Expanding the Use of Retinoids in Acute Myeloid Leukemia: Spotlight on Bexarotene

Commentary on Tsai et al., p. 5619

Suzan McNamara and Wilson H. Miller, Jr.

In this issue, Tsai et al. (1) report on a phase-I clinical trial of bexarotene in 27 non-M3 acute myeloid leukemia (AML). AML is characterized by abnormalities in the myeloid line at various stages of commitment and maturation, leading to an accumulation of granulocyte or monocyte precursors. The French, American, and British classification system divided the subtypes of AML, M1 through M7, based on the stage of development of myeloblasts at the time of diagnosis. With the exception of M3 AML, all AML subtypes are typically treated with intensive chemotherapy induction aimed to bring the patient into complete hematologic remission. Eradication of residual disease to prevent AML relapse requires consolidation therapy, which consists of intensive chemotherapy alone or in combination with stem cell transplantation. Nevertheless, there is a high risk of relapse, and long-term survival is less than 50%. Furthermore, the low tolerance to intensive chemotherapy observed in many elderly AML patients poses a treatment challenge in a disorder that is primarily diagnosed in older adults.

Retinoids serve as intracellular messengers or activating ligands for the retinoic acid receptors (RAR) and retinoid X receptors (RXR). Because of their potential to inhibit growth and promote differentiation, retinoids hold therapeutic promise in treating cancer, especially when used in combination with other chemotherapeutic agents. Most notably, in acute promyelocytic leukemia patients, the M3 AML subset, differentiation therapy induced by all-trans-retinoic acid has provided one of the first examples of a successful therapy that targets the molecular cause of an aggressive malignancy (2). Apart from acute promyelocytic leukemia, there has been little evidence that other AML subtypes could respond to retinoid differentiation therapy. This has been frustrating because in vitro studies have shown more promising results. For instance, the retinoid bexarotene (Targetin®) has been shown to be effective in AML cell lines by inhibiting proliferation and inducing differentiation (3). Moreover, the combination treatment of retinoids and cyclic AMP–elevating drugs triggered differentiation and apoptosis in AML patient blasts and all-trans-retinoic acid–insensitive AML cells (4). These encouraging preclinical results prompted Tsai et al. (1) to test the efficacy and safety of bexarotene in non-M3 AML patients.

Tsai et al. (1) report on a phase I clinical trial of bexarotene in 27 non-M3 AML patients who had relapse, had refractory AML, or were not eligible for chemotherapy. This study was designed to evaluate bexarotene tolerability, toxicity, and activity. Bexarotene was administered daily at escalating doses of 100 to 400 mg/m². Overall, bexarotene was well tolerated, with only one patient reaching dose-limiting toxicity. The most common adverse effects were hypertriglyceridemia and hypothyroidism, which were controlled with antihyperlipidemic agents and thyroid replacement hormone, respectively. However, due to the occurrence of a grade 3 rash in three of six patients who were treated at the highest dose of 400 mg/m², the maximum tolerated dose was determined to be 300 mg/m². Response was based on changes in peripheral blood counts and bone marrow blast percentage. Five patients achieved a significant clinical response, of whom four experienced a reduction in bone marrow blasts to ≤5% and one patient had a considerable reduction in blast count from 90% to 20%. Four patients who were thrombocytopenic at the time of study initiation had platelet responses, and seven patients had improved neutrophil counts. Medium overall survival rate was 3.4 months, with a range of 0.1 to 18.8+ months. After 1 year of study, three patients had continued improvements in their blood counts.

Evidence of myeloid differentiation was identified in the three patients with improved absolute neutrophil count and reduction in leukemic blasts. Fluorescence in situ hybridization analysis was done on peripheral blood granulocytes using probes for the patients’ known leukemic cytogenetic abnormality. Indeed, between 92% and 100% of the mature circulating granulocytes held the patients’ respective cytogenetic abnormality. These intriguing results suggest a leukemic origin with myeloid differentiation. Further evidence of myeloid differentiation was observed in two patients who developed symptoms consisting of respiratory distress, dry cough, pleural and/or pericardial effusions, edema, and a rapidly increasing neutrophil count. Symptoms were resolved within 48 hours of discontinuation of bexarotene and initiation of steroids. Interestingly, these adverse effects closely mirror the differentiation syndrome observed in ~25% of acute promyelocytic leukemia patients treated with all-trans-retinoic acid or arsenic trioxide. Although still not completely understood, it is thought that the syndrome is caused by the release of cytokines from differentiating malignant myelocytes.

Bexarotene is a synthetic retinoid compound that has shown efficacy in the treatment of cutaneous T-cell lympho-
ma (5, 6). Bexarotene selectively binds and activates all three RXR subtypes (RXR-α, RXR-β, and RXR-γ), whereas it has low affinity for RARs. RXRs form homodimers in vitro and serve as heterodimerization partners for several nuclear receptors (7). Consequently, RXR enhances the binding of the partner receptor to its cognate response element, which is required for proper activation function. Once activated, RXR heterodimers function as transcription factors that regulate gene expression. Thus, RXR serves as an integrative partner in multiple signaling pathways (Fig. 1). RXR signaling comprises two types of ligand-mediated transcriptional activation termed permissive and nonpermissive. Permissive partners can be activated by an RXR agonist or a partner receptor agonist, independently or together, to induce a synergistic activation. In contrast, nonpermissive nonliganded partners inhibit RXR agonist activation, a phenomenon called RXR subordination (8). Heterodimers formed by RAR and RXR are nonpermissive because they activate transcription only upon RAR ligand binding. However, in the presence of both RAR and RXR ligands, synergistic activation of transcription is induced through a heterodimeric allosteric mechanism (9, 10). In addition, a mechanism has been described by which protein kinase A activation leads to corepressor release from RAR that permits RXR agonists to activate the RXR/RAR heterodimer (4, 11). Whether bexarotene induces its effects in AML patients through synergy with RAR ligands or perhaps through a RAR-independent pathway via other heterodimer partners still remains unclear. To add further complexity, bexarotene may elicit its effects through epigenetic modulations, as observed with the ability of all-trans-retinoic acid to induce epigenetic changes associated with transcriptional activation (12, 13). These clinical results will encourage future studies to delineate the genes, signaling pathways, and molecular mechanisms responsible for bexarotene activity in AML blasts.

In conclusion, the trial by Tsai et al. (1) establishes bexarotene as safe and potentially useful for the treatment of non-M3 AML patients. This study provides the first evidence of differentiation syndrome in non-M3 AML patients and suggests that bexarotene has the ability to induce the maturation of AML blasts. The optimal dose of 300 mg/m² is now being evaluated in phase II trials, where bexarotene monotherapy will be tested in AML patients to further explore its safety, bone marrow response rates, and overall survival. However, it is likely that this agent will work best in combination with other agents and only in certain subtypes of AML patients. Additional studies will be needed to define combination treatments and profiles of responsive versus nonresponsive patients. Nonetheless, this study opens novel perspectives for a differentiation therapy that may offer real promise in the treatment of AML.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References


Expanding the Use of Retinoids in Acute Myeloid Leukemia: Spotlight on Bexarotene

Suzan McNamara and Wilson H. Miller, Jr.


Updated version
Access the most recent version of this article at:
http://clincancerres.aacrjournals.org/content/14/17/5311

Supplementary Material
Access the most recent supplemental material at:
http://clincancerres.aacrjournals.org/content/suppl/2008/09/18/14.17.5311.DC1

Cited articles
This article cites 13 articles, 8 of which you can access for free at:
http://clincancerres.aacrjournals.org/content/14/17/5311.full.html#ref-list-1

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.