Published in final edited form as:
Leuk Lymphoma. 2009 July ; 50(7): 1073–1074. doi:10.1080/10428190902995655.

Therapy-related acute promyelocytic leukemia: further insights into the molecular basis of the disease and showing the way forward in therapy

Farhad Ravandi
Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

Acute myeloid leukemia (AML) occurring as a second cancer in patients, who were successfully treated for a prior neoplasm, has been reported with increased frequency partly due to the success of antineoplastic radiation and chemotherapy. Many of such therapy-related leukemias have been associated with recurring chromosomal abnormalities; this is suggestive of a specific interaction between certain chemotherapeutic agents and the genome with different drugs predisposing patients to specific translocations [1]. Although acute promyelocytic leukemia (APL) occurring after prior chemotherapy for other tumors has been infrequent, several recent reports have better characterized this entity and have suggested an increase in its incidence possibly due to an increased used of topoisomerase II inhibitors, particularly in the treatment of breast cancer [2,3]. In general, the clinical features, response to therapy and long-term outcome of patients with therapy-related APL appears not to be different from *de novo* cases of APL [2,3].

A recent report suggested that translocation breakpoints in APL occurring after exposure to topoisomerase II inhibitors such as mitoxanterone, etoposide and doxorubicin were clustered in ‘hot spots’ within PML and RARA and were common sites of mitoxantrone-induced cleavage by topoisomerase II [4]. The presence of preferential sites of DNA damage induced by mitoxantrone in PML and RARA genes was further corroborated by another study of 12 patients with multiple sclerosis (MS), who developed APL after therapy with mitoxantrone [5]. This was further suggestive of the specific interaction of the topoisomerase II poison with preferential sites on the genes involved which was independent of a predisposing genetic instability (as would be suspected in a patient with multiple cancers).

In this issue of the journal, Aversa *et al.* report on a case of APL developing 4 years after receiving a combination of the Stanford V chemotherapy regimen with radiation in a patient with advanced Hodgkin lymphoma [6]. The topoisomerase inhibitors, doxorubicin and etoposide are amongst the agents used in the Stanford V regimen and as such, would be expected to predispose to the development of AML with associated translocation involving

Correspondence: Farhad Ravandi, Department of Leukemia, Unit 428, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, USA. Tel: +1-713-745-0394. Fax: +1-713-794-4297. fravandi@mdanderson.org.

Declaration of interest: The author has received honoraria from Cephalon Oncology. The author alone is responsible for the content and writing of the article.

the specific cleavage sites. However, and perhaps somewhat surprisingly, according to the authors, this is the first reported case of APL in patients treated with the Stanford V regimen with the only other previous reported case of AML being associated with a translocation involving the chromosome band11q23.

Of interest, Aversa *et al.* treated their patient successfully with the combination of all-trans retinoic acid (ATRA) and idarubicin and used a consolidation regimen including cytarabine, idarubicin, mitoxantrone and etoposide. This raises another question of what is the best regimen to treat a patient with secondary APL suspected to be the consequence of topoisomerase II inhibitor therapy? In addition to the intuitive concern for using the same agent to treat the disease as the one suspected to induce it, the issue of cumulative doses of anthracyclines and the attendant risk of cardiotoxicity has to be considered.

The introduction of arsenic trioxide (ATO) as an effective treatment for relapsed APL and recent studies suggestive of a role for ATO in frontline therapy of patients have provided us with an alternative to anthracycline and ATRA based regimens used to treat patients with APL [7–9]. We have recently reported that the combination of ATRA, ATO, possibly with the addition of gemtuzumab ozogamicin but without chemotherapy is effective in producing molecular remissions that are durable [10]. In this issue of the journal, Ammatuna *et al.* report on the use of ATRA and ATO for consolidating the remission in a patient with secondary APL after mitoxantrone therapy for MS [11]. Their main incentive for using ATRA and ATO for consolidation was to avoid further cardiotoxicity in light of the patient's prior extensive mitoxantrone exposure. In light of our experience, as well as that of others, one can argue for the use of this combination for induction and consolidation in all patients who have a significant risk of anthracycline induced cardiotoxicity.

There are other reasons that a ‘chemotherapy-free’ regimen may be particularly desirable. Patients with advanced age, poor organ function and poor performance status may not be good candidates for traditional cytotoxic chemotherapy and may benefit significantly from this approach. Furthermore, although the incidence of secondary myelodysplastic syndrome following treatment of APL with chemotherapy-based regimens is extremely low, there are several reported cases in the literature [12,13]. Therefore, if the ATRA plus ATO regimen is proven to be at least as effective as the standard chemotherapy plus ATRA regimens, it can be argued that it should be the preferred regimen in all patients, irrespective of their age, organ function or performance status. Ongoing clinical trials will attempt to address this question. In conclusion, despite significant strides in treating patients with APL, the story remains un-ended with future chapters hopefully introducing regimens with limited or no toxicity and universal success.

References

1. Pedersen-Bjergaard J, Rowley JD. The balanced and the unbalanced chromosome aberrations of acute myeloid leukemia may develop in different ways and may contribute differently to malignant transformation. Blood. 1994; 83:2780–2786. [PubMed: 8180374]
2. Pulsoni A, Pagano L, Lo Coco F, et al. Clinicobiological features and outcome of acute promyelocytic leukemia occurring as a second tumor: the GIMEMA experience. Blood. 2002; 100:1972–1976. [PubMed: 12200354]

3. Beaumont M, Sanz M, Carli PM, et al. Therapy-related acute promyelocytic leukemia. J Clin Oncol. 2003; 21:2123–2137. [PubMed: 12775738]
4. Mistry AR, Felix CA, Whitmarsh RJ, et al. DNA topoisomerase II in therapy-related acute promyelocytic leukemia. N Engl J Med. 2005; 352:1529–1538. [PubMed: 15829534]
5. Hasan SK, Mays AN, Ottone T, et al. Molecular analysis of t(15;17) genomic breakpoints in secondary acute promyelocytic leukemia arising after treatment of multiple sclerosis. Blood. 2008; 112:3383–3390. [PubMed: 18650449]
6. Aversa SML, Trentin C, Sorarů M, et al. Acute promyelocytic leukemia after Stanford V plus radiotherapy for advanced Hodgkin lymphoma. Leuk Lymphoma. 2009; 50:1214–1216. [PubMed: 19557643]
7. Soignet SL, Frankel SR, Douer D, et al. United States multicenter study of arsenic trioxide in relapsed acute promyelocytic leukemia. J Clin Oncol. 2001; 19:3852–3860. [PubMed: 11559723]
8. Mathews V, George B, Lakshmi KM, et al. Single-agent arsenic trioxide in the treatment of newly diagnosed acute promyelocytic leukemia: durable remissions with minimal toxicity. Blood. 2006; 107:2627–2632. [PubMed: 16352810]
9. Alimoghaddam K, Shariftabrizi A, Tavangar SM, et al. Antileukemic and anti-angiogenesis efficacy of arsenic trioxide in new cases of acute promyelocytic leukemia. Leuk Lymphoma. 2006; 47:81–88. [PubMed: 16321832]
10. Ravandi F, Estey E, Jones D, et al. Effective treatment of acute promyelocytic leukemia with all-trans-retinoic acid, arsenic trioxide, and gemtuzumab ozogamicin. J Clin Oncol. 2009; 27:504–510. [PubMed: 19075265]
11. Ammatuna E, Montefusco E, Pacilli M, et al. Use of arsenic trioxide in secondary acute promyelocytic leukemia developing after treatment of multiple sclerosis with mitoxantrone. Leuk Lymphoma. 2009; 50:1217–1218. [PubMed: 19479616]
12. Andersen MK, Pedersen-Bjergaard J. Therapy-related MDS and AML in acute promyelocytic leukemia. Blood. 2002; 100:1928–1929. author reply 1929, 2002. [PubMed: 12211197]
13. Garcia-Manero G, Kantarjian HM, Kornblau S, Estey E. Therapy-related myelodysplastic syndrome or acute myelogenous leukemia in patients with acute promyelocytic leukemia (APL). Leukemia. 2002; 16:1888. [PubMed: 12200720]