The optimal dosing of gemtuzumab ozagamicin: where to go from here?

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Incomplete eradication of the malignant clones in high-risk *de novo* acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) and secondary AML (sAML) is the main cause of treatment failure, demonstrated by a relatively low complete remission (CR) rate and a high early relapse rate of more than 50%, unless treated by allogeneic hematopoietic stem cell transplantation (AHCT). High-risk features include age 60 years or older, co-morbidities, preceding MDS, and adverse risk (cyto)genetic risk factors.[1] Therefore, new studies focus on new and better remission-induction and consolidation regimens containing innovative agents. Gemtuzumab ozogamicin (GO) consists of a humanized anti-CD33 monoclonal antibody linked to calicheamicin, a potent antitumor antibiotic.[2] GO binds to CD33, an antigen expressed on the surface of more than 90% of AML blast cells. Binding of GO is followed by internalization and toxin release intracellularly leading to DNA damage and cell death.[3] In studies of older patients with AML in first relapse, tolerable toxicity and a response rate of 30% was reported following two infusions of GO 9 mg/m^2, although full platelet recovery did not occur in roughly half of responders.[4] These results led to regulatory approval of the drug in the United States for use in older patients in first relapse for whom standard therapy was unsuitable, setting the stage for its evaluation in patients with newly diagnosed high-risk AML/MDS. However, GO was voluntarily withdrawn from the market in 2010 on the basis of preliminary results from a phase III Southwest Oncology Group (SWOG) randomized study in 673 young adults with untreated AML.[5] This study compared the addition of single infusion of 6 mg/m^2 on day 4 of the first remission-induction course (daunorubicin (45 mg/m^2 on days 1, 2, 3) and cytarabine (100 mg/m^2 per day by continuous infusion on days 1-7) *versus* standard induction therapy with daunorubicin (60 mg/m^2 on days 1-3) and cytarabine alone by continuous infusion on days 1 through 7 (DA). The CR rate was 69% for DA+GO and 70% for DA. The overall efficacy, as measured by the relapse-free survival and the overall survival (OS), was similar in both groups. However, the induction mortality was increased in the DA+GO group, at 5% *versus* 1% in the DA group.

Since then, several randomized studies combining GO with intensive chemotherapy in patients with newly diagnosed AML have been reported in the literature providing new evidence on the clinical efficacy and safety of the immunoconjugate. A recent meta-analysis of 5 prospective studies, including the final data from the SWOG[5] (total n=3325 patients)[6] showed that addition of GO did not increase the proportion of patients entering CR with an odds ratio (OR) of 0.91 and a 95% confidence interval (CI) of 0.77-1.07 (P=0.3). However, the addition of GO significantly improved survival (OR 0.90; 95%CI: 0.82-0.98, P=0.03), although the 5-year OS difference was only around 3%: 35.5% (GO arm) *versus* 32.2% (control group). Unfortunately, patients with adverse cytogenetic characteristics did not benefit from the addition of GO in contrast to patients with favorable or intermediate cytogenetic features who did benefit.[6] The great majority of patients in this meta-analysis were patients with *de novo* AML. Only two studies[7,8] included patients with sAML and only one study included HR-MDS patients.[8] Increased toxicity and an absence of clinical benefit were observed in the EORTC/GIMEMA study, in which single-agent GO administration preceded induction chemotherapy.[9]

As reported in this issue of the Journal, Burnett and coworkers evaluated two doses of GO (6 *vs*. 3 mg/m^2) in a large prospective, randomized trial: the National Cancer Research Institute (NCRI) AML17 trial.[10] GO was usually administered as a single infusion on day 1 of the remission-induction course. They assessed the toxicity profile and antitumor activity of GO in combination with a chemotherapy remission-induction regimen in 673 adults (85%) with untreated *de novo* AML, 42 patients (5%) with high-risk MDS (HR-MDS) (defined as MDS with BM blasts higher than 10%), and 73 patients (9%) with sAML. There was no difference in overall response rate [defined as complete remission (CR) or CR with incomplete hematopoietic recovery (CRi)] between the two evaluated dose levels. All patients received various schedules of chemotherapy without GO after the first remission-induction course, depending on the risk status after the first remission-induction course and the presence of FLT-3 abnormalities. The overall survival and relapse risk did not differ despite a higher non-relapse (early) mortality and veno-occlusive disease (VOD) in the higher GO group (6 mg/m^2). In addition, grade 3-4 serious adverse events (SAEs) were significantly higher in the higher dose GO group. Subgroup analysis did not show any difference in outcome in any subgroup. This large randomized study did not show any significant benefit of using GO at the 6 mg/m^2 dose, although there was a possible trend for benefit in the adverse risk patients, who have not been shown to benefit from addition of GO in other trials. The 6 mg/m^2 dose did have a detrimental effect with respect to liver toxicity and platelet count recovery; therefore, the outcome of this study suggests that, where a single dose schedule is used, the 3 mg/m^2 dose might be preferred.

The question remains as to whether fractionated dosing using the lower dose of 3 g/m^2 results in better outcome or whether addition of GO to the consolidation course(s) may increase the benefit without additional toxicity, and the authors present a comprehensive discussion of this. It is possible that a more fractionated schedule with a higher total dose of GO might be a more effective strategy, which may take advantage of the CD33-re-expression that occurs after initial exposure to GO.[11] The French ALFA group utilized a GO schedule of 3 mg/m^2/day on days 1, 4 and 7 during induction chemotherapy, followed by a single dose in each of two post induction courses, in patients aged 50-70 years with untreated *de novo* AML. Complete response was 81% and event-free survival was 40.8% compared to 17.1% in

the control group (P=0.003).[12] It is plausible that at least some of the benefit was achieved by dosing in consolidation, but also the fractionation of the total GO dose during induction may have contributed to the most prominent effect in this French ALFA group study. This benefit was also apparent in patients with unfavorable cytogenetic characteristics, but the impact of complex karyotype has not been analyzed separately.[12] In addition, early mortality seems to be reduced when a dose of 3 g/m^2 is used either as a single dose or in a fractionated schedule.[6] There was some hematologic toxicity, particularly to platelets. So, while a 3 mg/m^2 dose appears adequate, it is still not certain what is the optimal schedule.

However, the MRC AML15 trial did not show any additional benefit of adding GO to consolidation irrespective of whether it had been given with the first induction course;[7] therefore the urgent issue to be resolved is whether a single dose or a fractionated schedule is to become the standard approach. In an attempt to do this, the NCRI have initiated a direct comparison of a 3 mg/m^2 dose on day 1 *versus* days 1 and 4 in their ongoing trials.

In conclusion, data from this study and from studies published after the withdrawal of GO from the market support the need for a re-appraisal of the regulatory approval of GO by the responsible authorities, at least for certain subtypes of AML.

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HOXA-activated early T-cell progenitor acute lymphoblastic leukemia: predictor of poor outcome?

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The outcome for T-cell acute lymphoblastic leukemia (T-ALL) has strongly improved over the last decades using high-intensity treatment protocols approaching cure rates of 80% for pediatric patients and 60% for adult patients. Fifteen percent of pediatric ALL patients present with T-ALL, and they represent nearly half of the ALL patients who require the most intensive treatment. Intensive chemotherapy increases the risk for treatment related morbidity and mortality. For relapsed patients, the outcome is poor, as T-ALL cells in those patients are highly resistant to further treatment. Therefore, patient-tailored treatment and the introduction of high precision medicines remain important. Molecular cytogenetic characterization of T-ALL has greatly increased our understanding of the pathogenic events that drive this disease. In contrast to precursor B-ALL, this improved insight into T-ALL has not yet yielded prognostic factors that allow for the identification of patients at high-risk of relapse and who may be eligible to receive alternative treatment, including allogeneic stem cell transplantation.

One cytogenetic entity in pediatric and adult T-ALL patients that has been suspected to cause poor outcome include patients bearing a *CALM-AF10* (*PICALM-MLLT10*) fusion as a consequence of a t(10;11)(p13.14;q14-21) chromosomal translocation.[1] A first systematic study comprising unselected pediatric and adult T-ALL patients treated on FRALLE-93, FRALLE 2000 or LALA-94 protocols identified the *CALM-AF10* fusion in approximately 9% of patients. This fusion is associated with early and late T-cell developmental arrest in the γδ lineage. In this study, late *CALM-AF10*$^+$ T-ALL patients responded well to therapy, but 2 out of 12 *CALM-AF10*$^+$ patients with an immature phenotype did not respond to therapy, and another 8 patients with an immature phenotype