

IN VIVO PURGING OF CIRCULATING CD34+ PROGENITOR CELLS IN LOW-GRADE LYMPHOMA WITH RITUXIMAB AND HIGH-DOSE CHEMOTHERAPY.

A.M. Gianni, M. Magni,* M. Di Nicola,* L. Gandola,* F. Lombardi,* G. Dastoli,* P. Matteucci,* L. Devizzi,* M. Bregni,* S. Campana,* P. Corradini, A. Pileri,* C. Tarella.*

Istituto Nazionale Tumori e Università degli Studi, Milan; Roche SpA, Milan;
Cattedra di Ematologia, Turin, Italy.

Purpose.

With the aim to overcome the limitations of ex vivo bone marrow purging, we have assessed the ability of the anti-CD20 monoclonal antibody rituximab, given in combination with high-dose chemotherapy, to eradicate PCR-detectable disease, and to enable the harvesting of large amounts of uncontaminated peripheral blood progenitor cells (CPC) in pts with low-grade lymphoma (in vivo purging).

Patients and methods.

From 4/97 to 12/98, 24 consecutive pts entered the study. Eligibility included age ≤ 60 years, a diagnosis of untreated mantle cell lymphoma or of refractory/early relapsed follicular lymphoma, CD20 expression by tumor cells, histologic bone marrow infiltration, and availability of a molecular marker for minimal residual disease detection. The study included three consecutive series of pts, whose treatment was dictated exclusively by the availability of rituximab. Thus, the first 10 pts and the last 4 pts enrolled received rituximab, while the remaining 10 consecutive pts served as controls. Overall, 7 pts in the rituximab group, and 3 control patients had a diagnosis of mantle cell lymphoma.

Eligible pts received 2 to 4 courses of standard-dose chemotherapy, followed by one course of high-dose cyclophosphamide (CTX, 7 g/m²) plus GM-CSF and/or G-CSF and, three weeks later, by a second high-dose course of cytarabine (AraC, 1.5-2 g /m² Q12H for 6 days) with CPC and growth factor infusion. The patients allocated in the rituximab group received two i.v. doses of the antibody at 375 mg/m², approximately on day 2 and day 12 after the last infusion of high-dose cyclophosphamide and cytarabine, respectively. CPC were obtained by leukapheresis when the CD34+ cell count reached $\geq 50/\mu\text{L}$. The intention was to collect, after cyclophosphamide, a PCR-negative leukapheresis product containing a minimum of $11 \times 10^6/\text{kg}$ CD34+ cells. In case of PCR-positive products, additional leukaphereses were performed after cytarabine. If still PCR-positive, ex vivo immunological purging with anti-CD19 monoclonal antibody was performed, using a Miltenyi SuperMACS device.

Results.

At the time of this report, 20 overall pts have completed their treatment, and are thus evaluable for clinical response. The CR rate was 100% in the rituximab arm (11/11 pts), and 78% in the control arm (7/9 pts). After a median follow-up of 11 months (range: 4-21), no pt relapsed. Two pts died of toxicity within 100 days following discharge after their second transplant (1 reactivation of hepatitis C in the control arm, and 1 cardiac arrhythmia in the rituximab arm), for a total toxic death rate of 10% (2/20 evaluable pts). The results of in vivo purging are summarized as follows:

| | Rituximab | Controls | P |
|---|---------------|---------------|-------|
| % PCR-neg harvests post-CTX | 36 | 20 | NS |
| % PCR-neg harvests p- CTX & AraC | 93 | 40 | <0.01 |
| % PCR-neg harvests p- CTX & AraC & ex vivo purg | not applic. | 80 | - |
| PCR-neg CD34+ x10e6/kg (median & range) | 28.3 (0-75.6) | 15.9 (0-53.1) | 0.01 |

Conclusion.

We showed that rituximab, in combination with one or two courses of an effective high-dose anti-lymphoma therapy, allowed the harvesting of large amounts of tumor-free progenitor cells in 13 out of 14 evaluable pts, notably including all 7 pts with mantle cell lymphoma. The role of rituximab clearly emerged from comparison with the control group. In fact, only 4 of the 10 pts receiving chemotherapy only yielded a PCR-negative harvest (P <0.01), while the remaining 6 required ex vivo purging that was successful in 4. In addition, the total amount of PCR-negative progenitors harvested from the rituximab-treated pts was significantly superior (P=0.01). In conclusion, this in vivo purging strategy compares very favorably with ex vivo purging in terms of feasibility, costs, and overall success rate in harvesting an amount of uncontaminated CD34+ cells (i.e. $\geq 11 \times 10^6/\text{kg}$), fully adequate to support more than one cycle of subsequent myeloablative chemotherapy.