Sustained molecular remission after low dose gemtuzumab-ozogamicin in elderly patients with advanced acute promyelocytic leukemia

We report here a preliminary experience with gemtuzumab ozogamicin (GO) used at low dosage (3 mg/m²) in 3 elderly patients with acute promyelocytic leukaemia (APL) who presented molecular relapse and were unfit for intensive chemotherapy.

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A 72 year-old male with APL, presented with third molecular relapse after 4 months from last therapy. He had been treated previously with the AIDA protocol[1] as front-line therapy and, at first molecular relapse developed after 24 months of ATRA maintenance he had received GO at 6 mg/m² achieving a new molecular remission after two doses. He had then received a third dose of GO and had persisted in second molecular remission for 37 months. At time of second molecular relapse, due to concomitant cerebral hemorrhage, he was treated with only ATRA at 45 mg/m² for 30 days. He achieved a new (third) molecular remission, that persisted for only 4 months. At this time RQ-PCR revealed 72 copies of PML/RARα transcript. He was then treated with GO at 3 mg/m² and after 2 months (and 2 doses), RQ-PCR and RT-PCR showed 0 copies and negativity of the test, respectively. He was consolidated with another GO dose, again at 3 mg/m². Treatment was accompanied by only mild neutropenia during the first cycle (9 days duration) and no other relevant side effects. The patient remained in third complete molecular remission after 10 months, but then died suddenly of a stroke episode.

A 71 year-old male with APL received the AIDA protocol followed by two years ATRA maintenance. While receiving maintenance therapy for APL he developed non metastatic prostate cancer that was treated with hormonal therapy. After 36 months from last ATRA maintenance cycle he underwent molecular relapse with 60 PML/RARα hybrid transcript copies detected by RQ-PCR. He received two courses of GO at 3 mg/m² after which RQ-PCR revealed a new molecular remission. He was then consolidated with a further course of GO at the same dosage. Mild neutropenia of 6 days duration was observed after each GO course. At present, the patient maintains molecular remission thirteen months after initiating GO.

A 66 year-old man with APL developed first molecular relapse after 30 months from completion of the AIDA protocol. Because of antecedent cardiac ischemia, he was considered not eligible for intensive chemotherapy. At time of molecular relapse, RQ-PCR revealed 141 copies of the hybrid transcript. This value dropped to 2 copies after two GO courses at 3 mg and molecular remission with 0 copies of the PML/RARα transcript was achieved with the third GO dose which was followed by a 4th course. The patient is presently alive and in molecular remission 14 months after re-induction.

GO is a recombinant anti-CD33 monoclonal antibody conjugated to calicheamicin, a potent chemotherapeutic agent. Binding of GO to the CD33 antigen is followed by endocytosis, cleavage of the covalent link between calicheamicin and the antibody, and release of calicheamicin which causes site-specific double-stranded cleavage of DNA in target cells.[2-5]

GO has been successfully used in various settings related to APL therapy including front-line use with or without ATRA and arsenic trioxide. The high efficacy of this agent in APL has been attributed not only to CD33 expression but also to low levels of P-gp activity in leukemic promyelocytes.[6,10] More recently, Takeshita *et al.*[7] have shown that GO is effective in APL cells resistant to ATRA or arsenic trioxide (ATO). As to the doses adopted in newly diagnosed APL, GO has been generally used at 9 mg/m² both in induction and in post-remission therapy, with a CR rate of 84%.[8-10]

In our previous study on patients with advanced molecular relapse, GO was administered as single agent at 6 mg/mq for three doses and molecular remission was achieved in all patients after the third dose.[10] In the present report, we treated elderly APL patients with GO at very low dosage (3 mg/mq), because we considered these patients unfit for intensive chemotherapy due to co-morbidities. In addition, such low dose GO was chosen with the aim of avoiding or minimising myelosuppression and thrombocytopenia in particular that is commonly observed with GO at 6-9 mg/m², thus with the additional objective of preventing hospitalization. In all the 3 cases hereby reported GO was administered on an outpatient basis, by 2-hour i.v. infusion after premedication with acetaminophen and prednisone (Table 1). We didn't observe serious adverse reaction after completion of GO infusion nor any significant treatment related tox-

Table 1. Clinical and biological features before GO and administration.

Pt.	*Age/sex*	*Cause of non-eligibility*	*Time to relapse (mos)*	*CD33 expression (%)*	*GO administration (all outpatient)*	*Side effects observed*
1	72/m	Cerebral hemorrhage	4	96	2 h infusion premedication with PDN+ acetaminophen	Neutropenia (> 600/mmc)
2	71/m	Prostatic carcinoma	36	97	2 h infusion premedication with PDN+ acetaminophen	Neutropenia (> 700/mmc)
3	66/m	Cardiac ischemia and sub-aracnoidal hemorrhage	30	98	2 h infusion premedication with PDN+ acetaminophen	No side effects

icity. Mild neutropenia of short duration was observed in the three cases but neither thrombocytopenia nor hepatic side effects occurred. We observed rapid negativization of RQ-PCR after two doses in two patients, whereas in the third patient complete molecular response was obtained after 3 courses, probably due to the higher initial amount (141 copies) of PML/RARα hybrid detected prior to GO therapy. In addition, the use of RQ-PCR to assess the kinetics of PML/RARα decrease, allowed us to detect in all cases a rapid decline of the hybrid transcript after the first GO administration

In conclusion, our findings suggest that low-dose GO are effective to treat molecular relapse in elderly APL patients. Use of this schedule with other treatments of proven efficacy such as ATRA or ATO may be extended to other clinical settings including younger patients unfit to conventional chemotherapy.[11] Finally, whether confirmed in other series, this data may lead to explore a role for low dose GO in maintenance therapy of APL.

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