

inside blood

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● ● ● CLINICAL TRIALS & OBSERVATIONS

Comment on Petersdorf et al, page 4854, and on Rowe and Löwenberg, page 4838

Why is it so difficult to use gemtuzumab ozogamicin?

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In this issue of *Blood*, Petersdorf et al report negative results of the phase 3 study designed by the Southwest Oncology Group (SWOG), which tested the addition of gemtuzumab ozogamicin (GO) to a 3+7 regimen in a randomized fashion in adult patients newly diagnosed with acute myeloid leukemia (AML) who are younger than 60 years.¹ Also in this issue of *Blood*, Rowe and Löwenberg discuss results of this study in the context of 4 other controlled studies (1 negative and 1 positive in a predefined subset of patients, and 2 positive) performed during the same period in Europe.²

Rowe and Löwenberg mainly explain observed contradictory results as being a result of the different doses of daunorubicin or GO used across the studies. They also underline the apparent paradox of better outcomes being observed in positive studies

in patients treated with GO, despite there being no higher complete remission rate, which is likely explained by a better quality of remission. Indeed, results from minimal residual disease monitoring throughout the Randomized Study of GO With

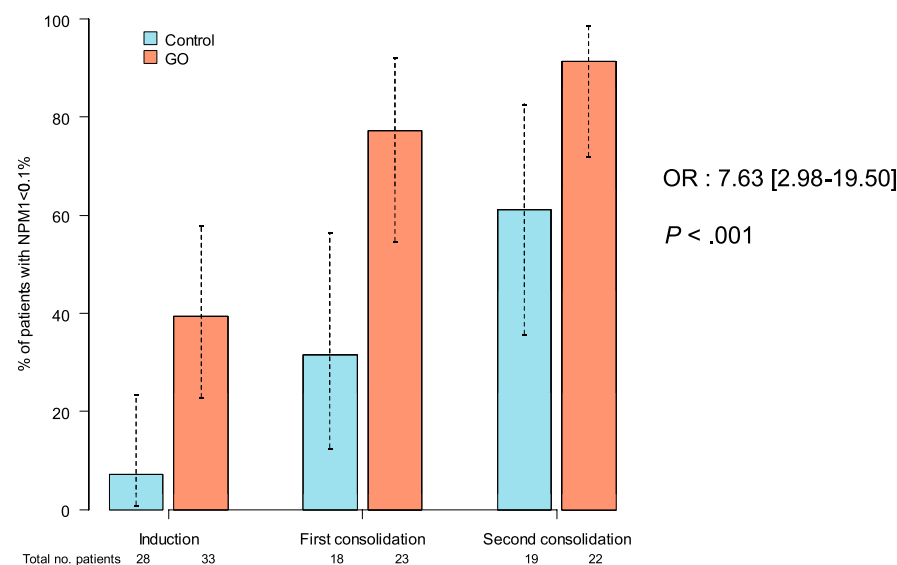
Daunorubicine and Cytarabine in Untreated AML Aged of 50–70 Years Old, known as the ALFA 0701 study, showed that a good MRD response was associated with an increase in overall survival and that *NPM1* minimal residual disease (MRD) good responders were significantly more frequent in the GO group compared with in the control group ($P < .0001$; see figure).³

Some other comments can be added: The 2 negative studies from the SWOG and the Groupe Ouest Est d'Etude des Leucémies et Autres Maladies du Sang (GOELAMS) have used nearly the same design. They were performed in younger patients, and allogeneic transplant may be a confounding factor on outcome. They used a single dose of 6 mg/m² GO, which is likely to be too toxic in combination with other chemotherapy. Indeed, the Medical Research Council (MRC) feasibility phase 2 study showed that a dose of 6 mg/m² GO in addition to chemotherapy was associated with an excess of liver and hematological toxicity.⁴ In particular, profound and prolonged thrombocytopenia is observed with GO.

The specific toxicity of GO on the platelet lineage is not fully understood. It may be a result of calicheamicin, as thrombocytopenia has also been described with the use of inotuzumab ozogamicin, a monoclonal antibody against CD22.⁵ Prolonged thrombocytopenia appears dose-related, with less platelet toxicity in the MRC studies than in the ALFA 0701 study.^{6,7}

The significant difference in early death rate observed in the SWOG study can be explained by a very low and unusual death rate in the control group and by an excess of death from hemorrhage in the GO group.

Finally, in the SWOG and GOELAMS studies, GO was added at day 4 of the induction course, perhaps when many of the CD33 antigens and blasts cells had been eliminated by the first 3 days of treatment with Daunorubicin and Cytarabine.



ALFA 0701 study. Minimal residual response assessed by *NPM1*^{mut} transcript levels in patients treated with or without GO.

How can we explain the difficulties in finding the best way to use GO? Calicheamicin is a very toxic intercalating agent that is 1000-fold more potent in vitro than doxorubicin. Its conjugation with a monoclonal antibody allows the drug to be delivered directly to leukemic cells and explains its efficacy, but the favorable risk–benefit ratio of the conjugate may be only within a narrow dose range. The use of repetitive low doses is likely a way to enhance the drug’s efficacy without increasing toxicity.^{6,8} The ongoing study AML18, from the United Kingdom, is testing a single dose vs 2 doses of 3 mg/m² of GO in addition to standard induction.

In addition, as underlined by Rowe and Löwenberg, the efficacy of GO is, unsurprisingly, observed in chemosensitive AML, as in AML with high CD33 expression. This was shown in acute promyelocytic leukemia and in the ALFA study in NPM1-positive AML.⁶ In this regard, future results from the ongoing controlled German study in NPM1-positive patients and detailed analysis of the interactions between the effect of GO and molecular AML subsets within the MRC studies will be of major interest.

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● ● ● LYMPHOID NEOPLASIA

Comment on Boyerinas et al, page 4821

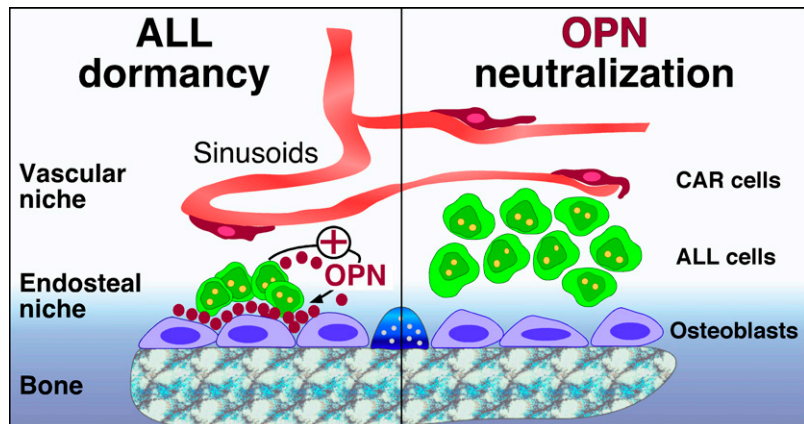
Osteopontin: an unhealthy sleep remedy for ALL

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In this issue of *Blood*, Boyerinas and colleagues report about a novel mechanism of leukemia cell evasion from chemotherapy.¹

Acute lymphoblastic leukemia (ALL) cells hijack endosteal bone marrow niches by adherence to osteopontin (OPN), a highly acidic extracellular matrix protein. Normally, OPN is secreted by osteoblasts and functions as a bridge between bone and blood, ie, between the endosteal marrow niche and hematopoietic progenitor cells (HPCs). In these niches, HPCs remain quiescent because of OPN-suppressed proliferation, presumably to maintain and limit the size of the HPC pool.^{2,3} The authors hypothesized that ALL cells may use a similar OPN-dependent mechanism to occupy endosteal niches, where quiescent ALL cells can replace HPCs and survive conventional cytotoxic chemotherapy.

The authors demonstrate that ALL cells adhere to OPN via integrins ($\alpha 4\beta 1$, $\alpha 5\beta 1$, $\alpha 9\beta 1$) and, in addition, actively secrete OPN, thereby participating in the remodeling of the niche. In a xenograft mouse model, highest levels of OPN were seen around dormant ALL cells. Through this OPN-mediated mechanism, ALL cells survive in endosteal niches and can become the seed for minimal residual disease and relapses. Consequently, the authors demonstrate that OPN neutralization with antibodies awakens ALL cells in the ALL mouse model, causing an increase in dividing/cycling ALL cells, which in turn sensitized ALL cells to cytarabine (Ara-C) therapy.



Potential role of OPN in ALL cell dormancy. In the marrow microenvironment, HPCs are maintained in perivascular and endosteal niches, which also can be occupied by ALL and other leukemia cells. In the osteoblast niches, osteoblasts and ALL cells secrete OPN, which becomes part of the extracellular matrix and builds a bridge between ALL cells and osteoblasts/the bone (left). Adherence of ALL cells to OPN via adhesion molecules causes ALL cell dormancy, which makes ALL cells less susceptible to cytotoxic drugs, such as Ara-C. ALL cell dormancy can be reversed by OPN neutralization (right), which causes an increase in dividing/cycling ALL cells. This reversal of ALL cell dormancy by OPN neutralization can potentially be used for “chemosensitization” to target dormant ALL cells that otherwise survive conventional polychemotherapy.