ties are found in combination with more than one residual normal metaphase.[11] In the study reported here, MK-AML shows statistically a slightly better survival at two years of follow up when normal metaphases are apparent, although the survival of even those patients remained very poor.[4]

Therapeutic implications of monosomal karyotype AML?

The excessively poor prognostic subgroup of AML with MK is explained by resistance against current treatment modalities resulting in a low CR percentage. CRs achieved following 3+7 anthracyclin-cytarabine induction chemotherapy in MK-AML are of poor quality which is evident from the high and early relapse rate after CR. This high relapse rate is also apparent in an analysis of the University of Minnesota showing a relapse rate of 62% at four years of patients with MK-AML who had been treated with an allogeneic stem cell transplantation in their first CR.[12] On the other hand, preliminary data from the HOVON-SAKK cooperative group suggest that patients submitted to an allogeneic stem cell transplantation have a better prognosis than those submitted to chemotherapy programs (HOVON-SAKK cooperative group, unpublished results). Thus, an allogeneic stem cell transplantation, which is the currently recommended consolidation treatment for poor-risk AML in general,[13,14] also seems to be the treatment of choice in patients with MK-AML as one of few available treatment options. Meanwhile, novel more active therapies are evidently badly needed for MK-AML. This means that MK-AML represents a subtype of AML that is heavily dependent on investigational explorative approaches and particularly suitable for new drug development even in front-line treatment situations.

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Therapy-related acute promyelocytic leukemia

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(Related Original Article on page 621)

Success in the treatment of cancer has led to an expanding population of survivors with their attendant long-term complications. Treatment with cytotoxic, DNA-interactive drugs and radiation is well known to predispose to the development of secondary tumors, in particular secondary myelodysplasia and acute myeloid leukemia (AML).[1] Such therapy related neoplasms have been associated with recurring chromosomal abnormalities such as translocations involving the *MLL* gene (commonly seen within a few years after therapy with topoisomerase II inhibitors) and loss of part or the whole of chromosomes 5 and 7 (frequently observed several years after treatment with the alkylating agents).[1] The occurrence of these recurring chromosomal aberrations and their association with specific chemotherapeutic agents is suggestive of a specific interaction between these drugs and the genome.[1]

Table 1. Characteristics of patients with therapy related acute promyelocytic leukemia; selected series in the literature.

Reference	Patient #	Age yrs median (range)	Male: female	Primary disease	Rx for primary	Rx for APL
Pulsoni[2]	51	57 (27-76)	17:34	Breast 15 Lymphoma 12 Female reproductive 9 Others 15	Surgery 14 Chemo 10 RT 17 Chemo + RT 10	AIDA 31; ATRA alone 8; Other chemo 12
Beaumont[3]	106	55 (12-82)	28:78	Breast 60 Lymphoma 15 Other cancers 29 MS 1 Other disease 1	Chemo 30 RT 27 Chemo + RT 49	ATRA + chemo 83 Chemo alone 16
Hasan[4]	14	40 (27-67)	6:8	MS 12	Mitoxantrone 12 Other 2	ATRA + chemo 13 NA 1
Dayyani[5]	29	54 (35-81)	15:14	Breast 9 Prostate 5 Lymphoma 4	Chemo 6 RT 10 Chemo + RT 13	ATRA + chemo 10 ATRA + ATO 19

ATRA: all trans retinoic acid; RT: radiation therapy; AIDA: ATRA plus idarubicin; NA: not available; ATO: arsenic trioxide

The incidence of therapy related acute promyelocytic leukemia (APL) occurring after prior chemotherapy for other tumors is low but appears to be increasing according to several recent reports which have better characterized this entity and explored its pathogenic mechanisms (Table 1).[2,3] Use of topoisomerase II inhibitors such as mitoxantrone, etoposide, doxorubicin and epirubicin, particularly in the treatment of breast cancer, has been suggested to be a potential culprit.[2,3] In a recent report, translocation breakpoints in therapy related APL occurring after exposure to topoisomerase II inhibitors such as mitoxanterone were clustered in "hot spots" within *PML* and *RARA* that are susceptible to these drugs.[6] In another study, similar clustering of breakpoints was observed in *PML* and *RARA* after exposure to epirubicin for the treatment of breast cancer, with the *PML* breakpoints lying outside the mitoxantrone "hot spot" region.[7] Another report of 12 patients with multiple sclerosis (MS) who developed APL after therapy with mitoxantrone, further corroborated the presence of preferential sites of DNA damage induced by mitoxantrone in *PML* and *RARA*.[4]

The enzyme topoisomerase II relaxes supercoiled DNA by cleaving and religating both strands of the double helix through the formation of transient intermediates. Inhibitors of the enzyme, such as mitoxantrone and epirubicin, disrupt this cleavage-religation equilibrium and increase the concentration of breakpoint complexes. This leads to the cleavage of *PML* and *RARA* by the topoisomerase II enzyme resulting in the observed translocation. The existence of different genomic "hot spots" for topoisomerase II-mediated cleavage in the presence of different drugs is further suggestive of the specific contribution of these drugs to the development of translocations. It can be speculated that such "hot spots" exist in the entire genome but only those translocations conferring a proliferative or survival advantage in the appropriate progenitor cells lead to the development of leukemia.[6]

In this issue of the journal, Ammatuna and colleagues report on a series of 33 patients with MS who developed APL (including some previously reported patients).[8] Thirty patients (91%) had been previously treated with mitoxantrone with a median time from the prior treatment of 32 months. There was a higher frequency of *PML-RARα* bcr1 isoform consistent with the reported "hot spots" within the *PML* gene susceptible to therapy with mitoxantrone.[8] This study confirms that the interaction of the topoisomerase II inhibitors with preferential sites on the genome is independent of a predisposing genetic instability (such as that seen in patients with multiple cancers) and further establishes mitoxantrone as a direct causative agent for the development of APL in these patients. However, it is curious to see 3 patients without a reported prior cancer and without prior treatment with topoisomerase II inhibitors developing APL. The incidence appears to be higher than would be expected by chance alone and may suggest another, as yet unidentified, predisposition to APL among patients with MS.

The majority of patients in this study received induction treatment with a combination of ATRA and chemotherapy but several received a modified consolidation, including 3 patients who were consolidated with all trans retinoic acid (ATRA) and arsenic trioxide (ATO).[8] All 28 evaluable patients achieved molecular remission after consolidation and the 5-year survival was 68%. This agrees with other reports suggesting that the outcome of therapy related APL is not inferior to that seen in patients with *de novo* APL. This is also further evidence for the high efficacy of ATRA and anthracycline based regimens in producing durable responses in this disease.

Table 2. Selected trials of front-line use of arsenic trioxide in acute promyelocytic leukemia.

Reference	Patient #	Induction	Consolidation	CR (%)	OS at x years (%)
Mathews[9]	72	ATO	ATO	86	5 (74.2)
Ghavamzadeh[10]	111	ATO	ATO	85.6	3* (87.6)
Hu[11]	85	ATO+ATRA	Chemo (D, A, H)	94.1	5 (91.7)
Ravandi[12]	82	ATO+ATRA±GO	ATO+ATRA	92	3 (85)
Powell[13]	481	ATRA+Chemo (D, A)	ATO+Chemo(D) +ATRA or	90	3 (86)
			Chemo(D)+ATRA	90	3 (81)

*ATRA: all trans retinoic acid; ATO: arsenic trioxide; CR: complete response; OS: overall survival; D: daunorubicin; A: ara-C; H: homoharringtonine; *3-year survival reported only for patients achieving CR.*

Recent studies have suggested a possible role for ATO in the initial therapy of patients with APL thereby providing us with an alternative strategy to chemotherapy-based regimens (both for induction and consolidation) in those patients deemed unfit to receive anthracycline-based chemotherapy (Table 2).[9-13] Several studies have used ATO as a single agent and have reported good tolerance and a high response rate with durable responses in the majority of patients.[9,10] Another strategy has been to combine ATO with ATRA with or without gemtuzumab ozogamycin thereby having a "chemotherapy-free" regimen.[14,15] Long-term follow up reports of these studies are again suggestive of durable responses further indicating that this approach is feasible and effective.[11,12] Alternatively, ATO can be used to consolidate the responses achieved after ATRA and chemotherapy based induction thereby avoiding additional anthracycline exposure. In the recently published North American Intergroup study, 2 cycles of ATO in consolidation significantly improved the event-free survival of patients in low- and high-risk groups.[13]

The prime incentive for using ATO earlier in the course of treatment in this population of patients with therapy related APL would be to avoid further use of anthracyclines, thereby reducing any potential cardiotoxicity in the light of patients' prior extensive exposure. Furthermore, there are other potential advantages for using a "chemotherapy-free" regimen in this patient population. For example, although the incidence of secondary myelodysplastic syndrome and AML following treatment of APL with chemotherapy-based regimens is low, it does occur, as was seen in a patient in this report as well as in other larger reports.[16-19] Eliminating chemotherapy and, in particular, anthracyclines in the treatment of patients with therapy related APL may potentially decrease the risk of this complication. A recent report comparing the outcome of patients with therapy related APL treated with ATRA and ATO to those treated with ATRA and chemotherapy did not detect an inferior outcome for the former group, further supporting the utility of this approach.[5]

In conclusion, although the clinical features, response to therapy and long-term outcome of patients with therapy related APL does not seem to differ from *de novo* cases, "chemotherapy-free" regimens or the use of ATO and ATRA in consolidation may be desirable in this population to avoid potential, albeit infrequent, complications. Further studies exploring the mechanisms of pathogeneisis of topoisomerase II induced APL may provide further insight into the etiology of other therapy related leukemias.[20] Potential reasons behind the development of APL in patients with MS not exposed to topoisomerase inhibitors should also be explored in future studies.

Farhad Ravandi graduated from the University of London, St. Mary's Hospital Medical School, underwent further training at the University of Texas – M. D. Anderson Cancer Center where he is currently Associate Professor of Medicine in the department of leukemia.

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