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ORIGINAL ARTICLE

Long-term results of gemcitabine plus oxaliplatin with and without rituximab as salvage treatment for transplant-ineligible patients with refractory/relapsing B-cell lymphoma

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Abstract
Purpose To determine the efficacy and safety of the combination of gemcitabine plus oxaliplatin, with and without rituximab, in patients with relapsed/refractory B-cell lymphoma unsuitable for high dose therapy.
Methods Patients were prospectively enrolled in two subsequent trials, GEMOX [gemcitabine (1200 mg/m^2, days 1 and 8) and oxaliplatin (120 mg/m^2, day 2), three-weekly] and R-GEMOX [rituximab (375 mg/m^2, day 1), gemcitabine (1200 mg/m^2, day 1) and oxaliplatin (120 mg/m^2, day 2), bi-weekly], up to six courses.
Results Sixty-two patients were enrolled: GEMOX [$n = 30$; median age, 66 years (range, 46–85); previous chemotherapy $\geq$2, 70%; PS ECOG $\geq$ 2, 57%]; R-GEMOX [$n = 32$; median age, 65 years (range 32–79); previous chemotherapy $\geq$2, 75%; PS ECOG $\geq$ 2, 47%]. Overall and complete response rates were 57 and 30% (95% CI, 15–49) for GEMOX and 78 and 50% (95% CI, 32–68) in R-GEMOX, respectively. Grade 3/4 neutropenia occurred in 57 and 47% of cycles and grade 3/4 thrombocytopenia in 26 and 17% of courses for GEMOX and R-GEMOX, respectively. At 42 months, the failure-free survival (FFS) was 7% (95% CI, 0–16) for GEMOX and 28% (95% CI, 9–47) for R-GEMOX ($P = 0.014$), with overall survivals of 7 (95% CI, 0–16) and 37% (95% CI, 20–55), respectively ($P = 0.016$).
Conclusions Both regimes showed good tolerability and appealing response rates. FFS was more prolonged in R-GEMOX, but patients continuously relapsed without a clear plateau on survival curves.

Keywords Gemcitabine · Oxaliplatin · Rituximab · Non-Hodgkin lymphoma · Salvage treatment

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Introduction

Despite significant advances in the treatment of B-cell non-Hodgkin's lymphoma (NHL), 40–50% of patients with aggressive histology and a larger fraction of those with indolent subtypes progress or relapse after rituximab-including induction treatments [1, 2]. While eligible patients can benefit from high-dose therapy (HDT) and autologous stem cell transplantation (ASCT), the overall prognosis remains dismal in those unsuitable for HDT and/or unfit due to age, comorbidities, poor functional status, and toxicities from previous treatments. Current salvage regimes, such as ICE (ifosfamide, carboplatin, etoposide), IEV (ifosfamide, epirubicin, etoposide), or the combination of cytarabine with cisplatin, cornerstone of regimes such as DHAP (dexamethasone, high-dose cytarabine, cisplatin) or ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin), with or without rituximab, have been mostly designed for and proposed to younger and fit

populations and can hardly be delivered for an adequate number of courses to different subsets of patients, due to the marked hematological and non-hematological toxicities, mainly renal and neurological [3–8].

In the effort to develop treatments with increased efficacy and reduced toxicity, regimes combining cisplatin with gemcitabine, a cytarabine congener with a selfpotentiating mechanism of action, prolonged intracellular retention, and higher single-agent activity in lymphomas [9–12], have been recently explored [13–15]. Similarly, oxaliplatin, a third-generation organoplatinum derivative, has emerged as a further attractive drug for progressing lymphomas, due to its relevant single-agent activity, a peculiar mechanism of DNA damage coupled to a significant cytoxicity toward chemoresistant tumor cells, and an advantageous toxicity profile as compared with cisplatin [16–18]. Oxaliplatin was also shown to synergize with gemcitabine in vitro and in vivo, mostly due to the distinct mechanisms of action and resistance of the two agents [19–21]. In this regard, we first described the safety and promising response rate of a three-weekly combination of gemcitabine and oxaliplatin (GEMOX) in patients with relapsed/refractory NHL [22]. The potency of GEMOX could be further increased by the addition of rituximab, due to the capacity of this antibody to synergize with platinum derivatives in relapsed lymphomas [7, 23] and to sensitize lymphoma cells to gemcitabine [24] by lowering the IC_{50} of this latter agent both in vitro and in animal models [25]. The multiple levels of synergy and the absence of overlapping toxicity among its components have prompted clinical evaluation of different versions and schedules of the rituximab, gemcitabine, and oxaliplatin combination (R-GEMOX, GEMOX-R, GROC) in the setting of refractory/relapsed lymphomas [26–28].

As a further contribution, we present here the final results of two prospective studies exploring the gemcitabine/oxaliplatin combination, with and without rituximab, in transplantation-ineligible patients. The prolonged follow-up of the present series may enable a proper evaluation of survival outcomes and provide insights into optimal application and improvement of these salvage treatments.

Methods

Patients and study design

Sixty-two consecutive patients with relapsed or primary progressive/refractory B-cell NHL not candidate for HDT due advanced age and/or poor Performance Status (PS) and comorbidities were eligible for inclusion in this study. Primary progressive/refractory disease was defined as disease progression or transient response [i.e., complete response (CR) or partial response (PR) lasting $\leq$ 3 months] at last chemotherapy line; relapse as progression from CR or PR lasting $\geq$ 3 months. All patients had a histologically confirmed B-cell lymphoma subtype according to WHO criteria and a CD20+ tumor [29]. Eligibility criteria included HIV negativity, age > 18 years, satisfactory organ function (creatinine clearance > 60 ml/min, serum transaminases less than three times the normal value, bilirubin < 2 mg/dL, left ventricular ejection fraction > 0.45), ECOG PS 0–3, absolute neutrophil count (ANC) $\geq$ 1,000/μL, hemoglobin level $\geq$ 10 g/dL, and platelets $\geq$ 100,000/μL. The primary endpoint was the ORR (CRs + PRs). Secondary endpoints included FFS and OS along with DFS in complete responders. The study was approved by local ethics committees and conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent to treatment and use of their clinical data for research. From March 2001 to September 2004, 30 patients were prospectively enrolled to receive a combination of gemcitabine and oxaliplatin (GEMOX). Subsequently, rituximab was added to the combination (R-GEMOX); the schedule was modified to improve dose intensity (DI) and optimize toxicity, and 32 further patients were enrolled between March 2004 and September 2005. Schedule design (Table 1) was based on preclinical evidences that the cytotoxic effect towards malignant hemopoietic cells was sequence dependent, gemcitabine followed by oxaliplatin being more cytotoxic than the reverse sequence [19]. Then, in the GEMOX regime, gemcitabine (Gemzar, Eli Lilly Italia, Sesto Fiorentino, IT) was administered at 1,200 mg/m^2 as a 30-min intravenous (i.v.) infusion on Days 1 and 8 of a 21-day cycle; in R-GEMOX, gemcitabine was administered at the same dose as on Day 1 of a 14-day cycle. In both regimes, oxaliplatin (Eloxatin, Sanofi Synthelabo, Milano, IT) was delivered at 120 mg/m^2 on Day 2 as a 2-h infusion diluted in 5% dextrose solution. Intravenous rituximab (Mabthera, Roche, Welwyn Garden City, UK) was given at 375 mg/m^2 on Day 1 of each R-GEMOX cycle, following acetaminophen and chlorphenamine pre-medication. Patients were scheduled to receive six courses of GEMOX or R-GEMOX unless evidence of progressive disease. Prior to treatment, disease was assessed by chest X-ray, total body computed tomography (CT), Fluorine-18 (^{18}F)-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) and bone marrow (BM)

Table 1 Chemotherapy regimes

	GEMOX		R-GEMOX	
Drug	Dose (mg/m^2)	Day	Dose (mg/m^2)	Day
Gemcitabine	1,200	1 and 8	1,200	1
Oxaliplatin	120	2	120	2
Rituximab			375	1
	3-week interval		2-week interval	

biopsy. *t*(14;18)-BCL2/IgH and *t*(11;14)-CCND1/IgH translocations were analyzed by Polymerase Chain reaction (PCR) on lymph node tissues, BM and peripheral blood (PB). While on treatment, patients were clinically evaluated at each treatment course. An intermediate restaging was scheduled after three courses and final response evaluation was performed at the end of the whole program (i.e., six courses) with FDG-PET and CT scanning reassessment. Bone marrow biopsy for patients who had BM involvement, and PCR analysis of BM and PB for those displaying a molecular marker, were performed at the end of treatment.

Toxicity and dose modifications

Toxicity was graded according to the National Cancer Institute Toxicity Criteria version 2.0. Dose reductions according to neutrophil or platelet nadir were as follows: grade 3 toxicity, 25% reduction for gemcitabine only; grade 4, 25% reduction for gemcitabine and oxaliplatin. Since the overall rate of nonhematologic toxicity for both gemcitabine and oxaliplatin, including grade 3/4 events, does not appear age-dependent, dose modulations relied only on toxicity grading: ≤grade 2, no dose reductions, except for creatinine > 1.5–3 of upper normal limits. For all grade 3 events but alopecia, the total drug dose was reduced by 25% in next courses and treatment interruption was to be considered for any grade 4 nonhematologic toxicity. Oxaliplatin dose was reduced by 25% for persistent (≥14 days) or temporary (7–14 days) painful paresthesia or functional impairment and the drug was omitted in case of persisting symptomatic paresthesia or other severe neurotoxicity despite a 25% dose attenuation. Treatment could be delayed for up to 2 weeks if toxicity persisted, ANC was lower than 1,000/μL, or platelets lower than 75,000/μL. Granulocyte colony-stimulating factor (5 μg/kg day^{-1} up to five consecutive days) was allowed only in case of grade 3/4 neutropenia.

Response and survival

Responses were evaluated by the NHL International Workshop Criteria [30] after the third course and 1 month after the end of the entire program. FFS was calculated from the first day of treatment, with failure defined as less than PR achievement, disease progression and death from any cause. Overall survival (OS) was measured from the date of treatment to the date of death or last follow-up. DFS was calculated from CR achievement until relapse or death from any cause.

Dose intensity

For GEMOX the planned gemcitabine and oxaliplatin DIs were 800 mg/m^2 week^{-1} and 40 mg/m^2 week^{-1}, respectively. In R-GEMOX the planned gemcitabine and oxaliplatin dose-intensities were 600 and 60 mg/m^2 week^{-1}, respectively. The agent-specific relative DI (RDI) for each drug was calculated as the ratio between the administered and the planned dose, as described [31].

Statistical analysis

Survival endpoints were analyzed using the approach of Kaplan and Meier and differences between curves were tested for statistical significance using the two-tailed log-rank test. Categorical variables were compared using the two-sided Fisher exact test while differences in distribution of ranks and comparisons between medians were assessed by Mann-Whitney test. All efficacy and toxicity endpoints were updated at December 2007. Statistical analysis was performed by using SPSS (version 14.0; SPSS, Chigago, IL, USA) and graphs plotted by GraphPad Prism (Version 4.0; GraphPad Software Inc., San Diego, CA, USA).

Results

Patient characteristics

Clinical characteristics and prognostic factors of patients treated with GEMOX and R-GEMOX are detailed in Table 2. No statistically significant differences in median age, gender, PS, stage and clinico-biologic prognostic factors at relapse were found between the two groups of treatment. Aggressive (diffuse large B-cell lymphomas—DLBCL, follicular lymphomas—FL G3b) and indolent histologies (FL G1/G2, marginal zone lymphoma—MZL, small lymphocytic and lymphoplasmocytic lymphomas—SLL/LPL) were comparably represented in the two groups, as well as the mantle cell lymphoma (MCL) subtype (Table 2). As to the aggressive histologies, both groups included at least 70% of high-risk patients according to the non-age adjusted International Prognostic Index. Sixteen patients (26%) were primary progressive/refractory to last chemotherapy and more than 70% of patients in both groups had received a minimum of two previous multiagent chemotherapy programs. In contrast, a significant difference emerged as to the exposure to rituximab. Only 10% of patients in the GEMOX group had received previous rituximab at study entry as opposed to 66% of those treated with R-GEMOX ($P < 0.0001$).

Treatment delivery

The median number of delivered courses was 5 (range, 1–8) and 6 (range, 3–8) for the GEMOX and R-GEMOX groups, respectively. Only 4 out of 62 patients (1 for GEMOX and

Table 2 Patient characteristics

Characteristics	GEMOX		R-GEMOX	
	No.	%	No.	%
Patients enrolled	30	100	32	100
Age, median (range), years	66 (46–85)		65 (32–79)	
Male gender	14	47	18	56
ECOG performance status				
0–1	13		17	
2	11		12	
3	6		3	
Relapse Stage				
II	4		5	
III	6		6	
IV	20	67	21	66
No of extranodal sites				
0	9		9	
1	13		13	
≥2	8	27	10	31
Bulky tumor (>10 cm)	8	27	11	34
Bone marrow involvement	13	43	14	44
Lactate dehydrogenase > ULN	21	70	22	69
Histology				
Diffuse large B cell	17	57	16	50
Follicular grade III	1		3	
Follicular grade I–II	4		5	
Marginal zone	2		4	
Mantle cell	3		3	
Small lymphocytic and lymphoplasmocytic	3		1	
Prior therapy				
Chemotherapy lines				
1	9		8	
2	11		15	
3	5		7	
4	3		2	
≥5	2			
Irradiation	7	23	10	31
Rituximab	3	10	21	66
ASCT	2		3	
Primary refractory	8	27	8	25

ULN upper limit of normal range

3 for R-GEMOX) received 2 additional courses, up to 8, after achieving PR at the final assessment. In the GEMOX group, Day 8 gemcitabine was omitted in 11 out of 129 courses (9%) and delayed to a maximum of 2 weeks in 5 courses, due to hematologic toxicity; no drug omissions occurred for R-GEMOX ($n = 162$), but delays of treatment were registered in 29 courses (18%) due to hematologic toxicity and in 10 other courses for neurological complications.

Treatment activity and survival outcomes

As shown in Table 3, the ORRs were of 57% in the GEMOX group and of 78% in R-GEMOX patients ($P = 0.103$), with 9 (30%; 95% CI: 15–49) and 16 (50%; 95% CI: 32–68) CRs, respectively ($P = 0.127$). According to disease status, the ORR for primary progressive/refractory patients was 25% (no CRs, 2 PRs) for the GEMOX regime and 50% (1 CR, 3 PRs) for R-GEMOX. Twenty-one out of 24 patients (ORR 87%) with relapsed disease were rescued by R-GEMOX as opposed to 15/22 patients (ORR 68%) for GEMOX.

As to disease histology, GEMOX treatment yielded CRs only in aggressive and MCL subtypes; in the R-GEMOX regime CRs were registered also in indolent histologies (i.e., FL and MZL). Interestingly, patients with MCL obtained objective responses both in the GEMOX (1 CR, 2 PRs) and R-GEMOX (2 CRs, 1 PR) treatment groups, with molecular response being documented in all of the CRs (data not shown). According to age, the ORRs in patients older than 70 years were 57% (6 CRs, 2 PRs) and 71% (7 CRs, 3 PRs) for GEMOX and R-GEMOX, respectively, and therefore not different from those achieved for the whole cohort of patients.

Survival outcomes are shown in Fig. 1. Median FFS was 9 months in GEMOX group, as opposed to 18.5 months for R-GEMOX ($P = 0.014$). At 42 months, the FFS was 7% (95% CI, 0–16) for GEMOX and 28% (95% CI, 9–47) for R-GEMOX ($P = 0.014$), with an overall survival of 7% (95% CI, 0–16) and 37% (95% CI, 20–55), respectively ($P = 0.016$). The median follow-up for patients who responded to treatment was of 19 months (range 7–60 months) in the GEMOX cohort and of 29 months (range 8–42 months) in the R-GEMOX group. However, no clear plateau was achieved due to a pattern of continuous recurrences also in complete responders as evidenced by DFS analysis ($P = 0.153$). Relapses occurred in 8 out of 9 and 12 out of 16 CR patients in GEMOX and R-GEMOX groups, respectively; 47 patients died as a result of progressive lymphoma and one of early septic shock while on GEMOX treatment. Overall 14 patients (23%) were alive at time of the present analysis with a statistically significant advantage in OS for patients in the R-GEMOX group (24 months) as compared with those treated with GEMOX (15 months) ($P = 0.016$).

Safety

Toxicities related to 129 delivered courses of GEMOX and 162 courses of R-GEMOX are detailed in Table 4. One early septic death, due to a clinically documented infection during grade 4 neutropenia, was recorded in a 74-year-old female with primary refractory DLBCL. Hematological

Table 3 Response to treatment according to disease status and histology

Response	Overall	Disease status		Histology							
		No. of patients (%)		No. of patients (%)							
		Relapsed	Refractory	Aggressive	Indolent[a]	Subtypes					
						DLBC	FL3	FL1-2	MZL	SLL/LPL	MCL
GEMOX											
Total	30	22		18	9	17	1	4	2	3	3
ORR	17 (57)	15 (68)	2 (25)	11 (61)	3 (33)	10	1	2	1		3
CR	9 (30)	9 (41)	0	8 (44)	0	8					1
PR	8	6	2	3	3	2	1	2	1		2
SD	6	4	2	1	5	1		2		3	
PD	6	2	4	5	1	5			1		
ED	1	1		1		1					
R-GEMOX											
Total	32	24	8	19	10	16	3	5	4	1	3
ORR	25 (78)	21 (87)	4 (50)	15 (79)	7 (70)	12	3	3	4		3
CR	16 (50)	15 (58)	1	10 (53)	4 (40)	9	1	1	3		2
PR	9	6	3	5	3	3	2	2	1		1
SD	2	1	1	1	1	1		1			
PD	5	2	3	3	1	3		1		1	

ORR overall response rate, *CR* complete remission, *PR* partial remission, *SD* stable disease, *PD* progression of disease, *ED* early death

[a] Without MCL

toxicity was acceptable in all patients despite several lines of previous chemo-radiotherapy and also taking into account that primary G-CSF prophylaxis was not provided. The most common grade 3/4 toxicities were neutropenia and thrombocytopenia, which, respectively, occurred in about a half and a quarter of the whole number of courses delivered to both treatment groups (Table 4). Nonhematologic toxicity was overall mild. In particular, severe renal toxicity was not documented and neurotoxicity, although frequent, was always mild and transient in both groups of treatments. Grade 2/3 infections complicated 18 and 30 courses of GEMOX and R-GEMOX, respectively (Table 4).

Dose intensity

Delivering of both regimes resulted in the achievement of significant DIs for both gemcitabine and oxaliplatin (Fig. 2a, b). Median RDI values of 75 and 85% were calculated for gemcitabine in GEMOX and R-GEMOX groups, respectively. Similarly, agent-specific RDI for oxaliplatin was of 90% for GEMOX and 80% for R-GEMOX. Interestingly, despite a lower RDI of gemcitabine, patients treated with GEMOX received a median actual DI of 600 mg/m^2 week^{-1}, i.e., a 18% more gemcitabine (plus 90 mg/m^2 week^{-1}) as compared to those in the R-GEMOX group ($P = 0.034$) (Fig. 2b). Vice versa those treated with R-GEMOX received a median actual DI of oxaliplatin of 48 mg/m^2 week^{-1}, i.e., a 33% more oxaliplatin (plus 12 mg/m^2 week^{-1}) with respect to patients given GEMOX ($P = 0.001$) (Fig. 2b). No statistically significant differences in median agent-specific RDIs were observed in patients younger or older than 70 years with both GEMOX (gemcitabine: 66% $\geq$ 70 years vs. 74% < 70 years; oxaliplatin: 92% $\geq$ 70 years vs. 79% < 70 years) and R-GEMOX (gemcitabine: 67% $\geq$ 70 years vs. 84% < 70 years; oxaliplatin: 89% $\geq$ 70 years vs. 90% < 70 years).

Discussion

This study evaluates at a long-term follow-up the activity of the combination of gemcitabine and oxaliplatin, with and without rituximab, in patients with recurrent B-cell NHL not candidate for HDT. The development of regimes with increased efficacy and a lower burden of toxicity remains a priority for this subset of patients, and the evaluation of failure and relapse proportions at a protracted follow-up time remains the most valuable tool to prove their efficacy [1, 8].

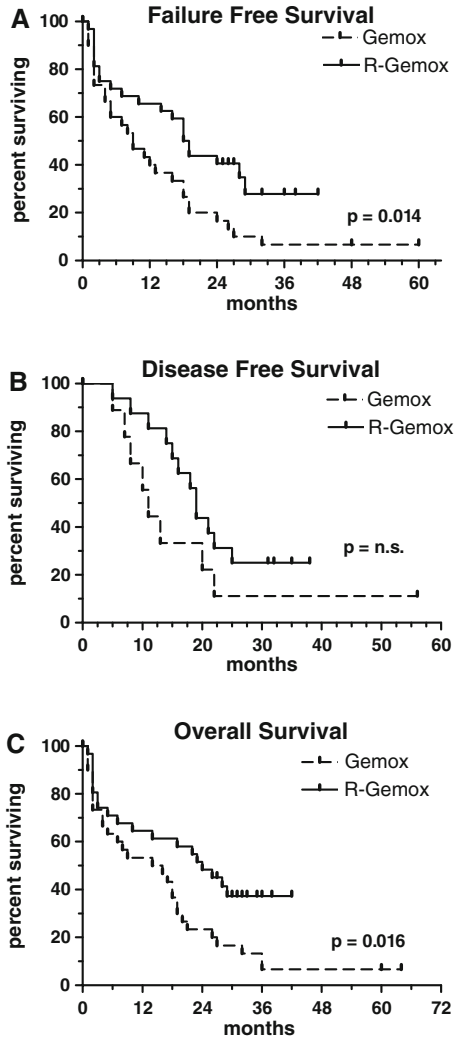

Fig. 1 Survival curves failure-free (**a**) and overall survival (**c**) of 30 (GEMOX) and 32 (R-GEMOX) patients with recurrent B-cell NHL. Disease-free survival (**b**) of 9 (GEMOX) and 16 (R-GEMOX) patients. *P* denotes the two-tailed log-rank test value, *ns* not significant, *perpendicular symbol* censored patients

In our study a remarkable antitumor activity was documented for both GEMOX (57% ORR; 30% CRs) and R-GEMOX (78% ORR; 50% CRs), with a statistically significant advantage for the R-GEMOX combination on survival outcomes. At 42 months, actuarial FFS was only 7% for GEMOX while patients treated with R-GEMOX displayed a FFS of 28%, with a median FFS 9 months and 18.5 months, respectively ($P = 0.014$). Similarly, R-GEMOX was associated with an overall survival of 37% as opposed to 7% of GEMOX ($P = 0.016$). We pointed out that reducing the intervals in drug recycling from a three-weekly (GEMOX) to a bi-weekly (R-GEMOX) timing, produced a lower overall amount of actually delivered gemcitabine without affecting its DI and a relevant escalation of the oxaliplatin dose size. This fact and the addition of rituximab, may explain the statistically significant gain of 9 months in both FFS and OS in R-GEMOX towards GEMOX, together with the occurrence of CRs also in patients with indolent histologies (FL, MZL); in contrast GEMOX yielded to CRs only in aggressive subtypes (DLBCL, MCL). Since about two-third of patients given R-GEMOX had received rituximab as a part of their previous therapy, our data support the activity of rituximab re-treatment in the setting of recurrent lymphoma. Noteworthy, all 6 MCL patients achieved a response, including three clinical and molecular CRs, confirming preclinical evidences [32, 33] and previous clinical reports [10, 18, 34], which may prompt this therapeutic platform even as an upfront strategy for in this 'difficult to treat' lymphoma. As to age-specific activity, response rates and even DIs for patients younger and older than 70 years did not differ in the two treatment groups. The hematologic toxicity profile of both GEMOX and R-GEMOX was favorable even without primary growth factor prophylaxis. Peripheral neurotoxicity was always transient, despite a median total delivered dose of oxaliplatin of 640 mg/m^2, and no renal toxicity was recorded. This supports the good feasibility of these combinations in those patients which are usually excluded from current platinum- or ifosfamide-based salvage regimes due to comorbidity, or are forced to interrupt ongoing treatment due to an excess of hematologic toxicity and renal and/or neurologic adverse events.

The high response rate and good tolerability in comparable series of transplant-ineligible recurring patients, including elderly subjects, of the combination of rituximab with gemcitabine and oxaliplatin, have been concordantly reported for different variants of such regime with bi-weekly and three-weekly schedules [22, 26–28, 35]. However, reports on survival outcomes are somewhat conflicting among these studies with series showing short FFS and other even a plateau in survival curves [22, 26–28, 35]. Spanish investigators reported a progression-free survival (PFS) of 29% and an OS of 41% at 12 months, in recurrent DLBCL patients treated with three-weekly GEMOX-R [27]. Similarly, preliminary results of the bi-weekly pegfilgrastim-supported GROC regime, indicate a PFS of 29% at 24 months in relapsed aggressive NHL, with an OS of 33% [28]. These results are somewhat different from those of the French cooperative group with a bi-weekly R-GEMOX, reporting 62% of patients free from relapse at 2 years [26, 35]. In our series, only 11 (GEMOX) and 31% (R-GEMOX) of patients were still in CR at 24 months, with a continuous pattern of relapse and step-wise survival curves. Only a few patients, 7% at 60 months (GEMOX) and 28% at 42 months (R-GEMOX), were failure-free and without evidence of a plateau. Different factors may account for such discrepancies. First, our longer follow-up after closure of enrollment, i.e., more than 3 years for GEMOX and more than 2 years for R-GEMOX, might have better appreciated fractional survival at a later plotted time [36].

Table 4 Treatment-associated toxicity for all courses of therapy with gemcitabine and oxaliplatin, with and without rituximab

NCTC v2.0 Toxicity	GEMOX (N = 129)				R-GEMOX (n = 162)			
	No. of cycles (%)				No. of cycles (%)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic								
Anemia	49 (39%)	23 (18%)	8 (6%)	5 (4%)	29 (18%)	21 (13%)		
Neutropenia	18 (14%)	14 (11%)	45 (35%)	21 (16%)	18 (11%)	15 (9%)	47 (29%)	29 (18%)
Thrombocytopenia	18 (13%)	49 (38%)	24 (19%)	9 (7%)		42 (26%)	28 (17%)	
Nonhematologic								
Vomiting	23 (18%)	30 (23%)	14 (11%)		39 (24%)	47 (29%)	15 (9%)	
Diarrhea	21 (16%)	18 (13%)	9 (7%)		34 (21%)	7 (4%)	7 (4%)	
Alkaline phosphatase	13 (10%)	9 (7%)	5 (4%)		13 (8%)	7 (4%)	3 (2%)	
Aspartate aminotransferase	10 (8%)	12 (9%)	8 (6%)		18 (11%)	8 (5%)		
Laryngopharyngeal	34 (26%)	8 (6%)			50 (31%)	5 (3%)		
Paresthesias	48 (37%)	4 (3%)			104 (64%)	23 (14%)	10 (6%)	
Alopecia	50 (39%)	23 (18%)			47 (29%)	16 (10%)		
Stomatitis	35 (27%)	15 (12%)	8 (6%)		31 (19%)	7 (4%)	11 (7%)	
Infection		6 (5%)	12 (9%)			16 (10%)	24 (15%)	
Anorexia	41 (32%)	23 (18%)	9 (7%)	4 (3%)	39 (23%)	23 (14%)	10 (6%)	3 (2%)

Second, while El Gnaoui et al. [26] remarked a 22% conversion of PRs to CRs from induction, i.e., the first 4 R-GEMOX courses, to consolidation, i.e., after additional four courses, our evaluation was made after six courses of R-GEMOX, with results (50% of CRs) fully comparable to those of the French study at post-induction evaluation. So, if protracting upfront chemotherapy beyond six courses does not significantly improve the overall outcome of aggressive NHL [37], the scenario may turn different in recurrent disease. The comparison of our and French results, rather suggests that prolonged R-chemotherapy may confer an added value to salvage strategies in patients not consolidated with HDT. This may turn more relevant than DI itself since the 20% increase in DI of our R-GEMOX with respect to the regime from French investigators did not yield any apparent advantage.

Results achieved with gemcitabine and oxaliplatin appear overall superior to those of gemcitabine/cisplatin combinations, with and without rituximab, in terms of both response rate and survival outcomes [14, 15, 38, 39]. These latter associations do not usually yield durable responses if not followed by HDT, and most recent updating of GEM-P (gemcitabine, methyl-prednisone and cisplatin) and GDP (gemcitabine, dexamethasone and cisplatin) results has shown a median DFS of few months and a median progression-free survival (PFS) of 5–8 months, together with a disappointing rate (up to 53% of courses) of dose reductions/delays [14, 15, 39]. Probably, the substitution of cisplatin with the less toxic oxaliplatin, allowed a more frequent delivery of gemcitabine, due to a negligible rate of dose reductions/delays, and a more adequate exposure to the organoplatinum compound by increasing both dose size and administration frequency of this latter agent.

All studies evaluating R-GEMOX regimes support the hypothesis that this combination may provide a less toxic salvage platform with broad age- and morbidity-related eligibility criteria, with respect to currently adopted regimes, such DHAP, ICE or ESHAP. Differently, the excellent toxicity profile and the appealing ORR may yet not render R-GEMOX a concrete alternative to conventional salvage regimens, given the high rate of recurring patients in the absence of HDT consolidation. In addition, the unexplored ability to mobilize stem cells (SC) and preclinical evidences that all its drug components display a poor central nervous system (CNS)-penetrating capacity [40, 41], may hamper the straightforward inclusion of R-GEMOX among current strategies for patients eligible for HDT and/or at high risk for CNS involvement [42]. Even though the actual risk of CNS recurrences for patients treated with R-GEMOX has not been yet formally rated, it is noteworthy that all the most effective current salvage regimes include CNS-penetrating agents [1]. A possible strategy to further boost the antitumor efficacy of R-GEMOX and widen the possible applications of this regime, by also exploiting its favorable toxicity profile, can be represented by the addition of ifosfamide. This bifunctional alkylator, among the most active second-line agents for lymphomas, displays a significant cytoreductive and SC-mobilizing activity and efficiently penetrates the blood-brain barrier [3, 4, 6, 43]. A pilot study from our group has shown the feasibility,

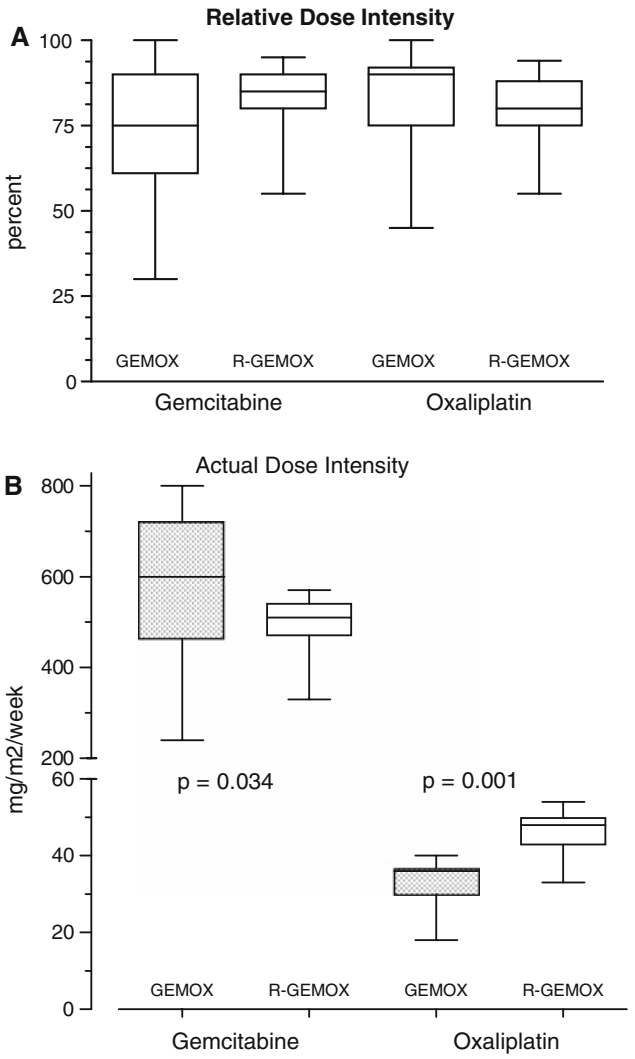

Fig. 2 Relative and actual dose intensity. Despite a lower RDI of gemcitabine (**a**), patients treated with GEMOX received a median actual DI of 600 mg/m^2 week^{-1}, i.e., a 18% more gemcitabine as compared to those in the R-GEMOX group ($P = 0.034$) (**b**). Differently, those treated with R-GEMOX received a median actual DI of oxaliplatin of 48 mg/m^2 week^{-1}, i.e., a 33% more oxaliplatin with respect to patients given GEMOX ($P = 0.001$) (**b**), in spite of lower RDI (**a**). *P* denotes the two-tailed Mann–Whitney test

tolerability, and very high-response rate (83% of ORR and 71% of CR rate) of such strategy (R-GIFOX) in patients of all ages, coupled to the ability to mobilize SC [44, 45].

Within the limits of single-arm experiments, we have shown here that R-GEMOX represents an active and safe salvage option for heavily pretreated unfit and HDT-ineligible subjects, ensuring dose-intensive delivery of effective agents without primary growth factor support. By providing an appropriately long post-enrollment follow up, we have been also able to show that R-GEMOX, despite its remarkable response rate, is associated with a pattern of continuous relapse and a still unsatisfactory impact on survival. Its excellent toxicity profile, however, may allow further improvements yielding to a unique therapeutic platform allowing a full salvage program to be safely delivered for six to eight courses to aged or unfit patients and even a valuable option for pre-HDT cytoreduction/mobilization.

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Conflicts of interest statement All of the authors have no financial or other conflicts of interest to declare.

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