Prolonged disease-free survival in elderly relapsed diffuse large B-cell lymphoma patients treated with lenalidomide plus rituximab

Although the clinical outcome in diffuse large B-cell lymphoma (DLBCL) has dramatically improved over the last decades, and is likely to improve further with the introduction of novel specific anti-cancer agents and therapeutic approaches, relapsed/refractory DLBCL remains a major cause of morbidity and mortality.

In particular, the management of patients ineligible for high-dose chemotherapy (HDC) and autologous stem cell transplant (ASCT) or with disease relapsing after HDC-ASCT is very difficult, and the only remaining treatment option for these patients includes participation in phase I/II clinical trials with novel experimental agents or palliative therapy.[1,2] Thus, for the remainder of these patients with relapsed/refractory and high-risk biological subtypes of DLBCL, further improvements in therapy and novel therapeutic strategies are urgently needed. Data emerging from early clinical trials demonstrated that lenalidomide has a significant activity against relapsed/refractory DLBCL either as monotherapy or in association with rituximab.[3-7]

Here we report up-dated long-term results of a single-center phase II trial on the combination of lenalidomide and rituximab (induction phase, four cycles) plus lenalidomide maintenance for eight months.[5]

Twenty-three elderly patients with relapsed/refractory DLBCL were enrolled in 2009 at our institution. Cases were all *de novo* DLBCL (no transformations from low-grade lymphomas) and all patients were biopsied prior to entry onto study to confirm lymphoma relapse. Briefly, the treatment schedule was: four 28-day cycles of oral lenalidomide (20 mg/day for 21 days) and rituximab (375 mg/m^2, on days 1 and 21); after this induction phase, patients achieving at least stable disease were given lenalidomide maintenance therapy for an additional 8 cycles (20 mg/day for 21 days if the patients had no dose reduction due to adverse event during induction phase). The overall response rate at the end of the induction phase was 35% (n=8). Ten patients were eligible for lenalidomide maintenance: 7 patients completed the 8 scheduled cycles (4 with a dose of 20 mg/day and 3 with a dose of 15 mg/day) and 3 patients stopped the treatment after the 6th cycle due to a grade 3 hematologic adverse event (3 at a reduced dose of 15 mg/day and 3 at a dose of 10 mg/day). Finally, the complete response (CR) rate on completion of maintenance phase was 35% [one patient in partial response after induction converted to CR during the second phase, while the 2 patients with stable disease (SD) maintained their disease status].

Subsequently, the original protocol was amended to extend study follow-up procedures. Participants gave written informed consent to this protocol amendment. Disease status was evaluated again three months after the end of maintenance through physical examination, and computed tomography (CT) and positron emission tomography (PET) scans. Patients' follow-up assessment included: blood count and physical examination every 3-4 months for the first two years and then every six months for the following three years, CT scan every six months for the first two years, followed by physical examination and annual imaging studies with CT or PET/CT up to ten years from treatment completion. Potential long-term toxicity was also taken into account. The study was registered at *EudraCT 2008-005631-14*.

Response assessment was made following the revised response criteria for malignant lymphomas and end points (i.e. overall, progression-free and disease-free survivals) were defined accordingly.[8]

After a first update at three years,[9] at January 2016 (at 6.5 years) overall survival was 34.8% with 16 deaths and progression-free survival (PFS) of 26.1%. Five out of 8 of the responder patients were still in continuous CR (CCR); in addition, another patient was in CCR for 5.8 years until June 2015 when he died due to cardiac problems (not related to lymphoma). Overall, median duration of the CR was five years (range 30-78 months) with a disease-free survival of 75% at six years as 2 of 8 patients progressed and died due to lymphoma (Figure 1).

Regarding long-term safety, no second malignancies occurred.

Table 1 summarizes the characteristics of the 6 long-term responders.

According to the cell of origin (COO) of DLBCL, the material was sufficient and evaluable (according to immunohistochemistry method defined by Hans criteria)[10] only for 3 of these 6 patients: one was germinal center B-cell-like, one non-germinal center B-cell-like, and the last was null-like; in the remaining 3 patients the histological tissue was not sufficient to stratify according to the COO.

Despite the small sample size, our data indicate the potential activity of lenalidomide and rituximab regimen followed by lenalidomide maintenance in relapsed/refractory elderly DLBCL. Six out of 23 patients

Table 1. Characteristics of the 6 long-term responders.

Patient ID and age (years)	Ann Arbor stage at enrollment	Previous treatments	Cell of origin	Status at enrollment	Duration of CR (months)
1 (74)	IV	VNCOP-B-R; rituximab	na	relapsed	70
2 (79)	III	VNCOP-B-R; ibritumomab tiuxetan	na	relapsed	72
3 (74)	III	VNCOP-B-R; rituximab; gemcitabine	null-like	relapsed	42
4 (78)	II	R-CHOP; ibritumomab tiuxetan; gemcitabine	na	relapsed	78
5 (68)	IV	R-CHOP; IEV; radiotherapy	GC-like	refractory	73
6 (68)	IV	R-CHOP; IEV; ASCT	non-GC-like	relapsed	75

ASCT: autologous stem cell transplantation; IEV: ifosfamide, epirubicin, etoposide; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; VNCOP-B-R: etoposide, mitoxantrone, cyclophosphamide, vincristine, prednisone, bleomycin, rituximab; CR: complete response; na: not available; GC: germinal center.

(26%) obtained a very long-term CCR which may represent a first indication of high efficacy of lenalidomide and rituximab regimen plus maintenance phase in this population with an unmet medical need. Further studies considering the different COO could be useful to improve the application of this regimen in DLBCL patients. The maintenance strategy used in the present study resulted in very prolonged PFS, and this could indicate that the continuous lenalidomide used in other ongoing studies may not be necessary: more data are needed to address this issue. The value of a maintenance phase in addition to induction as well as the optimal length of induction remain undefined and worthy of additional investigation.

Pier Luigi Zinzani, Cinzia Pellegrini, Lisa Argnani, and Alessandro Broccoli

Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Italy

Correspondence: pierluigi.zinzani@unibo.it
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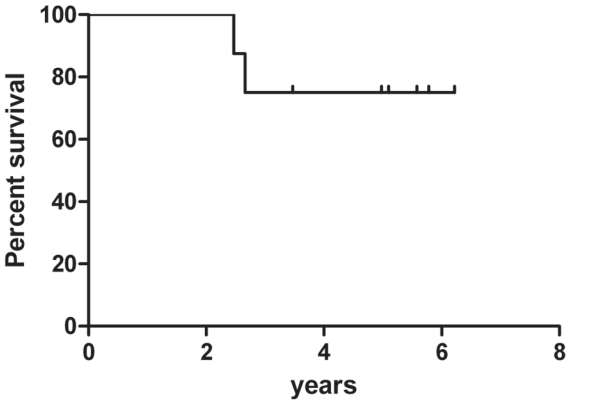

Figure 1. 6-year disease-free survival.

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