currently not evident to what extent the higher rate of t-MDS/AML will reduce the benefits of ASCT in indolent lymphoma.[13]

The incidence of t-MDS/AML after ASCT is related to previous chemotherapy, but rates are even higher in patients treated with total body irradiation and transplanted with peripheral blood stem cells.[46] Thus, certain components of the autologous transplantation procedure itself may also contribute to the risk of t-MDS/AML. Specifically, priming chemotherapy, total body irradiation and the extensive cellular proliferation that occurs during engraftment may all play a role in the development of t-MDS/AML.[39, 44, 46] There are no recent reports on the cumulative risk of t-MDS/AML in patients with multiple myeloma. In the past, a 10% risk at 8 years was reported by Cuzick *et al*.[47] in patients treated with melphalan, while the incidence in patients treated with cyclophosphamide was lower. This incidence appears exceptionally high, considering that the incidence of secondary leukemia is very low also in patients submitted to a double ASCT.[48]

In contrast, second malignancies remain a major problem in patients with ALL in remission, particularly in children. Pui *et al*.[49] recently analyzed all cases of malignancies developing in 827 ALL patients treated between 1984 and 1999 and observed 40 secondary malignancies (incidence 4.8%): 15 AML, 2 MDS, 2 ALL and 1 CML. In a previous paper, the same group reported 20 secondary hematologic malignancies in 412 ALL children: 16 AML, 3 MDS and 1 CML.[37] The risk of t-AML was higher in ALL children who received a high cumulative dose and prolonged epipodophyllotoxin therapy in weekly or bi-weekly schedules. An additive risk factor was the short-term use of G-CSF and central nervous system irradiation.[36, 37] The 6-year cumulative incidence of secondary malignancy ranged from 2.7% in patients who did not receive G-CSF or radiotherapy to 12.3% in patients treated with radiotherapy alone.[37] In adults, a GIMEMA (*Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto*) study showed a low incidence of t-AML, which could be explained by the reduced survival rates, the lower doses of epipodophyllotoxin administered and by the different susceptibility of elderly patients.[50]

The occurrence of t-MDS/AML was considered very rare in patients with CLL treated with chlorambucil alone, but recently some cases have been reported, most likely related to the introduction of new protocols incorporating fludarabine and ASCT.[14, 30] The Cancer and Leukemia Group B identified six cases of t-MDS/AML in 521 CLL patients (1.15%) treated with fludarabine.[30] A more recent study reported ten cases of t-MDS/AML (8 after ASCT) in 115 patients (65 ASCT), corresponding to a 12.4% 5-year risk after ASCT conditioned by radiotherapy.[14]

The risk of t-MDS/AML in patients with polycythemia vera (PV) and essential thrombocytemia is related to the type of therapy, even if a natural evolution in AML cannot be excluded.[33] A recent study by ECLAP analyzed 1638 patients with polycythemia vera: 22 t-MDS/AML cases were collected, with a higher risk in patients treated with radioactive phosphorus and pipobroman, and a lower risk in patients receiving hydroxyurea.[33] The rate of evolution into AML is extremely low in patients with essential thrombocythemia (2-3%), treated or not with hydroxyurea, interferon or anagrelide.[34-54] 17p deletions suggest hydroxyurea-related leukemia.[57]

Recently, t-MDS/AML has been reported in long term survivors of APL treated with anthracyclines, cytarabine with and without retinoic acid.[58,59] The incidence ranged from 1% to 6.5%.[58,59] It is noteworthy that complex cytogenetic aberration frequently involved chromosomes 5 and 7, although none of the patients had received alkylating agents.[58,59]

Non-hematologic diseases

In most studies, an increased risk of t-AML was reported in breast cancer patients treated with chemo-radiotherapy.[60,61] Furthermore, an increased incidence of t-MDS/AML in patients treated with surgery alone and in patients with a family history of breast cancer suggests a possible association between the two diseases.[61-63] More aggressive therapy could even increase the rate of t-MDS/AML.[64-66] Praga *et al*. analyzed 19 randomized trials, including patients treated with epirubicin and cyclophosphamide. Thirty acute leukemias were observed in 9796 patients: 25 t-MDS/AML, 3 ALL, 1 hairy cell leukemia and 1 CLL.[64] The cumulative 8-year risk was 0.55%, but there was a wide variability between patients treated with standard or high cumulative doses of epirubicin (0.37% vs 4.97%, respectively).[64] In a large French case-control study, the risk of t-MDS/AML in women recently treated for breast cancer was higher in those who received mitoxantrone-based chemotherapy than in those given anthracycline-based chemotherapy. The risk was further increased by the addition of G-CSF.[65] These data were confirmed by a very recent epidemiological study,[66] stressing the need to monitor the long-term effects of G-CSF support. Unlike previous reports, in a recent American epidemiological study the risk of any type of leukaemia was not increased following either doxorubicin-containing or non-doxorubicin-containing regimens, regardless of the addition of radiotherapy.[67] t-AML and t-MDS/refractory anemia with excess blasts were exclusively observed in

Table 2. Risk of MDS/AML in patients receiving chemo/radiotherapy for Hodgkin's lymphoma, according to treatment.

References	*No. of pts*	*Therapy*	*Cases of t-MDS/AML*	*Cumulative Risk (%)*
Brusamolino *et al.*[35]	348	RT	2	0.3
Josting *et al.*[37]	677		4	0.6
Brusamolino *et al.*[35]	124	MOPP	3	2.2
Josting *et al.*[37]	1775	COPP+ABVD	15	0.8
Brusamolino *et al.*[35]	277	MOPP+RT	18	10.2 (15 yrs)
Delwail *et al.*[36]	374	(involved field)	5	2.4 (15 yrs)
Delwail *et al.*[36]	36	(extended field)	4	13.9 (15 yrs)
Brusamolino *et al.*[35]	24	ABVD	0	0
Josting *et al.*[37]	304		1	0.3
Brusamolino *et al.*[35]	129	ABVD+RT	1	0.8
Delwail *et al.*[36]	279	(involved field)	2+1 (ALL)	1.2
Delwail *et al.*[36]		(extended field)	0	0
Josting *et al.*[37]	500	BEACOPP baseline	2	0.4
	460	BEACOPP escalated	8	1.7

RT: radiotherapy; MOPP: mechlorethamine, vincristine, procarbazine, prednisone; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; COPP: cyclophosphamide, vincristine, procarbazine, prednisone; BEACOPP: bleomycin, etoposide, cyclophosphamide, vincristine, procarbazine, prednisone.

Table 3. Incidence and relative risk of t-MDS-AML in breast cancer. Distribution of leukemia cases by treatment.

References	*No. of pts.*	*Therapy*	*Cases of t-MDS/AML (No.)*	*Cumulative risk (%)*
Praga *et al.*[64]	7110	Epirubicin regimens	28	0.55 (8 y)
	1427	CMF	1	0.07
	903	Hormone therapy	1	0.11
Smith *et al.*[60]	4483	B15-Doxorubicin +CTX (2400 mg/m^2)	11	0.27 (8 y)
	763	B16-Doxorubicin +CTX (4800 mg/m^2)	4	0.40 (8 y)
	772	B18-Doxorubicin +CTX (4800 mg/m^2)	6	0.52 (8 y)
	849	B22-Doxorubicin +CTX (4800 mg/m^2)	4	0.47 (8 y)
	847	B23-Doxorubicin +CTX (4800 mg/m^2)	10	1.19 (8 y)
	849	B25-Doxorubicin +CTX (9600 mg/m^2)-G-CSF	8	0.95 (8 y)
Hershman *et al.*[66]	1569	Doxorubicin regimens	18	1.14
	3330	CTX regimen	40	1.20
	2837	Radiotherapy	38	1.33
	890	G-CSF/GM-CSF treatment*	16	1.79
Kapplan[67]	154	Surgery only	1/2**	0.65/1.30**
	1403	Surgery + Radiotherapy	0/4**	0/0.29**
	352	Surgery + Chemotherapy	0/0**	0/0**
	957	Surgery + Chemotherapy + Radiotherapy	2/2**	0.21/0.21**
Howard *et al.*[68]	89560	Surgery only	133**	0.14**
	99275	Radiotherapy, no chemotherapy	221**	0.22**
	11941	Chemotherapy, no radiotherapy	14**	0.11**
	15130	Chemotherapy and radiotherapy	14**	0.09**

*The distribution of leukemia cases by treatment. CMF: cyclophosphamide (CTX), methotrexate, and fluorouracil; *p value: 0.06, compared to patients who did not receive G-CSF/GM-CSF; **all cases of leukemia (CML, AML and ALL) were included.*

patients who received combined chemo-radiotherapy (Table 4). However, larger epidemiological studies, analyzing more than 350,000 patients from North Europe confirmed an increased risk of secondary leukemia in patients treated for breast cancer, but did not find significant differences between patients treated with chemotherapy, radiotherapy or combined chemo-radiotherapy[68] (Table 4). In general, the leukemia risk seems to be decreasing in recent years, due to changes in treatment.[68]

A large proportion of patients with testicular cancer can be cured by radio-chemotherapy, including topoisomerase II inhibitors and cisplatin, but t-MDS/AML represents a major problem with a mean cumulative risk of 1.3 to 4.7% at 5 years.[69] Radiotherapy (mean dose to active bone marrow, 12.6 Gy) without chemotherapy was associated with a 3-fold elevated risk of leukemia and the risk increased with increasing doses of radiation. The estimated relative risk of leukemia at a cumulative dose of 650 mg cisplatin, which is commonly administered in current testicular cancer treatment regimens, was 3.2. Larger doses of 1000 mg were correlated with a 6-fold increased risk. The total amount of etoposide did not contribute to

leukemia risk when doses of cisplatin and radiation were taken into account.[69] Myeloablative therapy followed by autologous bone marrow transplantation did not increase the risk: in 113 patients with refractory germ cell tumors, observed between 1987 and 2001, a 2.6% incidence of t-MDS/AML was reported.[70] The risk of t-MDS/AML in children deserves particular consideration, considering the long life- expectancy of oncological patients cured by chemo- radiotherapy.[35,71] A case-control study on the risk of t-MDS/AML after a solid tumor in childhood was conducted within the *Societe´ Francaise d'Oncologie Pediatrique*, including 61 patients with leukemia, matched with 196 controls. Only two factors were found to increase the risk of leukemia in multivariate analysis: the type of the first tumor, with an excess risk in patients with Hodgkin's lymphoma (relative risk 6.4; 95% confidence interval [CI], 1.6 to 24) or osteosarcoma (relative risk 5; 95%CI 1.3 to 19), and exposure to epipodophyllotoxins or anthracyclines.[71]

An increased incidence of AML was found in children with non-testicular germ cell tumors after chemo-radiotherapy, with a cumulative incidence at 10 years of 1.0% for patients treated with chemotherapy and of 4.2% for patients treated with combined chemotherapy and radiotherapy.[72] No cases of leukemia were found in patients treated with radiotherapy only. Three and two cases of t-AML were observed in, respectively, 95 and 119 patients treated with ^{131}I-metaiodobenzylguanidine for neuroblastoma, with a cumulative risk of 20% at 15 years.[73]

Concluding remarks

Radiotherapy and/or chemotherapy are effective anticancer treatment in a large proportion of patients and only a small number of them develop a secondary leukemia. In most patients treated with alkylating agents t-AML is preceeded by MDS; however, topoisomerase inhibitor- associated leukemia does not have the MDS-phase and presents acutely. Cytogenetic aberrations are found in 80% of t-MDS/AML and may preceed overt MDS. Cytogenetic patterns are mostly related to the drug category, however there are no specific patterns. The primary malignancy seems to have less of an influence.

Secondary prevention includes avoiding the use of alkylating agents, methyl-CCNU, procarbazine and epipodophyllotoxins, when less leukemogenic compounds, such as antimetabolites, are equally effective in the treatment of a specific disease. For example, alkylating agents should be avoided in the treatment of polycythemia vera and hydroxyurea and should be considered only when phlebothomy has been unsuccessful or thrombotic complications have occurred. The treatment of Hodgkin's lymphoma with drug combinations that include doxorubicin, bleomycin, vinblastine, dacarbazine, or methotrexate should be preferred to the MOPP regimen. It is worth noting that the risk of t-MDS/AML following Hodgkin's lymphoma has been decreasing over time, likely due to modifications in chemotherapy. Furthermore, drugs of the same class known to be less leukemogenic should be preferred whenever possible. Cyclophosphamide is less leukemogenic than busulphan, and adriamycin is less leukemogenic than mitoxantrone. Etoposide seems to be more leukemogenic in young people; the rate of secondary malignancy can be reduced *in vivo* by the use of schedules in which the treatment is administered, over a longer time, but at reduced dosage. Epidemiological studies suggest an increased carcinogenic effect of vumon due to the addition of asparaginase. The leukemogenic effect of chemotherapy may be increased by the use of G-CSF and this risk, although low, should be factored into clinical decisions. The introduction of new antineoplastic drugs (e.g. purine analog and temozolomide) and the diffusion of aggressive treatments, such as autologous stem cell transplantation, have drawn attention to new risk categories, such as patients with CLL.

It is currently difficult to define individual susceptibility, because only few pathological conditions, mostly constitutional and mostly arising in childhood, are known to predispose to leukemia. Furthermore, the observation of secondary leukemias in patients who did not receive chemo-radiotherapy for their primary tumor suggests the existence of a common predisposing condition, possibly a general *cancer* susceptibility.

Other than established genetic diseases (Fanconi anemia, Down syndrome, etc), it has been hypothesized that differences in drug catabolism, membrane transport or inefficient DNA repair could explain the predisposition to leukemia. Some polymorphisms have been studied in large patient cohorts, including several t-MDS/AML patients. Among such polymorphisms, the *CYP3A4-wild type* genotype, the *GSTP1* codon 105Val allele and the homozygous 465CT variant of *NQO1*, have been shown to increase the risk of t-MDS/AML. DNA repair defects, in particular defective mismatch repair and defects in homologous recombination, such as the *RAD51*-G135C polymorphism combined with a variant *XRCC3*-241Met allele were shown to be associated to t-AML. Reduced repair may lead to the persistence of mutations, whereas elevated levels of repair may enable a cell with damaged DNA to mis-repair and survive. Pitfalls of many of the susceptibility studies are the scarse reproducibility of the results due to heterogeneity, the small number of patients included and the lack of prospective studies. In addition, variations in cumulative risk of t-MDS/AML in epidemiological studies may be due to different racial and geographic origins of the patients, but more likely to different data collection methods. Tumor registries usually gather information on disease stage and type of initial cancer treatment, expressed in broad categories, but do not often report the specific drug used, the dose, and eventually addition of hematopoietic growth factors and radiotherapy, which have been changing during the years. Younger patients have biologically different tumors, are treated according to different schedules and should be analyzed separately. Follow-up times are variable and often too short to pick up late complications, which are frequently diagnosed by

physicians different from those who made the primary tumor diagnosis, leading to incomplete data collection. Incidences derived from epidemiological studies cannot be compared to those in case-control studies, given the different accrual methods. The creation of a t-MDS/AML registry may help to identify the genetic profile of patients at risk, allowing patient-tailored treatment, and avoid treatment-related complications.

Conflicts of Interest

GL, LP, DBY, MTV have no potential conflict of interest relevant to this paper.

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