# original article

# Immunochemotherapy with *in vivo* purging and autotransplant induces long clinical and molecular remission in advanced relapsed and refractory follicular lymphoma

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**Background:** To evaluate the clinical outcome of patients with relapsed or refractory follicular lymphoma treated with immunochemotherapy, *in vivo* purging and high-dose therapy with autotransplant.

**Patients and methods:** Sixty-four patients were enrolled in the trial. Primary end point was progression-free survival (PFS). Secondary end points were the *in vivo* purging effect on stem-cell harvest and the impact of molecular response on the outcome.

**Results:** At enrollment, 59% of patients were PCR+ for bcl-2 rearrangement in bone marrow (PCR-informative). After the immunochemotherapy, before mobilization, 97% obtained complete response or partial response and 87% of patients informative for bcl-2 were molecularly negative. Sixty-one patients proceeded to *in vivo* purging and peripheral blood stem cell (PBSC) mobilization with rituximab and high-dose AraC. The median number of CD34+ cells collected was $16.6 \times 10^6$/kg. Of 33 PCR-informative patients, the harvests resulted in PCR− in all. Fifty-eight patients received high-dose therapy and autotransplant of *in vivo* purged PBSC. After a median follow-up of 3.5 years, 41 patients are in complete remission. Five-year PFS is 59%.

**Conclusion:** This study demonstrates that patients with advanced relapsed or refractory follicular lymphoma treated with immunochemotherapy, *in vivo* purging and autotransplant may obtain long-lasting PFS. In bcl-2-positive patients, *in vivo* purging allows the harvest of lymphoma-free PBSC. Absence of the bcl-2 rearrangement after autotransplant is associated with persistent clinical remission.

**Key words:** autotransplant, follicular lymphoma, in vivo purging, rituximab

## introduction

Autologous stem-cell transplantation has been shown effective in the long-term control of follicular lymphoma [1, 2]. The randomized CUP trial demonstrated the superiority of autotransplant in prolonging progression-free survival (PFS) and overall survival (OS) in patients with chemosensitive recurrent follicular lymphoma [3]. It has also been demonstrated that the achievement of bcl-2-negative status is associated with a lower risk of recurrence [4–6].

As lymphoma contamination of the harvest may hamper the outcome of autotransplant, several methods have been attempted to abolish graft contamination such as *in vitro* treatment with anti-B-cell monoclonal antibodies and

complement [7], immunomagnetic beads [8, 9] and positive selection of CD34+ cells [10].

Preliminary studies using rituximab as *in vivo* purging during mobilization were effective in collecting lymphoma-free progenitor cells [11–16]. It has also been shown that the efficiency of harvested peripheral blood stem cell (PBSC) is not adversely affected by rituximab, and that engraftment and hematopoietic recovery are not compromised [17, 18]. The optimal combination of rituximab with the mobilization schemes, however, is not defined.

We have previously reported that concurrent administration of rituximab and high-dose AraC is a safe and efficient method to obtain *in vivo* purged PBSC. Immunochemotherapy before PBSC mobilization produced a profound B-cell depletion which seems a useful preparative step [19].

On the basis of our pilot study, we conducted a multicenter prospective trial that comprises a sequence of

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immunochemotherapy, *in vivo* purging and autotransplant in 64 patients with advanced refractory or relapsed follicular lymphoma. This program produced long-lasting PFS. Durable molecular response was associated with favorable outcome

## patients and methods

### patients

This study was carried out as a prospective, multicenter phase II trial. Between April 1999 and December 2005, 64 patients with relapsed or refractory follicular lymphoma were enrolled in the trial (ClinicalTrials.gov Identifier: NCT00366275). The study received approval by the local ethics committees of the participating institutions. All patients gave written informed consent. The study was carried out in accordance to the Helsinki Declaration of 1964, as revised in 2000. Patients were required to have histological diagnosis of follicular lymphoma either relapsed or refractory after at least one line of therapy, expression of CD20 by lymphoma cells, age ≤60 years, normal cardiac, renal and hepatic function and no viral infections (hepatitis B and C and human immunodeficiency virus).

### treatment plan

After a debulking with 6 weeks of VACOP-B, immunochemotherapy consisted of two to four courses every 3 weeks with rituximab 375 mg/m$^2$ on day 1, vincristine 1.4 mg/m$^2$ on day 2 and cyclophosphamide 400 mg/m$^2$ on days 2–6. Courses were started if granulocytes >1.5 × 10$^9$/l. The phase of PBSC mobilization coupled rituximab 375 mg/m$^2$ on days 1 and 9 with high-dose AraC 2 g/m$^2$ every 12 h on days 2 and 3. Granulocyte colony-stimulating factor (5 µg/kg/day s.c.) was administered from day 6. PBSCs were collected with a continuous-flow blood cell separator Spectra (COBE BCT, Lakewood, Colorado), processing a total volume per leukapheresis of 2–3 blood mass volumes. High-dose chemotherapy with autotransplant consisted of high-dose therapy with BEAM (BCNU, etoposide, AraC, melphalan) [20] followed by the infusion of *in vivo* purged PBSC (minimum dose of CD34+ cells reinfused 3 × 10$^6$/kg), plus two consolidation doses of rituximab 375 mg/m$^2$ on days +14 and +21 after autotransplant.

### study end points

The primary end point of the study was the PFS. Secondary end points were the *in vivo* purging effect on the PBSC harvest and the percentage and duration of molecular responses.

### molecular evaluation

DNA samples of peripheral blood, bone marrow and leukapheresis products were studied using nested PCR amplification of the bcl-2/IgH rearrangements as previously described [13]. The sensitivity of PCR method was 10$^{-6}$.

### response criteria and statistical analysis

Response to treatment was defined according to the International Working Group recommendations [21]. Clinical and molecular response was assessed by complete restaging after each phase of the treatment plan, 3 months after autotransplant, and every 6 months thereafter. In patients informative for bcl-2, molecular response was defined as the absence of bcl-2 rearrangement in the bone marrow. Harvests were considered lymphoma free if PCR-negative for bcl-2 rearrangement. All patients who received at least one course of immunochemotherapy were considered assessable for response and outcome on an intention-to-treat basis. Survivals were calculated according to the standardized definitions of end points provided by the International Harmonization Project [22]: OS was measured from the start of therapy to the date of death or last follow-up; PFS for all patients was taken from the start of therapy until disease progression or death as a result of lymphoma and disease-free survival (DFS) for patients in complete response (CR) was measured from the first assessment of CR to the date of progression. Continuous variables are summarized as median and range. Categorical variables are reported as count and relative frequency. OS, PFS and DFS were calculated according to the Kaplan and Meier method. The log-rank test was used to compare survival curves.

To identify prognostic variables for PFS and DFS, the following parameters were evaluated in univariate analysis: histological grade, CR achievement before autotransplant, bcl-2 positivity or negativity at enrollment, bone marrow involvement, histological subtype, disease status (relapsed or refractory at study entry), PCR negativity of collected PBSC and molecular response. These parameters were also evaluated in multivariate analysis. All computations were carried out using STATISTICA for Windows 5.5, StatSoft, Inc. (2000).

## results

### patient characteristics

The clinical characteristics at enrollment of the 64 patients are summarized in Table 1. Of these, 29 had follicular lymphoma grade 1, 27 grade 2 and 8 grade 3. Thirty-seven (58%) patients had histological bone marrow involvement. Fifty-three patients (83%) were in stage III/IV. Of 64 patients, 36 were in relapse (21 after one line of therapy and 15 after two or more lines of therapy) with a median PFS of 6 months and 28 had refractory disease (10 after more than one line of therapy). At enrollment, 78% of patients had a Follicular Lymphoma International Prognostic Index (FLIPI) score ≥2. All patients but 5 had previously received anthracycline-containing regimens and 10 patients were previously treated with rituximab plus chemotherapy. Two patients had received high-dose therapy with autotransplant. All patients were evaluated for the presence of bcl-2 rearrangement and 38 (59%) were positive on bone marrow (PCR-informative patients).

### immunochemotherapy with *in vivo* purging and PBSC mobilization

After debulking with 6 weeks of VACOP-B, 7 patients were in CR, 52 in partial response (PR) and 5 had stable disease.

**Table 1.** Patient characteristics

| Characteristic | $n$ | % |
|---|---|---|
| Total number | 64 | |
| Sex M/F | 35/29 | 55/45 |
| Median age (range), years | 50 (44–60) | |
| Histology | | |
| Follicular grade 1 | 29 | 45 |
| Follicular grade 2 | 27 | 42 |
| Follicular grade 3 | 8 | 13 |
| Ann Arbor stage | | |
| II bulky | 11 | 17 |
| III–IV | 53 | 83 |
| Bone marrow involvement | 37 | 58 |
| Relapsed | 36 | 56 |
| After one line | 21 | 33 |
| After two line | 15 | 23 |
| Refractory | 28 | 44 |

Of 38 bcl-2+ patients, 9 (24%) achieved molecular response. After immunochemotherapy, 40 patients achieved CR, 22 PR and 2 progressed; of 38 PCR+ patients, additional 24 achieved molecular response. Overall, 33 patients were molecularly negative before mobilization. All the courses of immunochemotherapy were administered on an outpatient basis. The immunochemotherapy was well tolerated with no World Health Organization (WHO) grade 3–4 hematological toxic effects. Three patients did not proceed to mobilization: two (bcl-2-positive) because of disease progression and one in molecular response for refusal. Sixty-one patients received PBSC mobilization. Leukaphereses were started after a median of 12 days (range 5–16) after the first dose of AraC. The median number of CD34+ cells collected was $16.6 \times 10^6$/kg (range 3.8–80.6) with a median of one procedure (range 1–3). Toxicity consisted of grade 3–4 granulocytopenia in 72%. Median neutrophil nadir was $0.490 \times 10^9$/l (range $0.0$–$2.5 \times 10^9$/l), median platelet nadir was $11.5 \times 10^9$/l (range $3$–$55 \times 10^9$/l) and median hemoglobin nadir was 9.9 g/dl (range 7–12 g/dl). Forty-seven patients received platelet transfusion and 10 needed erythrocyte support. One patient who developed *Escherichia coli* sepsis during cytopenia did not harvest and required intensive support and i.v. antimicrobial therapy. Of 35 patients informative for bcl-2 who collected PBSC, in 33 the harvests were tested for bcl-2 and resulted PCR-negative in all.

### high-dose therapy and autologous transplantation

Two patients did not proceed to autotransplant: one (always PCR-positive) because of disease progression and one because of the detection of lung neoplasm at pretransplant evaluation. Autotransplant was carried out in 58 patients (49 in CR and 9 in PR), 34 of whom were PCR-informative for bcl-2. Of these last, 33 were PCR-negative at the evaluation pre-transplant. All 58 patients engrafted successfully. The median time to neutrophils recovery over $0.5 \times 10^9$/l was 10 days (8–14) and to platelets over $20 \times 10^9$/l was 10 days (6–13). The two rituximab doses post-transplant did not affect hematopoietic recovery. One patient developed vasculitis during the cytopenic phase that resolved completely with steroids. Forty-six had fever over 38°C for a median of 2 days (range 1–9) and required i.v. antimicrobial therapy. No patient needed systemic antifungal therapy. No episodes of combination chemotherapy with methotrexate, vinblastine and cisplatin reactivation were observed. Asymptomatic WHO grade 3–4 neutropenia developed in 10 patients after a median of 90 days after autotransplant and resolved spontaneously in a median of 2 months (range 1–8 months).

### outcome

At a median follow-up of 3.5 years (maximum follow-up 8 years), of 64 enrolled patients, three patients died (two for disease progression after autotransplant and one of lung cancer).

Of the 58 patients autografted, 41 are still in complete remission and 17 relapsed after a median of 16 months from transplant (range 5–59 months). Of 34 patients autografted who were positive for bcl-2 at enrollment, 25 are still in complete clinical and molecular remission (14 after >4 years)

while 9 relapsed after a median of 16 months after transplant (range 5–40). In eight of these last, clinical relapse was preceded by molecular relapse at a median of 3 months before. One patient who never obtained molecular response relapsed 8 months after autotransplant.

The 5-year OS is 94% [95% confidence interval (CI) 88% to 100%]. The 5-year PFS of the whole series is 59% (95% CI 44% to 73%) (Figure 1), the 5-year DFS is 63% (95% CI 48% to 77%) and the 5-year event-free survival of the whole series is 54% (95% CI 40% to 69%).

### prognostic factors

PFS and DFS were not influenced by age, sex, histological grade, presence of bcl-2 rearrangement, prior treatment with rituximab or a prior attainment of CR. Bone marrow involvement influenced DFS ($P = 0.02$) but not PFS (Table 2). Persistence of clinical remission after autotransplant was always associated with the absence of the bcl-2 rearrangement. Loss of molecular response was invariably followed by clinical relapse (Figure 2).

## discussion

We treated 64 patients with advanced relapsed or refractory follicular lymphoma with a program of immunochemotherapy, *in vivo* purging and high-dose therapy with autotransplant of purged PBSC.

One aim of the study was to collect lymphoma-free PBSC, hence eliminating the risk of disease recurrence associated with PBSC contamination by lymphoma [7, 23–25]. For this purpose, *in vivo* purging consisted of an initial immunochemotherapy phase followed by four doses of high-dose AraC combined with two doses of rituximab (on days 1 and 9). Prior studies showed that harvesting PBSC
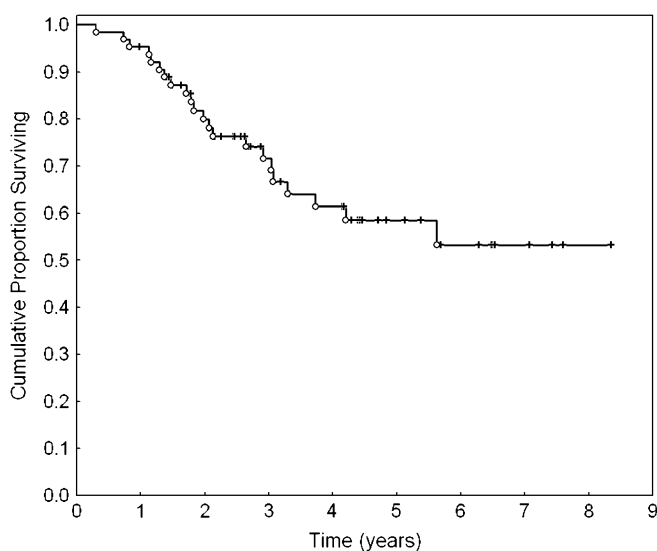


**Figure 1.** Progression-free survival of the whole series of 58 patients with advanced follicular lymphoma who received high-dose therapy with autotransplant of *in vivo* purged peripheral blood stem cell.

in presence of high serum levels of rituximab is a simple and effective procedure to collect PCR-negative PBSC [13, 19]. Applying this method to 33 patients informative for bcl-2, we obtained PCR-negative harvests in all. These results, the largest
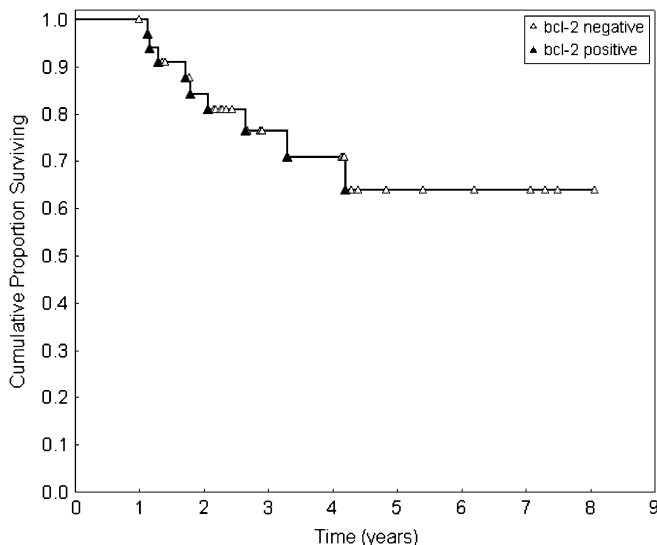


Figure 2. Progression-free survival of the 34 autografted patients who were bcl-2-positive in the bone marrow at study entry.

Table 2. Prognostic factors for progression-free survival (PFS) and disease-free survival (DFS)

| Parameter | P value | |
| --- | --- | --- |
| | PFS | DFS |
| Age <45 versus ≥45 years | 0.5 | 0.5 |
| Age 30–40 versus 40–50 versus ≥50 years | 0.5 | 0.3 |
| Sex | 0.5 | 0.5 |
| Bcl-2 informative | 0.6 | 0.5 |
| Histology grade (1–2 versus 3) | 0.5 | 0.6 |
| Stage I–II versus III–IV | 0.5 | 0.5 |
| Bone marrow involvement | 0.12 | 0.02 |
| Prior rituximab therapy | 0.5 | 0.5 |
| Prior CR versus no CR | 0.07 | 0.08 |

CR, complete response.

reported so far with immunological purging in follicular lymphoma, indicate the high potential of this approach for obtaining lymphoma-free PBSC. Table 3 shows the results of the present study and prior reports on in vivo purging on the basis of the combination of rituximab with chemotherapy.

The data reported in this study compare favorably with chemotherapy-only programs. In fact, the use of extensive chemotherapy as in vivo purging before stem-cell collection resulted in PCR-negative harvests in only 50% of patients with follicular lymphoma [6].

Regarding the outcome, in this study durable negativity for bcl-2 rearrangement was associated with long-term PFS. On the contrary, patients with loss of bcl-2 negativity invariably experienced progression. This lends additional support to the concept that persistent molecular negativity is the principal determinant of long DFS in patients with follicular lymphoma undergoing high-dose chemotherapy with autotransplant [27].

Recently, it has been shown that rituximab maintenance after response to combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or R-CHOP produces favorable PFS in patients with relapsed follicular lymphoma [28]: these results may question the need for high-dose treatments in recurrent follicular lymphoma. The long-term advantages of the two approaches, one intensive and relatively short and the other mild and much longer, are not known and should be compared prospectively. It should, however, be considered that 65% of patients in the present study had either refractory disease or a history of multiple relapses, therefore representing a category with dismal prognosis. Nevertheless, most of them experienced prolonged PFS. Probably, this subset of patients may benefit from an intensive approach. Long-term follow-up of patients with relapsed follicular lymphoma autotransplanted with high-dose cyclophosphamide and TBI at St Bartholomew's Hospital and Dana Farber Cancer Institute shows an apparent plateau in the remission curve after 12 years [2]. Although the attainment of molecular response does not preclude relapses, the long-term survival in the absence of PCR-detectable disease indicates that an intensive molecularly controlled approach is an effective strategy toward the eradication of the neoplastic clone and possibly the cure of the disease.

Table 3. In vivo purging results of the present study and prior studies in follicular lymphoma (FL)

| Reference | In vivo purging scheme | No. of patients with FL | PCR+ patients | Harvests | | |
| --- | --- | --- | --- | --- | --- | --- |
| | | | | PCR-tested, n | PCR-negative, n | % purged |
| Voso et al. [11] | R + HAM | 15 | 7 | 7 | 7 | 100 |
| Magni et al. [12] | R + HDS | 7 | 7 | 7 | 7 | 100 |
| Flinn et al. [18] | R + HD-Cy | 11 | 5 | 5 | 5 | 100 |
| Flohr et al. [15] | R + DexaBEAM | 12 | 8 | 8 | 6 | 75 |
| Galimberti et al. [16] | R + HD-Cy | 11 | 7 | – | – | 86 |
| Belhadj et al. [14] | R + HD-Cy/VP16 | 11 | 11 | 8 | 6 | 75 |
| Ladetto et al. [26] | R + HDS | 92 | 42 | 42 | 20 | 48 |
| Present study | R + HD-AraC | 64 | 34 | 33 | 33 | 100 |

R, rituximab; HAM, high-dose AraC (2 g/m$^2$/12 h, days 1 and 2) + mitoxantrone (10 mg/m$^2$, days 2 and 3); HDS, high-dose sequential; HD-Cy, high-dose cyclophosphamide; DexaBEAM, dexamethasone (8 mg three times a day, days 4–7), BCNU (60 mg/m$^2$, day 2), etoposide (75 mg/m$^2$, days 4–7), AraC (100 mg/m$^2$/12 h, days 4–7), melphalan 20 mg/m$^2$, day 3); VP16, etoposide.

Concerning the use of rituximab as consolidation after autotransplant, 17% of patients in this series showed transient asymptomatic neutropenia after a median of 3 months after transplant. This late-onset neutropenia has been previously reported with high-dose programs that include rituximab consolidation [21]. In one series of aggressive non-Hodgkin's lymphoma treated with rituximab and autotransplant, 54% of patients developed neutropenia [29].

In conclusion, this study shows that in patients with advanced relapsed or refractory follicular lymphoma a combination of immunochemotherapy with *in vivo* purging, followed by high-dose therapy with autotransplant of lymphoma-free PBSC may give long-lasting PFS. Absence of the bcl-2 rearrangement after autotransplant is associated with persistent clinical remission.

## acknowledgements

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