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Oral CHOP-like chemotherapy in 60–80 years-old patients with diffuse large B-cell lymphoma

The cancer treatment paradigm is moving towards oral therapy. In this context, we developed a R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone)-like regimen: R-oroCIEP, an all-oral chemotherapy, for patients with diffuse large B-cell lymphoma (DLBCL). Preclinical studies have identified idarubicin, an oral anthracyclin, as one of the most potent anthracyclines (Kuffel *et al*, 1992). Although no clear superiority was identified in clinical studies for lymphoma (Hohloch *et al*, 2014), its oral bioavailability, cerebral diffusion (Boogerd *et al*, 1999) and (probably) less cardiac toxicity make idarubicin an important anthracycline for DLBCL study treatment.

We hypothesized that newly diagnosed DLBCL patients aged between 60 and 80 years old would particularly benefit from a more ambulatory all-oral oroCIEP regimen, with a similar activity and safety profile. We performed an open label multi-centre phase 1/2 trial evaluating escalating doses of oral idarubicin (3 + 3 design) to determine the maximum tolerated dose (MTD) of this drug given orally on day 1 every three weeks. The oroCIEP regimen combined idarubicin, at 4 planned dose levels (20, 30, 40 and 50 mg/m^2), with cyclophosphamide, etoposide, prednisolone and rituximab. Cyclophosphamide and etoposide were given orally at a fixed dose of 150 mg/m^2/day and 100 mg/m^2/day respectively, days 1 to 3. Prednisolone was given orally at the fixed dose of 60 mg/m^2/day, days 1 to 5. Rituximab was administrated intravenously (IV) on day 1 at the fixed dose of 375 mg/m^2. Granulocyte colony-stimulating factor was systematically used from day 6 to time of haematological reconstitution. Granisetron was given orally on day 1 to 4 for nausea. (Table SI). Eight courses were proposed, based on the historical study by Coiffier *et al* (2002). Dose limiting toxicity (DLT) was defined as grade 4 neutropenia lasting more than 4 days, grade 4 thrombocytopenia, grade 3 or 4 non-haematological toxicity other than nausea and alopecia, at Cycle 1. If toxicity occurred during a cycle, the next cycle dose was adapted according to the neutrophil and platelet levels at day 21 and the nadir during the cycle (Table SII). The inclusion criteria were similar to those selected by Coiffier *et al* (2002). Response to treatment was evaluated after 4 courses and at the end of treatment, according to Cheson *et al* (1999). Statistical analysis is described in Data S1.

Table I. Baseline characteristics.

Characteristic	*N*	Percentage
Gender		
Male	11	42
Female	15	58
Age, years		
60–69	10	39
70–80	16	61
ECOG performance status		
0–1	11	42
>1	15	58
Disease stage		
II	1	4
III	6	23
IV	19	73
B symptoms	5	19
Bulky tumour (>5 cm)	8	31
Aged-adjusted IPI score		
1	10	38
2	12	46
3	4	16

ECOG, Eastern Cooperative Oncology Group; IPI, International Prognostic Index.

Twenty-six patients were enrolled from five French centres across phase 1 ($n = 12$) and 2 of the study. The baseline characteristics are summarized in Table I. No DLT was observed at dose level 1 (20 mg/m^2), whereas 2 of 6 patients developed a DLT at dose level 2. At level 3, all of the first 3 patients developed a DLT. The recommended phase 2 dose of oral idarubicin was thus considered at the MTD of 30 mg/m^2, and 14 patients were enrolled in the phase 2 part of the study. The idarubicin relative dose intensity (DI) in comparison with the planned DI, was 99·3%, 93·8% and 79·7% at dose level 1, 2 and 3, respectively. No toxic death was observed.

A total of 180 cycles were administered and 176 were assessable for toxicity. Grade 3 and 4 neutropenia occurred in 21%, 26% and 100% of cycles for levels 1, 2 and 3 respectively. Grade 3 and 4 thrombocytopenias were observed in 4%, 3% and 50% for levels 1, 2 and 3 respectively. Across non-haematological toxicities, grade 3 and 4 infections were reported in 5% at level 2, and 50% at level 3. Four patients experienced cardiac toxicity: atrial fibrillation (2 cases) ventricular extra systole (1 case) and diastolic heart failure (1 case). Second primary malignancies were reported in three patients: a fatal breast carcinoma observed 9 years post-treatment, a surgically cured lung cancer observed 2 years post-treatment and two skin cancers for the same patient: *in situ* melanoma and epidermal carcinoma, both surgically cured. The most common adverse events are listed in Table SIII.

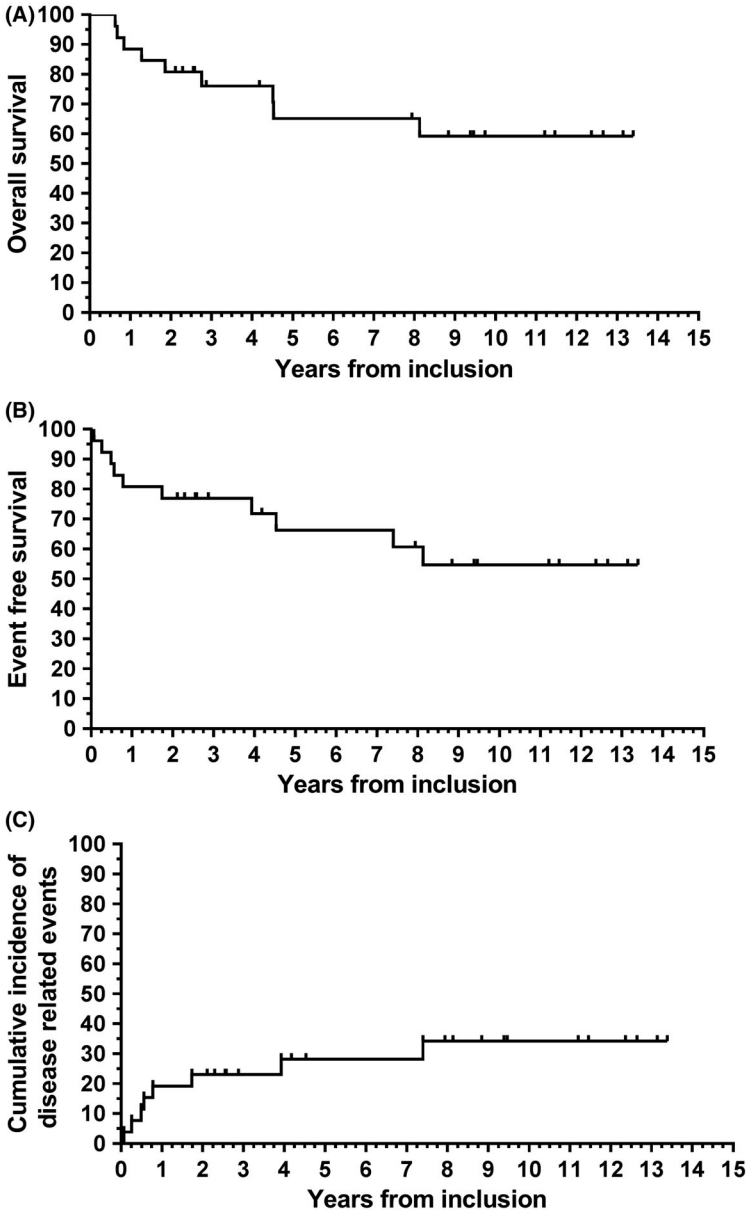

Fig 1. Survival curves. (A) Overall survival; (B) Event-free survival; (C) Cumulative incidence of disease-related events.

The overall response (ORR) and complete response (CR) rates were 85% and 77%, respectively (Table SIV). With a median follow-up of 8·8 years (6·1–11·0), 7 patients died from the disease and 2 from other causes. The median overall survival (OS) and median progression-free survival (PFS) were not reached in our study (Fig 1) with a 3- and 5-year OS rate of 74% (95% confidence interval [CI] 48–88%) and 65% (95%CI 41–81%), respectively.

Six phase 3 randomized clinical trials have documented the efficacy and safety of R- CHOP for the treatment of fit DLBCL patients aged 60–80 years (Coiffier *et al*, 2002; Habermann *et al*, 2006; Pfreundschuh *et al*, 2008; Merli *et al*, 2012; Cunningham *et al*, 2013; Delarue *et al*, 2013), with reported CR rates between 71% and 78% and 3-year OS from 67% to 78%. Our results seem to be acceptable in term of disease control and safety profile. We did not observe any secondary leukaemia or myelodysplastic syndrome. No left ventricular cardiac failure was seen, in line with the known safe cardiac profile of idarubicin. The most important weakness of the study was a relatively large PFS and OS 95% CI. However, our phase 1/2 study suggests that R-OroCIEP was safe and seemed to be as active as standard R-CHOP in first-line treatment for fit DLBCL patients aged 60–80 years. These data need to be confirmed in a larger cohort. A phase 3 randomised study with pharmaco-economic and quality of life evaluations may ultimately demonstrate the novel aspect of this regimen.

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Conflict of interests

The authors declare no potential conflicts of interest

Author contributions

Conception and design: VD, IP, MC, LLT, JG. Development of methodology: VD, LLT, BD, KD, GO, AC, JB, AM, EF, CT, CM, CDD. Acquisition of data: VD, CDD, SG, JG. Analysis and interpretation of data: VD, SG, XL, JG. Writing, review and/or revision of the manuscript: VD, SG, BD, KD, GO, AC, JB, AM, EF, CT, CM, IP, MC, CDD, XL, JG. Administrative, technical, or material support: VD, XL. Study supervision: VD, SG, XL, JG.

Stephanie Guidez[1,2]
Laurence Lacotte-Thierry[1,2]
Cecile Tomowiak[1,2]
Isabelle Princet[3]
Brigitte Dreyfus[1,2]
Gaelle Olivier[4]
Emmanuel Fleck[5]
Anne Corby[5]
Carine Motard[4]
Jocelyn Barrier[6]
Antoine Machet[1,2]
Katell Le Dû[7]
Celine Debiais-Delpech[8]
Michele Chabin[3]
Xavier Leleu[1,2]
Joëlle Guilhot[2]
Vincent Delwail [1,2]
[1]Oncology-Hematology and Cell Therapy, CHU, [2]INSERM CIC 1402, CHU, [3]Central pharmacy, CHU, Poitiers, [4]Internal Medecine, CH, Niort, [5]Oncology-Hematology, CH, La Rochelle, [6]Internal Medecine, CH, Chatellerault, [7]Hematology department, Clinique Victor Hugo, Le Mans and [8]Histopathology, CHU, Poitiers, France.
E-mail: vincent.delwail@chu-poitiers.fr

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Treatment schedule.
Table SII. Dose modification.
Table SIII. Adverse events.
Table SIV. Response rate assessment, N (%).
Data S1. Statistical analysis.

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High-dose therapy and autologous transplantation for POEMS Syndrome: effective, but how to optimise?

POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes) is a rare paraneoplastic phenomenon secondary to plasma cell dyscrasia. Treatment is aimed at the underlying plasma cell clone and its survival factors. Autologous stem cell transplantation (ASCT) is selected for patients who have multifocal skeletal disease and/or bone marrow involvement with adequate performance status (Dispenzieri, 2017). Because of the rarity of the disease, there are relatively few papers describing outcomes following ASCT. This analysis seeks to add further to the emerging evidence and elucidate prognostic factors.

All patients attending the University College London Hospitals (UCLH) Centre for POEMS who had previously undergone ASCT were reviewed. Forty-two patients had undergone ASCT between 1998 and July 2018. Details are shown in Table I. Disease status on admission for ASCT was used as the baseline. Response assessment was carried out at 3, 6 and 12 months, with a tailored frequency thereafter. The time to maximal vascular endothelial growth factor (VEGF), haematological, radiological and clinical responses were calculated, using previously published definitions (D'Souza et al, 2012). Anonymised data collection was covered by local policies.

Median (range) follow-up time was 62·2 (6–226) months. Clinical response was observed in 38 patients. Three patients died and one patient did not have a discernible clinical response within the follow-up period. Haematological response was evaluable in 33 patients: 14 (33·3%) patients achieved complete response ($HR_{CR,}$), seven (16·7%) patients achieved very good partial response (HR_{VGPR}), three of whom could not be classified as HR_{CR} because they had not undergone repeat bone marrow examination. Three (7·1%) patients achieved partial response (HR_{PR}), whereas nine patients were classified as haematological non-responders (HR_{NR}). Of the patients who were not assessable by haematological criteria, seven had solitary plasmacytomas and hence did not have bone marrow involvement, and two died before having repeat bone marrow examination.

Regarding VEGF response, 23 of the 36 evaluable patients achieved complete response ($VEGF_{CR}$), five patients partial response ($VEGF_{PR}$) and seven patients had no response ($VEGF_{NR}$). Average pre-ASCT VEGF was 4959 pg/