Advanced Philadelphia chromosome positive acute lymphoblastic leukemia patients relapsed after treatment with tyrosine-kinase inhibitors: successful response to clofarabine and cyclophosphamide

by Antonella Vitale, Sara Grammatico, Saveria Capria, Carina Fiocchi, Robin Foà, Giovanna Meloni

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Advanced Philadelphia chromosome positive acute lymphoblastic leukemia patients relapsed after treatment with tyrosine-kinase inhibitors: successful response to clofarabine and cyclophosphamide

Philadelphia chromosome positive acute lymphoblastic leukemia (Ph+ ALL) includes at least one-quarter of adults with ALL. Treatment with tyrosine-kinase inhibitors (TKIs), with or without chemotherapy, represents today the most appealing management both in terms of complete remission (CR) and disease-free survival (DFS), and towards providing eligible patients a bridge to hematopoietic stem cell transplantation (HSCT). However, relapsed Ph+ ALL is still regarded as an almost incurable disease. Clofarabine, a second generation deoxyadenosine analog, has demonstrated significant activity in children and adults with refractory lymphoid and myeloid leukemia in early clinical trials. To improve its single-agent antileukemic activity different clofarabine combinations are being studied. With the clofarabine-cyclophosphamide combination, two phase I studies testing different doses and schedules have been reported in relapsed adult ALL; several dose-limiting toxicities were observed.

We report our experience on two adult female patients with Ph+ ALL in advanced phase and refractory to treatment with chemotherapy and TKIs. The first patient was a 57-year-old female, diagnosed in August 2005 with BCR-ABL p190 ALL, and treated according to the GIMEMA LAL 2000 protocol, which provided a maintenance therapy with imatinib 600 mg/day. The patient, 17 months from the first CR (after 15 months of imatinib), suffered a first relapse and molecular analysis revealed the presence of the ABL point mutation Y253H. Salvage treatment with vincristine, daunorubicin and prednisone (PDN) allowed to obtain a second CR; consolidation therapy was planned according to the GIMEMA LAL 0288 protocol. The patient started maintenance treatment with dasatinib (70 mg BID) and monthly intrathecal methotrexate. After 5 months (8 months from the second CR), a second relapse occurred.

The second patient was a 59-year-old female, diagnosed in February 2007 with BCR-ABL p210 ALL and treated according to the GIMEMA LAL 1205 protocol, consisting of front-line therapy with dasatinib and PDN alone. After achieving CR, the patient continued therapy with imatinib (600 mg/day) up to the first relapse 4 months later (5 months from CR). Molecular analysis revealed the presence of the E255K-ABL point mutation. She received salvage treatment and consolidation as the other patient. Three months after the second CR, a second relapse occurred and dasatinib (70 mg BID) was re-administered; the patient achieved a new CR, but a third relapse occurred 4 months later (1 month after the third CR) and the molecular analysis showed a T315I-ABL point mutation. Patient received clofarabine 40 mg/m² by a 1 hour intravenous (iv) infusion followed by cyclophosph-

Figure 1. The graphics show the molecular monitoring of BCR-ABL levels by quantitative reverse-transcriptase polymerase-chain-reaction (Q-RT-PCR) in the two patients. Values obtained were normalized with respect to the number of ABL transcripts and expressed as a percentage of ABL (BCR-ABL/ABLx10⁻²); patient transcript ratios were converted to a logarithmic (base 10) scale of reduction from individual baseline ratio BCR-ABL/ABL assayed at diagnosis. A. BCR-ABL p190 levels in patient n° 1 during follow-up. After the consolidation cycle, the combination of clofarabine + cyclophosphamide produced a molecular response with a >2 log reduction of the BCR-ABL transcript, which was maintained until the time of transplant. B. BCR-ABL p210 transcript levels in patient n° 2. A 1 log reduction of BCR-ABL was observed after the consolidation cycle of therapy with clofarabine + cyclophosphamide. The transcript levels decreased further at the start of maintenance treatment with imatinib and remained at low levels at the time of the report.
phamide 400 mg/m² by a 1 hour iv infusion, from day 1 to 5, as induction phase. G-CSF was initiated at the onset of neutropenia and continued up to a neutrophil count ≥1.0x10⁹/L. Prophylactic PDN (10 mg/m²/daily) was given to prevent potential systemic inflammatory response. Allopurinol 300 mg/day was administered to prevent the occurrence and complications of tumor lysis—induced hyperuricemia. Antimicrobial, viral and fungal prophylaxis consisting of trimetoprim-sulfametoxazole and ciprofloxacin, acyclovir and itraconazole was administered. Consolidation with clofarabine and cyclophosphamide was given, at the same doses as the first cycle, for 3 days with the same supportive treatment. The trial was approved by the local ethic committee and executed in accordance with the Declaration of Helsinki. All analyses of peripheral blood (PB) and BM are part of the investigatory work-up for all adult ALL cases entering the GIMEMA trials. The presence of ABL point mutations was assayed as previously described. The first patient exhibited an hematologic recovery at day +20 and a BM aspirate performed at day +21 confirmed the CR. Moreover, after consolidation, a molecular response consisting of a 2-log reduction of the BCR-ABL transcript (Figure 1A) was also seen. One month later, the patient underwent an HSCT from a mismatched unrelated donor and died of respiratory distress syndrome. The second patient exhibited an hematologic recovery on day +16 and the BM aspirate performed on day +17 confirmed the CR. Moreover, after the consolidation, a molecular response consisting of a 1-log reduction of the BCR-ABL transcript (Figure 1B) and absence of the T315I-ABL mutation was also evident. The patient was unsuitable for an HSCT and imatinib (600 mg/day) was re-started as maintenance therapy, taking into account both the disappearance of the ABL point mutation and the possibility of utilizing a second-generation TKI as further salvage therapy. After 5 months from clofarabine-cyclophosphamide treatment, she is still in CR with a low number of BCR-ABL transcript copies (Figure 1B) and absence of ABL mutations. The clofarabine-cyclophosphamide combination was very well tolerated. No patient suffered from nausea, vomiting or dose-limiting toxicities. Possibly in view of the rapid hematologic recovery and strict antimicrobial prophylaxis, both patients did not develop infections. Clofarabine followed by cyclophosphamide seems to be a very promising salvage treatment for adult patients with advanced ALL, even in the presence of adverse prognostic factors like the BCR-ABL rearrangement, relapse after TKI administration and presence of the T315I mutation. Clinical trials on large series of patients will conclusively elucidate the efficacy and safety of this combination.

Antonella Vitale,1 Sara Grammatico,1 Savëria Caprina,1 Carina Fiacchi,1 Robin Foà,1 Giovanna Meloni1
1Division of Hematology, Department of Cellular Biotechnologies and Hematology, “Sapienza” University Rome, Italy; 2Genzyme (Genzyme S.R.L, Italy)

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Correspondence: Giovanna Meloni, MD, Division of Hematology, Department of Cellular Biotechnologies and Hematology, “Sapienza” University Via Benevento 6, Rome, 00161 Italy. Phone: international +39 06 85735751/85735773. Fax: international +39 06 4466516. E-mail: meloni@bce.uniroma1.it

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