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Obinutuzumab and miniCHOP for unfit patients with diffuse large B-cell lymphoma. A phase II study by Fondazione Italiana Linfomi

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ABSTRACT

Objective: To evaluate activity and safety of obinutuzumab-miniCHOP (Ga101-miniCHOP) combination in older patients with Diffuse Large B-Cell Lymphoma (DLBCL) unfit to receive full dose immunochemotherapy.
Materials and Methods: We conducted a Simon's two-stage phase II multicenter trial to investigate response rate (primary endpoint) and safety of six courses of Ga101-miniCHOP in older patients with DLBCL (≥65 years), prospectively defined as unfit according to a simplified Comprehensive Geriatric Assessment (sCGA).
Results: Overall, 34 patients were enrolled (median age 82 years; range 68–89), with 27 out of the 33 eligible patients completing all six planned courses. Complete Remission (CR) rate was reported in fourteen patients (42%). After a median follow-up of sixteen months, the two-year Progression Free and Overall Survival (PFS and OS) were 49% (95% Confidence Interval (CI), 28 to 67) and 68% (95% CI, 49 to 81), respectively. The most frequent grade 3–4 adverse event was neutropenia in thirteen patients (26%).
Conclusions: Based on the observed CR rate, study accrual was interrupted due to the very low probability of demonstrating the initial study hypothesis that Ga101-miniCHOP could improve results of historical data obtained with R-miniCHOP in this group of patients. Nonetheless, results achieved with the 33 treated patients confirm activity and good tolerability of the Ga101-miniCHOP regimen for older unfit adult patients with DLBCL.

1. Introduction

Treatment of very old or unfit patients with Diffuse Large B-Cell Lymphoma (DLBCL) is challenging due to the presence of comorbidities or concomitant medical or physical conditions which are frequent in elderly patients and which limit available therapeutic options. Combination of rituximab with full dose CHOP (cyclophosphamide,

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doxorubicin, vincristine, and prednisone) chemotherapy is the undisputed standard treatment for all patients, including elderly subjects, but it is not usually prescribed in patients who are older than 80 years or in those who are not fit enough to receive full dose chemotherapy. An attenuated version of R-CHOP, namely R-miniCHOP, has been recommended as standard regimen for patients older than 80 years based on the positive results of a large phase II study [1,2]. Obinutuzumab (Ga101) is a glycoengineered, type II anti-CD20 monoclonal antibody with greater direct cell death induction and antibody-dependent cellular cytotoxicity and phagocytosis than rituximab [3]. In parallel with the identification of the most active immunochemotherapy regimen similar efforts are required to grant for an accurate and objective pretreatment selection of the older patient with DBLCL in order to optimize risk to benefit ratio of treatment. We conducted a prospective phase II study (FIL_GAEL Study; ClinicalTrials.gov Identifier: NCT02495454) to evaluate activity and safety of Ga101-miniCHOP combination in older patients with DLBCL who were prospectively defined as unfit according to a simplified Comprehensive Geriatric Assessment (sCGA) [4].

2. Methods

The study was approved by local Ethics Committee and Institutional Review Board of each participating centres and registered on ClinicalTrials.gov with number NCT02495454.

Older adults (≥65 years) with a newly diagnosed DLBCL were considered eligible if they were unfit on the sCGA. Simplified CGA was performed during staging procedures, after written informed consent, through application of the following instruments: comorbidity score according to the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) [5]; the Index of Independence in Activities of Daily Living (ADL) [6]; the Instrumental Activity of Daily Living (IADL) scale [7].

Patients were classified as unfit with different criteria according to age: for patients aged ≥80 years old; no limitations in ADL and IADL scores, no grade 3–4 comorbidities and less than five grade 2 comorbidities at CIRS-G were required. Patients younger than 80 years were classified as unfit with a at least one of the following; ADL score of 5, IADL score of 6–7, 5 to 8 grade-2 comorbidities without any grade 3–4 comorbidity at CIRS-G [4]. Frail patients, as per Tucci et al., [4] and patients with transformed lymphoma were excluded.

Patients received miniCHOP (400 mg/m^2 cyclophosphamide, 25 mg/m^2 doxorubicin, 1 mg vincristine on day 1 of each cycle, and 40 mg/m^2 prednisone on days 1–5 every 21 days), combined with obinutuzumab 1000 mg on days 1,8, and 15 of cycle one, and on day 1 of subsequent cycles. Treatment plan consisted of six cycles of Ga101-miniCHOP followed by two additional doses of Ga101, every 21 days. The use of G-CSF was mandatory.

The primary endpoint was Complete Response Rate (CRR) according to Cheson 1999 criteria [8]. Secondary endpoints included assessment of adverse events (AE), response rate according to Cheson 2007 criteria [9], Overall Response Rate (ORR), Overall Survival (OS), and Progression-Free Survival (PFS). The sample size was estimated according to Simon's optimal two-stage design. The study was designed to assess whether Ga101-miniCHOP could increase the CRR compared to historical data. The null hypothesis (p0) was set at 0.60 on the basis of Peyrade et al.'s findings [1] and the alternative hypothesis (p1) was set at 0.75, with type I and II errors of 10% and 90%. A total of 71 patients were required, with at least 48 in complete remission (CR), to draw a conclusion on the efficacy of treatment. The second stage could be activated with at least 22 CR out of the first 34 patients. Analysis was by intention to treat. Here we report the results of the first stage.

3. Results and Discussion

From August 2015 to June 2016, 34 patients were enrolled by sixteen Italian centers: one patient was subsequently excluded due to violation of inclusion criteria (Richter syndrome) (Table 1). Overall, 228 cycles were delivered, with 27/33 patients completing all six planned courses; four patients interrupted treatment because of AEs and two because of lack of response. Adverse events that caused treatment interruption included infection in two cases, hepatic toxicity and worsening of performance status in one case each. Treatment delays were reported in 34 out of 228 delivered cycles and were evenly distributed among cycles. Final response was reported as complete in fourteen patients (42%), and partial in eight (24%); ten patients had stable or progressive disease (30%) and one patient (3%) was not assessed for response. 2-fluoro-2-deossi-D-glucose Positron Emission Tomography (FDG-PET) was used in 25 patients to define response; complete metabolic response was observed in seventeen cases. Thirty-three patients experienced AEs (details are provided in Table 2). An adverse event leading to death was reported in one patient (heart failure in a patient in CR five months after the last dose of chemotherapy).

After a median follow-up of sixteen months, eighteen patients experienced lymphoma progression, one relapsed, and ten died (nine due to lymphoma progression, and one due to AE during follow up in CR). The two-year PFS and OS were 49% (95% Confidence interval (CI), 28 to 67) and 68% (95% CI 49 to 81), respectively. Based on the observed CR rate, study accrual was interrupted due to the very low probability of demonstrating the initial study hypothesis that Ga101-miniCHOP could improve results of historical data obtained with R-miniCHOP in this group of patients. Nonetheless, results achieved with the 33 treated patients in first stage are available to confirm activity and good tolerability of the Ga101-miniCHOP regimen for older unfit patients affected by DLBCL.

These results are consistent with those from the recently published randomized Goya trial [10], which compared Ga101-CHOP

Table 1
Characteristics of patients enrolled in the study (N = 33) and summary of study endpoints.

		N	%
Clinical features			
Age	Median (range)	82	(68–89)
	≥80 years	23	70
Gender	Male	19	55
Stage	III-IV	27	81
ECOG PS	2	2	6
LDH	>UNL	23	70
IPI	3–5	21	64
Geriatric assessment			
Unfit patients for age		23	70
ADL = 5		6	18
IADL = 7–6		1	3
ADL + IADL		2	6
CIRS grade-2 comorbidities (N = 5–8)		1	3
Cardiac comorbidity grade 1–2		18	54
Treatment activity and survival			
Response	CR rate	14	42
	PR rate	8	24
	SD/PD	10	30
	Not evaluable	1	3
2-year PFS	% (95% CI)	49%	(28 to 67)
2-year OS	% (95% CI)	68%	(49 to 81)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; LDH, lactate dehydrogenase; IPI, International Prognostic Index; ADL, Activity of Daily Living; IADL, Instrumental Activity of Daily Living (IADL), CIRS-G, Cumulative Illness Rating Scale – Geriatric; CR, Complete Remission; PR, Partial Remission; SD, Stable Disease; PD, Progressive Disease; PFS, Progression Free Survival; OS, Overall Survival; CI, Confidence Interval.

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Table 2
Summary of hematological and extra-hematological adverse events.

Adverse event (N = 33)	Grade 1–2		Grade 3–4	
	N	%	N	%
Hematological				
Anemia	6	18	–	–
Leucopenia	2	6	2	6
Neutropenia	2	6	13	26
Thrombocytopenia	10	30	1	3
Extra-hematological				
Cardiac disorders	3	9	2	6
Gastrointestinal disorders	11	33	1	3
Hepatobiliary disorders	–	–	2	6
General disorders	4	12	2	6
Infections and infestations	6	18	1	3
Injury/poisoning/				
Procedural complications	–	–	2	6
Investigations	2	6	1	3
Metabolism and nutrition disorders	5	15	3	9
Musculoskeletal - connective tissue dis.	5	15	3	6
Neoplasms benign, malignant and unspec.	–	–	2	6
Nervous system disorders - psychiatric dis.	6	18	1	3
Renal and urinary disorders	2	6	–	–
Respiratory/thoracic and mediastinal	5	15	–	–
Vascular	1	3	–	–
Other	8	24		

Legend to table: dis, disease; unspec, unspecified.

with standard R-CHOP in 1418 previously untreated DLBCL patients and which was not able to demonstrate superiority of Ga101 chemotherapy. The Goya results and those from our small study suggest that the increase in treatment efficacy in DLBCL likely cannot be achieved by potentiating the anti-CD20 monoclonal antibody part of therapy. This observation is also confirmed by the results of a phase II study where rituximab was substituted with ofatumumab, another second generation anti-CD20 antibody, and combined with mini-CHOP in 120 DLBCL patients older than 80 years [11]. Although a formal comparison between the two phase II studies is not appropriate, Peyrade et al. achieved similar results with ofatumumab (Ofa) or rituximab combined with miniCHOP, and the greatest improvement in the Ofa-miniCHOP study was likely an effect of the adoption of a mandatory pre-phase therapy with steroids and vincristine that actually reduced the rate of early fatal events.

Regarding the prospective use of sCGA this work is part of a larger project for older patients with DLBCL for whom a preliminary sCGA is required to define patient fitness status and to adapt treatment goals. This project is conducted by the FIL (Fondazione Italiana Linfomi) as an observational study (NCT02364050), with about 1400 enrolled patients with the aim to validate the use of sCGA and to define separate groups of patients to enroll into dedicated clinical trials. Patients prospectively enrolled in this so-called "Elderly Project" were categorized into one of three groups namely FIT, UNFIT and FRAIL. FIT patients were then offered a standard R-CHOP treatment or clinical trials with curative intent; UNFIT patients were better candidates for adapted R-CHOP regimens, or to dedicated clinical trials, like the Ga101-miniCHOP used in this trial. Finally FRAIL patients were offered low toxic regimens or clinical trials with palliative intent. To the best of our knowledge the elderly project is the first attempt to try to objectify and standardize treatment choices and goals of older patients with DLBCL and to better approach clinical research in this population.

4. Conclusions

In conclusion, our phase II study confirmed the activity and safety of Ga101-miniCHOP for the treatment of older, unfit patients with DLBCL, but was not able to show it as a promising regimen to challenge the current standard R-miniCHOP. To improve treatment efficacy in this hard-to-treat patient population, different strategies should be adopted that include better patient and/or lymphoma profiling and the use of new drugs with a novel non-cross-resistant mechanism of action.

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Declarations of Competing Interest

Francesco Merli holds a consultancy/advisory role from Roche, Gilead, Takeda, Janssen, Celgene, and Mundipharma.

Stefano Luminari holds a consultancy/advisory role from Roche, Celgene, Sandoz and Gilead.

Simone Ferrero holds a consultancy/advisory role and speakers honoraria from Janssen, advisory role and speakers honoraria from Pfizer, and speakers honoraria from Gilead.

The remaining authors declare no competing financial interests.

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