

## LACK OF EFFICACY OF A DOUBLE AUTOGRAFT PROGRAM TO PROLONG SURVIVAL OF CHRONIC MYELOGENOUS LEUKEMIA PATIENTS IN BLASTIC TRANSFORMATION

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### ABSTRACT

The prognosis of patients in blast crisis of chronic myelogenous leukemia treated with conventional polychemotherapy is extremely poor. Autologous blood stem cell transplantation has been proposed by several authors, and the possibility of achieving a second chronic phase (CP), albeit very short lived, has been reported. In our study, we evaluated the feasibility and efficacy of a double sequential autograft program utilizing two different conditioning regimens. Nine patients underwent the first autograft, but only three were eligible for the second because of one early death, four relapses and one patient who underwent mismatched alloBMT. Of the three patients receiving the second graft, we observed 2 toxic deaths and one relapse six months after transplantation. We conclude that our experience with double autograft in this phase of the disease is very disappointing, since it was associated with prohibitive toxicity in the absence of any advantages in terms of survival for these patients.

*Key words:* chronic myelogenous leukemia, double autograft

The prognosis of patients with CML in blast crisis treated with conventional chemotherapy is very dismal, and only high-dose chemotherapy followed by allogeneic stem cell reinfusion gives a possibility of DFS in 15% of patients.

Autologous bone marrow transplantation has been proposed by some authors, but regardless of the conditioning regimen employed the second chronic phase (CP) was of very short duration;<sup>1-3</sup> an improvement in median survival has been achieved by double autografting in selected categories of patients.<sup>4,5</sup>

In our Institution, nine patients affected by CML in BT (6 myeloid and 3 lymphoid), with unmanipulated PBSC collected at diagnosis, were enrolled in a double sequential autograft program utilizing two different conditioning regimens. Clinical characteristics of the subjects

are shown in Table 1.

All patients were first conditioned with VP16 (250 mg/m<sup>2</sup> days 1-4) and thiotepa (300 mg/m<sup>2</sup> days 5-7) and rescued with PBSC. The number of PBSC infused was 1×10<sup>9</sup>/kg of body weight. If a second CP was achieved, patients underwent bone marrow harvest followed by splenectomy, with the aim of accelerating hematological recovery after the second transplant.<sup>6</sup> Splenectomy was actually performed in only three patients and then removed from the treatment protocol in order to shorten the interval between the two autografts. The conditioning regimen for the second autograft consisted of busulphan 4/mg/kg/day for 4 days and melphalan 60 mg/m<sup>2</sup> on the 5<sup>th</sup> day.

Five out of the six patients with myeloid phenotype achieved a second CP after VP16+thiotepa, while the three patients with a lymphoid

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Table 1. Patient characteristics.

Patient number (M/F)	9 (6/3)
Median age (range)	26 (9-51)
Phenotype	
myeloid	6
lymphoid	3
First chronic phase (months)	
median	19
range	9-68
Previous therapy	
Hu	1
Hu + IFN	7
Hu + IFN + alloBMT	1

phenotype were already in second CP that was achieved with VCR+idarubicin chemotherapy before the ablative regimen.

One patient died on day +11 of ileotyphlitis; 8 patients were evaluable for engraftment, with a median granulocyte count exceeding  $0.5 \times 10^9/L$  by day 14 (range 11-20) and platelet count exceeding  $50 \times 10^9/L$  by day 21 (range 12-65).

Four patients, three with a myeloid and one with a lymphoid phenotype, relapsed within two months; one patient in lymphoid blast crisis went off study because he was eligible for a mismatched alloBMT; three patients underwent a second graft.

### Case reports

**Patient one:** the 25-year-old male was splenectomized and underwent the second graft 75 days after the first one (N.C.:  $2.5 \times 10^8/kg$  of body weight). On day +26 marrow examination showed the presence of granulocytic and erythrocytic precursors, but one week later bone marrow biopsy showed marked hypocellularity (<5%) and a  $^{99}Tc$  colloid marrow scan suggested extremely decreased marrow activity. The patient received subcutaneous G-CSF therapy ( $5 \mu g/kg/day$ ) for 30 days and then subcutaneous IL3 ( $5 \mu g/kg/day$ ) for 20 days, but the marrow pattern did not show any improvement and the patient died of disseminated aspergillosis 8 months after the second graft.

**Patient two:** a 36-year-old female was not splenectomized and received marrow reinfusion 93 days after the first graft, because of a delay in peripheral platelet reconstitution after the VP-16+thiotepa regimen. A total of  $1.1 \times 10^8/kg$  of body weight one marrow nucleated cells were reinfused.

On day +43 marrow was still aplastic so the patient received subcutaneous GM-CSF therapy ( $5 \mu g/kg/day$ ) until the peripheral WBC count reached  $1.2 \times 10^9/L$  and Plts  $8 \times 10^9/L$ . On day +92 bone marrow aspirate showed the presence of erythroid and myeloid precursors, but no megakaryocytes. The patient returned home to the care of her referring physician, but she died on day +100 of G.I. hemorrhage.

**Patient three:** a nine-year-old child was not splenectomized and received the second graft 63 days after the first one. Forty days after infusion, bone marrow aspiration showed 100% cellularity with all cell lines present and no evidence of leukemia; disease relapse occurred six months later and the child died four months after that, of progressive disease.

### Discussion

Our experience with autografting blast crisis CML, although limited to a small number of patients who were heavily pretreated with IFN during the chronic phase, was very disappointing and suggests the opportuneness of evaluating very carefully the use of autograft as salvage therapy in this setting;<sup>7</sup> as a matter of fact, this approach does not seem to offer any benefit with respect to conventional chemotherapy since it is often associated with unacceptable toxicity. The persistence of non clonal hematopoietic progenitor cells in blastic phase chronic myelogenous leukemia has been reported, but likely represents an exception and cannot be taken as a biological basis for autografting.<sup>8</sup> Unfortunately, apart from the possibility of cure reported with allogeneic BMT in some patients, the only therapeutic strategy for blast crisis is to prevent it;<sup>9,10</sup> for this reason the administration of high-dose therapy during chronic phase, associated with the recently reported techniques of *ex vivo* or *in vivo* purging, could help to

improve survival by prolonging the duration of the first chronic phase.<sup>11,12</sup>

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