Rituximab, gemcitabine and oxaliplatin: an effective salvage regimen for patients with relapsed or refractory B-cell lymphoma not candidates for high-dose therapy

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Background: High-dose therapy (HDT) with stem-cell support is the reference treatment for relapsed lymphoma, but is not appropriate for all patients. Conventional salvage chemotherapies have been used with limited efficacy and significant toxicity. Rituximab, gemcitabine and oxaliplatin are active as single agents in relapsed or refractory lymphoma, and have demonstrated synergistic effects in vitro and in vivo.

Patients and methods: Forty-six patients with relapsed or refractory B-cell lymphoma received up to eight cycles of R-GemOx (rituximab 375 mg/m² on day 1, gemcitabine 1000 mg/m² and oxaliplatin 100 mg/m² on day 2). The majority (72%) had diffuse large B-cell lymphoma.

Results: After four cycles of R-GemOx, the overall response rate was 83% [50% complete response (CR)/unconfirmed CR (CRu)]. High CR/CRu rates were observed in all histological subtypes. In patients who had previously received rituximab, the CR/CRu rate after eight cycles was 65%. The 2-year event-free and overall survival rates (median follow-up of 28 months) were 43% and 66%, respectively. Among responders, the probability of being disease free for 2 years was 62%. Treatment was generally well tolerated.

Conclusion: R-GemOx shows promising activity with acceptable toxicity in patients with relapsed/refractory B-cell lymphoma who are not eligible for HDT.

Key words: gemcitabine, lymphoma, oxaliplatin, refractory, R-GemOx, rituximab

introduction

Multiagent chemotherapy has been a major advance in the treatment of non-Hodgkin’s lymphoma. Although some patients can be cured with this approach, disease relapse and refractory disease constitute significant problems for the treatment of all histological subtypes of lymphoma. To date, high-dose therapy (HDT) with hematological stem-cell support is the reference treatment for patients with chemosensitive, relapsed aggressive lymphoma [1]. In relapsed indolent lymphoma, this approach also appears to be more effective than conventional salvage chemotherapy [2]. However, many patients cannot benefit from HDT as a result of advanced age, significant comorbidities, previous use of HDT or resistance to salvage chemotherapy. Conventional salvage regimens without HDT, such as dexamethasone, cytarabine and cisplatin (DHAP) or etoposide, methylprednisolone, cytarabine and cisplatin, are associated with poor long-term disease control and significant toxicity [3]. Thus, regimens based on innovative drug combinations with better efficacy and less toxicity are needed for the management of patients with advanced lymphoma who are not eligible for HDT.

Gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) offers advantages over its parent compound, cytarabine, in terms of delivery of highly effective intracellular concentrations [4]. Gemcitabine has demonstrated single-agent efficacy in relapsed or refractory aggressive lymphoma, including mantle cell lymphoma (MCL) [5–7]. The anti-CD20 monoclonal antibody, rituximab (Mabthera; Rituxan Roche, Neuilly-sur Seine, France), has also shown single-agent activity in lymphoma and can enhance the efficacy of standard chemotherapy regimens in the first- and second-line setting [8–11]. In addition, the platinum derivative oxaliplatin (Eloxatin; Sanofi Aventis, Paris, France) has similar efficacy to cisplatin, with improved renal safety [12, 13] and reduced induction of chemoresistance [14]. The favorable safety profile of oxaliplatin makes this agent potentially suitable for elderly patients with comorbidities.
Mechanistic synergy and nonoverlapping toxicity profiles of rituximab, gemcitabine and oxaliplatin (R-GemOx) indicate that combination regimens containing these three agents may offer advantages over conventional regimens in terms of efficacy, safety and tolerability.

Based on these considerations, we conducted an open-label phase II study of the combination of R-GemOx in the treatment of patients with relapsed or refractory B-cell lymphoma.

**patients and methods**

**patient selection and evaluation**

Patients were treated at the Hematology Department of the Henri Mondor Hospital, Créteil, France. Patients with recurrent or refractory CD20-positive lymphoma of any performance status were eligible for inclusion if they were unsuitable for HDT because of age, previous HDT, serious comorbidities or a combination of these factors. Histopathological material was reviewed systematically at the institution’s Pathology Department and diagnoses were established according to the World Health Organization classification [15]. The protocol was approved by the Institutional Review Board and all patients gave written informed consent, as required by the Declaration of Helsinki.

Patients were evaluated before treatment by clinical examination, computed tomography (CT) scans of the thorax, abdomen and pelvis, and bone marrow trephine biopsy. All patients underwent blood sampling for complete blood counts and routine chemistry, including assessment of hepatic and renal function and measurement of lactate dehydrogenase levels.

**treatment protocol**

Rituximab 375 mg/m² was administered on day 1 according to the standard infusion rate escalation protocol [16]. Premedication with methylprednisolone 1 mg/kg i.v., acetaminophen 1000 mg orally and dexchlorpheniramine 6 mg orally was administered to avoid infusion-related side-effects. Gemcitabine 1000 mg/m² (in 500 ml of normal saline) was administered on day 2, at a fixed dose rate of 10 mg/m²/min. This prolonged administration schedule has been shown to achieve superior intracellular drug concentrations than the standard 30-min i.v. schedule [17]. Oxaliplatin 100 mg/m² over 2 h was administered on day 2 after gemcitabine. Cycles were repeated every 14 days.

A complete blood count was carried out on days 7, 10 and 14 of each treatment cycle to assess hematological toxicity. Patients underwent clinical examination and routine chemistry assessment before each new cycle. No dose adjustment was planned in the event of hematological toxicity, but cycles were postponed until the absolute neutrophil count reached 1.0 × 10⁹/l and the platelet count reached 100 × 10⁹/l. Dose adjustment of oxaliplatin was carried out in the event of peripheral neuropathy. The oxaliplatin dose was to be reduced to 75 mg/m² in the event of significant paresthesia lasting between 7 and 13 days after each administration. In the event of abnormal results by neurological examination or if a patient experienced significant paresthesia lasting for 14 days or more, oxaliplatin was to be stopped until symptoms improved and then restarted at a dose of 75 mg/m². In the event of pharyngolaryngeal dysesthesia, the duration of the oxaliplatin infusion was to be prolonged from 2 to 6 h.

Primary prophylaxis with colony-stimulating factors was not permitted, but if a chemotherapy cycle was delayed, filgrastim [granulocyte colony-stimulating factor (G-CSF)] was administered with subsequent cycles to aid maintenance of the dose intensity. Use of filgrastim was also recommended if febrile neutropenia had been observed during a previous treatment cycle.

**toxicity and response assessments**

Hematological and non-hematological toxic effects were graded according to the National Cancer Institute–Common Toxicity Criteria (Version 3.0).

Toxicity evaluation was conducted on day 1 of each treatment cycle and included neurological examination and laboratory assessment with complete blood cell count and serum chemistry tests.

Thoracic, abdominal and pelvic CT scans and bone marrow biopsy (in patients with bone marrow involvement at initial diagnosis) were conducted to assess response after both induction therapy and completion of consolidation therapy. The International Working Group Criteria [18] were used for definition of responses. After four treatment cycles (induction therapy), patients achieving a complete response (CR), unconfirmed complete response (CRu) or partial response (PR) were eligible for up to four further cycles of R-GemOx (consolidation therapy).

**statistical methods**

The primary end point of the study was the overall response rate (ORR) after four cycles of treatment. Secondary end points were event-free survival (EFS), defined as the time interval from the date of enrollment in the study until disease progression, relapse or death—whichever occurred first—and overall survival (OS) calculated from the date of enrolment until death from any cause.

For patients who responded after four cycles, time to relapse was defined as the time interval from the date of response evaluation until the date of progression or relapse—whichever came first. Data were censored at the date of last evaluation when the stopping date was not reached. Survival curves were estimated using the product-limit method of Kaplan–Meier and compared using the log-rank test. Relative dose intensity (RDI) for gemcitabine and oxaliplatin was calculated according to Hryniuk et al. [19]. The Fisher’s exact test was used for comparisons of proportions. Statistical tests were considered significant when the two-sided P value was <0.05. Confidence intervals (CIs) were computed with a 95% coverage; 95% CI binomial exact bounds were computed for proportions. All statistical analyses were carried out using SAS software (Version 8.2; SAS Institute, Cary, NC).

**results**

**patient population**

From January 2002 to June 2005, 46 patients were enrolled and were eligible for analysis. Median follow-up was 28 months (data cut-off December 31, 2005). Pretreatment patient characteristics are summarized in Table 1.

**treatment exposure**

The overall number of cycles administered was 314 (range, 1–8). Most patients received the intended number of cycles and the median duration of exposure was 16 weeks. Only eight patients required oxaliplatin dose reduction owing to significant neurotoxicity in seven patients and preexisting renal insufficiency in one patient. No dose reductions were required for rituximab or gemcitabine. Thirteen patients (28%) required a dose delay, most commonly because of myelosuppression, and 13 patients required G-CSF. Of the 268 cycles considered for this analysis (first cycles were excluded), 215 (80%) were delivered on time and at the planned dose. The average RDI was 84% for gemcitabine and 82% for oxaliplatin.

Treatment was delayed in a total of 53 cycles; 42 cycles (16%) were postponed because of neutropenia or thrombocytopenia and 11 cycles (4%) were postponed because of non-hematological toxicity (febrile neutropenia in nine cases and cardiac failure in two cases). In total, 31 patients (64%) completed the planned eight cycles. Reasons for stopping...
R-GemOx, rituximab, gemcitabine and oxaliplatin.

Prior radiation therapy 12 (26)
Prior biological or experimental therapy 16 (35)
Prior high-dose therapy 14 (30)
Prior rituximab 26 (57)
Prior anthracycline 45 (98)

Median no. of previous treatment regimens (range) 2 (1–5)

Disease status
- Duration of last remission
  - 0–1 year 31 (67)
  - >1 year 15 (33)
- Stage
  - I/II 10 (22)
  - III/IV 36 (78)
- Elevated lactate dehydrogenase (>1 N) 12 (26)
- Age-adjusted International Prognostic Index score
  - Low/low–intermediate 29 (63)
  - High/intermediate–high 17 (37)
- Bone marrow involvement 21 (46)
- Median time from initial diagnosis to R-GemOx treatment, months (range) 63 (3–230)
- Median time from last treatment to R-GemOx treatment, months (range) 19 (1–173)
- Duration of last remission
  - ≤1 year 9 (20)
  - >1 year 31 (67)

Disease status
- Primary refractory 6 (13)
- First relapse 12 (26)
- Second or multiple relapse 28 (61)
- Median no. of previous treatment regimens (range) 2 (1–5)
- Prior anthracycline 45 (98)
- Prior rituximab 26 (57)
- Prior high-dose therapy 14 (30)
- Prior biological or experimental therapy 16 (35)
- Prior radiation therapy 12 (26)

R-GemOx, rituximab, gemcitabine and oxaliplatin.

treatment were disease progression (eight patients), severe cardiac failure (one patient), diagnosis of secondary acute leukemia (one patient previously treated with HDT, including total body irradiation), physician decision (two patients) and patients request (two after five cycles and one after seven cycles).

response to treatment

Response rates were calculated after induction therapy (four cycles) and at completion of therapy for patients who completed at least six cycles. Eight patients progressed during the induction phase. After four cycles, 10 patients achieved a CR, 13 had a CRu and 15 had a PR, resulting in an ORR (CR + CRu + PR) of 83% (95% CI, 69% to 92%) (Table 2). Response rates were similar for the following three histological subtypes: diffuse large B-cell lymphoma (DLBCL), 82% (95% CI, 65% to 93%); follicular lymphoma (FL), 75% (95% CI, 35% to 97%) and MCL, 100% (95% CI, 48% to 100%).

R-GemOx seemed to be as efficacious in patients who had previously undergone HDT as in those who had not (86% versus 81%, respectively; not significant). A trend towards a better response rate to induction therapy was observed for rituximab-naive patients compared with those previously treated with rituximab (95% versus 73%, respectively; \( P = 0.11 \)). Response rates were lower among patients who had experienced no response to their last treatment or a response duration < 1 year than among patients who had a previous response duration ≥ 1 year (53% versus 97%, respectively; \( P < 0.001 \)).

At the end of treatment, 33 patients (72%; 95% CI, 57% to 84%) had achieved a CR/CRu, one patient (2%) had a PR and nine patients progressed, translating into an ORR of 74%.

Three patients were withdrawn from the study after five cycles of treatment owing to severe cardiac failure in one patient and absence of response at that time in two patients. These three patients were alive and disease free at last follow-up. At this time point, R-GemOx consolidation therapy had improved the quality of response compared with induction therapy alone from one CR/CRu (20%) and four PRs (80%) to four CR/CRus (80%) and one PR (20%) in the MCL cohort (Table 2).

Similarly, consolidation therapy improved the number of CR/CRus in patients with DLBCL and FL. At the end of therapy, 73% and 63% of patients in the DLBCL and FL cohorts, respectively, had a CR/CRu. R-GemOx induction and consolidation therapy achieved high response rates in patients who had previously been treated with rituximab (Table 2). Absence or short duration of response (< 1 year) to last treatment was associated with a lower response rate than longer duration of previous response (> 1 year) (47% versus 87%, respectively; \( P < 0.05 \)). However, some of these high-risk patients still achieved a CR/CRu.

event-free and overall survival

At the time of this analysis (median duration of follow-up 28 months for the 38 patients who responded to induction treatment), 11 patients had relapsed, translating into a 2-year progression-free survival of 62% (95% CI, 44% to 81%). For the 27 responders with DLBCL, seven had relapsed. Only one relapse (at 4 months) was observed among the six patients with FL who responded to R-GemOx. Among the five patients with MCL who responded to treatment, three relapsed between months 12 and 18. Of note, for the 19 responders not previously treated with rituximab, the probability of remaining relapse free at 2 years was 81% (95% CI, 61% to 100%) compared with 37% (95% CI, 7% to 68%; \( P < 0.05 \)) for the 19 patients previously treated with rituximab.

Kaplan–Meier curves for OS and EFS are shown in Figure 1. With a median follow-up of 28 months, the 2-year EFS and OS rates were 43% (95% CI, 27% to 60%) and 66% (95% CI, 50% to 82%), respectively.

The median time to progression (TtP) was 22 months (range, 1–24 months). No patient died during the treatment period. Of the 15 deaths that occurred to date, nine (60%) were attributed to progressive disease, two to infection, two to...
cardiovascular events, one to an esophageal varice bleed and one to another type of cancer.

Among patients with DLBCL, the 2-year EFS was 42% (95% CI, 22% to 62%) and the median TtP was 24 months, with no significant difference between patients previously treated with rituximab and rituximab-naive patients (median TtP of 16 and 24 months, respectively).

safety
No fatal toxicity was observed. Treatment was generally well tolerated, with the majority of patients hospitalized for only one night with the first administration of rituximab during the first cycle of treatment. Neutropenia grades 2, 3 and 4 were reported in 23%, 27% and 17% of cycles, respectively, while thrombocytopenia grades 2, 3 and 4 were reported in 12%, 19% and 4% of cycles, respectively. Febrile neutropenia was observed in 4% of cycles. Grade 2 neurotoxicity occurred in 9% of cycles, but no grade 3/4 neurotoxicity was reported. Thirteen patients (28%) received red cell transfusions with a median of 2 (range, 2–8) and nine patients received platelet transfusions with a median of 3 (range, 1–11). No renal toxicity was observed. No other grade 3/4 non-hematological toxicity was observed. Finally, a subsequent hospitalization occurred in 11 patients corresponding to 4% of treatment cycles.

discussion
In this study of 46 patients with relapsed or refractory B-cell lymphoma, four cycles of R-GemOx achieved a high ORR of 83%. The high CR/CRu rate of 72% at the end of treatment is encouraging in this high-risk and predominantly elderly patient population, which consisted of patients who were not candidates for HDT because of comorbidities (n = 4), relapse after prior HDT (n = 14) or advanced age (median age of the remaining 28 patients: 69 years). In our practice, such patients represent approximately half of those who relapse after first- or second-line therapy. It is of note that 23 patients (50%) achieved a CR/CRu early in the course of treatment (after the first four cycles). The high proportion of patients free from relapse for 2 years (62%) among the patients who responded to induction therapy is also encouraging. These results compare favorably with data for conventional chemotherapy regimens, which show low response rates and few durable responses [3].
Our results also compare favorably with those of other combinations of rituximab and chemotherapy in the relapsed/refractory setting: Kewalramani et al. [10] reported a 78% ORR and 53% CR rate in a population of 36 younger patients treated with rituximab, ifosfamide, carboplatin and etoposide, none of whom had been previously exposed to rituximab. Jermann et al. [11] reported a 68% ORR and 28% CR rate with the rituximab, etoposide, doxorubicin, vincristine, cyclophosphamide and prednisolone regimen in a population of 30 patients among which only 4% had received prior rituximab.

R-GemOx achieved responses in patients who had previously received rituximab and in patients who had failed HDT/autograft, although response rates were lower in these patient groups. At the end of treatment, very high ORR and CR/CRu rates were seen in patients who had not previously received HDT (78% and 75%, respectively), and in rituximab-naive patients (85% and 80%, respectively). Among the histologies which are the most susceptible to respond to single-agent rituximab, it is of note that only four of eight FL patients and zero of five MCL patients had not been exposed to this drug previously. In addition, high ORR and CR/CRu rates (both 87%) were seen in patients in whom relapse had occurred more than a year after previous therapy.

The R-GemOx regimen had a very favorable toxicity profile. No nephrotoxicity was seen, and hematological toxicity was manageable with the help of growth factor support. Rates of compliance and delivery of the intended number of cycles at the intended dose were good. There were few serious infections and few deaths unrelated to progression. Oxaliplatin-associated neurotoxicity occurred in only 9% of cycles and no grade 3/4 neurotoxicity was observed. These results are particularly encouraging for the treatment of elderly patients with lymphoma.

Each component of the R-GemOx regimen may contribute to its efficacy; indeed, the results of this study support a synergistic or supra-additive action for rituximab when combined with gemcitabine and oxaliplatin. This observation is consistent with results from previous studies in lymphoma and other cancers. Response rates of 20% to 25% have been reported for single-agent gemcitabine in relapsed or refractory aggressive lymphoma (including MCL) [5, 7], although activity in indolent lymphoma is limited [5, 20, 21]. Based on in vitro synergism between the two drugs and nonoverlapping toxicity profiles, gemcitabine–cisplatin combinations (with or without steroids) have been tested in several phase II studies of patients with advanced lymphoma [22–25]. Reported ORRs range from 45% to 79% and hematological toxicity was significant but manageable. Gemcitabine and oxaliplatin display supra-additive effects in human colon cancer cell lines [26], and the feasibility and safety of this combination has been shown in various solid tumors [27, 28] and in patients with lymphoma [29, 30].

Owing to the favorable toxicity profile of oxaliplatin compared with cisplatin, studies have been conducted to investigate the substitution of oxaliplatin for cisplatin in the standard DHAP regimen. The dexamethasone, cytarabine and oxaliplatin (DHIAOx or DHAX) regimen has been assessed by two different study groups, demonstrating response rates of 50%–73% in patients with advanced lymphoma [12, 13]. Treatment was associated with frequent (66%–75%) but manageable grade 3/4 hematological toxicity. The lack of renal toxicity reported for oxaliplatin-containing regimens is particularly advantageous when treatment is considered for elderly patients with multiple comorbidities.

Rituximab has shown in vitro synergy with gemcitabine [31, 32]. On the basis of data from a very limited series of seven patients, the combination of rituximab plus gemcitabine has been proposed as a therapeutic option for elderly or frail patients with aggressive lymphoma who has relapsed after cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or for patients who are medically unfit to tolerate first-line CHOP [33]. The addition of rituximab to the DHAOx regimen achieved promising response rates in comparison with DHAOx alone [13, 34].

The use of R-GemOx is currently under further investigation in a larger, multicenter study being conducted by the Groupe d’Etudes des Lymphomes de l’Adulte in patients with relapsed/refractory B-cell lymphoma, with DLBCL.

In conclusion, the R-GemOx regimen shows promising activity with an acceptable toxicity profile, and may be a favorable treatment option for patients with relapsed/refractory B-cell lymphoma who are not eligible for HDT.

**Acknowledgements**

We address thanks to the following collaborators who participated in the management of patients: P. Gaulard, M. Bouanane, B. Zegai and A. Luciani, Hôpital Henri Mondor, Créteil, France. We gratefully thank A. Allain for his help with data management and N. Nio for his help with statistical analyses. I. Tabah-Fisch works as an employee of Sanofi-Aventis. The other authors have no competing financial interests to disclose.

**Specific contributions:** F. Reyes, I. Tabah-Fisch and C. Haioun designed the study; T. El Gnaoui, J. Dupuis and C. Haioun analyzed the data and wrote the manuscript; T. El Ganoui, J. Dupuis, K. Belhadj, I. Guillard, M. Divinié, F. Reyes and C. Haioun treated and documented the patients; J.-P. Jais carried out the statistical analyses; A. Rahmouni reviewed the imaging studies and C. Copie-Bergman carried out the histopathological review. Presented in abstract form at the 46th annual meeting of the American Society of Hematology, San Diego, CA, USA, December 3–7, 2004 and at the 42nd annual meeting of the American Society of Clinical Oncology, Atlanta, GA, USA, June 2–6, 2006. This study was sponsored by Sanofi-Aventis.

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