Leukemia Research 38 (2014) 891–895

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Chemoimmunotherapy with oral low-dose fludarabine, cyclophosphamide and rituximab (old-FCR) as treatment for elderly patients with chronic lymphocytic leukaemia

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ARTICLE INFO

Article history:
Received 5 February 2014
Received in revised form 21 May 2014
Accepted 22 May 2014
Available online 2 June 2014

Keywords:
Chronic lymphocytic leukaemia
Fludarabine
Cyclofosphamide

ABSTRACT

Median age at diagnosis for chronic lymphocytic leukaemia (CLL) patients is now 72 years, thus a consistent number of patients may not tolerate standard doses i.v. of fludarabine, cyclophosphamide and rituximab (FCR), the best available therapy, due to unacceptable myelotoxicity and risk of severe infections. We studied safety and efficacy of the addition of rituximab to the oral low-dose FC regimen (old-FCR) in a selected population of 30 elderly (median age 75, 15 untreated, 15 treated with 1 prior therapy) CLL patients. Complete remission (CR) rate was 80% in the untreated patients (overall response rate, ORR 93%), and 30% in pretreated patients (ORR 74%). Progression free survivals (PFS) were 45 months and 30 months in the untreated and treated patients, respectively. In patients achieving CR, old-FCR led to PFS of 67 months. Moreover, haematological toxicity was mild (grade 3–4: 15%) and patients were treated mostly in outpatient clinic. Old-FCR could be a good therapy option for elderly CLL patients outside clinical trials, larger studies are needed to confirm our findings.

1. Introduction

Current standard therapy for fit young patients with chronic lymphocytic leukaemia (CLL) is fludarabine, cyclophosphamide and rituximab (FCR) [1–3]. This chemo-immune treatment is highly effective in standard risk patients with CLL, however in the elderly can be troublesome since it can give unacceptable myelotoxicity and increase risk of infection [4]. As median age at diagnosis for CLL patients is now 72 years, the majority of patients may not be elegible to receive standard FCR, the best available therapy. Fludarabine and cyclophosphamide (FC) given intravenously at low doses in relapsed or refractory indolent chronic lymphoid malignancies (CLD) can reduce the incidence of severe myelosuppression and infectious complications [5,6]. Based on this background in the past we already demonstrated that oral low-dose FC (old-FC) given to pretreated elderly patients with CLD enabled response rates that were comparable to those obtained with standard i.v. regimens with very few side effects and complications [7]. These favourable responses were also confirmed in a population of untreated elderly low-grade non-Hodgkin lymphoma patients [8]. Finally we showed that in 26 elderly CLL patients who could not benefit of more aggressive schedules, old-FC was very effective especially in the untreated population [9]. In every study performed, this regimen was easy to administer on an outpatient basis with mild haematological toxicity.

Given the great efficacy of the anti-CD20 monoclonal antibody rituximab (R) in CLL, we recently added R to old FC (old-FCR), administered at day 1 of each cycle, to treat 30 elderly patients with CLL. Aims of the study were (i) to test regimen's safety in an elderly population of patients, (ii) to evaluate feasibility of a treatment schedule that should allow to treat elderly CLL patients on an outpatient basis, letting them come to the hospital just once a month, (iii) to test regimen's efficacy.

2. Materials and methods

We retrospectively analyzed data on elderly CLL patients treated with low doses oral fludarabine–cyclophosphamide and rituximab (FCR). These data came from the analysis of 30 elderly CLL patients consecutively treated at our centre during a selected period, January 2007–January 2014. Diagnosis was made according to guidelines defined by the International Workshop on CLL [1]. Biological

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http://dx.doi.org/10.1016/j.leukres.2014.05.016
0145-2126/

Table 1
Patient's characteristics.

	OLD-FCR		OLD-FC	
	U	T	U	T
N	15	15	12	15
Age median (range)	75 (67–88)	74 (69–82)	72 (65–81)	73 (67–80)
M/F	9/6	8/7	10/2	11/4
RAI stage				
I–II	13	12	10	12
III–IV	2	2	2	3
ECOG PS				
0	2	1	2	2
1	10	12	8	10
2	3	2	2	3
CIRS median	6	7	7	6
Range	(0–11)	(0–12)	(0–8)	(0–10)
FISH				
N-del13q-+12	14	12	9	9
Del11q/del17p	1	3	3	6
IGHV				
U/M	8/7	7/8	5/7	4/11
ZAP70 positive	7	9	4	9
CD38 positive	10	8	3	7
WBC median $\times 10^6$/ml	72	81	79	92
Range	(23–179)	(18–210)	(38–178)	(35–232)
Bulky adenopathy	2	3	1	3
Median (range)	3.6 (1.9–7.6)	4 (2.1–6.5)	2.9 (1.8–7.1)	3.7 (2–8)
LDH median (range)	369 (156–579)	384 (125–786)	389 (137–8)	356 (115–654)

U = untreated patients; T = patients previously treated; M/F = male/female; IGHV U = Unmutated; old = oral low dose; B_2m = beta 2 microglobulin; WBC = white blood cells.

prognosticators were assessed as described [10]. In particular IGHV gene mutational status was determined, ZAP-70 protein and CD38 expression were evaluated by flow cytometry; deletions of 11q22.2, 13q14.1, 17p13.1 loci and chromosome 12 trisomy were determined by fluorescent in situ hybridization (FISH) as previously reported [11,12]. Main reason for oral low doses treatment was age: we use to treat with this regimen patients over the age of 70 usually because at major risk for toxicity from standard doses IV FCR. All patients gave written informed consent in accordance with the Declaration of Helsinki. At pre-treatment evaluation physical examination, complete blood cell count, a biochemistry panel including lactate dehydrogenase and B_2-microglobulin, standard chest X-ray and abdominal ultrasound were performed.

Rituximab 500 mg/m^2 was administered day 1 of each 28 days cycle, except for cycle 1 in which it was administered at the dose of 375 mg/m^2 on day 8, in order to limit infusion reactions. Fludarabine 40 mg total dose was administered to all patients orally days 2, 3, 4, 5; cyclophosphamide 200 mg total dose was administered to all patients orally days 2, 3, 4, 5 (except for cycle 1 in which they were administered days 1, 2, 3, 4 at the same total dose). Bacterial prophylaxis of *P. jiroveci* was given during all period of treatment and for at least 6 months after treatment ending (trimethoprim/sulfamethoxazole 160/800 mg twice a day, two times a week). Four cycles of therapy were planned, providing that haematological recovery (neutrophil count >1.5 $\times$ 10^9/l, platelet count >100 $\times$ 10^9/l) had occurred. Haematological toxicity was assessed at day 10 and day 27. G-CSF was given if neutropenia >grade 2 occurred in order to prevent adverse events and allow subsequent cycles. If well tolerated or when an unsatisfactory response (less than PR) was present after four cycles, patients received a maximum of six cycles. Cumulative illness rating scale (CIRS) was evaluated for each patient as well as creatinine clearance with the Cockcroft–Gault formula.

Response assessment was done at 3 months after therapy and was defined according to IWCLL guidelines practice criteria. Minimal residual disease assessed by four colours flow cytometry was evaluated in all patients on peripheral blood. Yet due to patient poor compliance, bone marrow aspirate and biopsy were not performed in all patients. When available data on bone marrow aspirate are reported. Toxicity was defined according to NCI-CTCAEv.3 criteria after each course of treatment. OS and PFS were calculated using the Kaplan–Meier method. The log-rank test was used to compare survival curves. Categorical variables were compared by chi-square or Fisher exact tests when appropriate. Statistical analyses were performed using MedCalc software (Med-Calc Software, Broekstraat, Mariakerke, Belgium). Significance was set at $p = .05$. Results were retrospectively compared to PFS and OS reported in a similar cohort of 27 CLL patients treated with a median of four cycles of old-FC (data published in part, period of treatment June 2003–May 2008) [9].

3. Results

Patient's characteristics are listed in Table 1. Thirty patients were treated with old-FCR: 15 were untreated and 15 received one prior therapy. Median age was 75, range 67–88; time from diagnosis to treatment was at median of 4.3 years (range 0–11 years) in the untreated population. All treated patients were treated with clorambucil and received old-FCR at a median of 30 months (range 6–56) from first treatment. RAI stage was III–IV only in five patients and ECOG PS was >1 only in five patients. CIRS were a median of 6 (range 0–12), and median creatinine clearance was 58 ml/min (range 35–123).

Unfavourable FISH (del 11q/del 17p) was present in four patients. IgHV were unmutated in 15 patients. Patients received a median of four cycles (range 3–6).

Treatment with old-FCR led to an overall response in 25/30 (83%) patients (Table 2); in particular haematological and clinical CR was achieved in 18/30 (60%) patients (10 CR's were confirmed at bone marrow biopsy and MRD negative by flow cytometry) and PR in 7/30 (23%). After a median follow up of 35 months, median OS has not been reached and 7/30 patients died (but only one of them was in first line treatment and died from progressive disease). Median PFS was 39 months.

In the untreated patients, old-FCR led to an ORR in 14/15 (93%) patients; PFS was 45 months vs 30 months ($p = 0.08$) when compared to a similar group of patients previously treated with old-FC (Fig. 1). A CR was seen in 12/15 patients (80%), 7/15 (46%) patients who achieved CR were confirmed at bone marrow biopsy and flow cytometry; projected PFS was 67 months vs 39 months compared to patients untreated at diagnosis who received old-FC and achieved CR ($p = 0.002$) (Fig. 2).

Patients with del 11q/del 17p had a worse PFS compared to patients with normal FISH/other abnormalities (12 months vs NR, $p = 0.001$).

Toxicity of old-FCR was acceptable and manageable and mostly haematological (Table 3), grade III–IV neutropenia and thrombocytopenia was observed in 5/30 (16%) patients. G-CSF was given to those patients for a median of 2 days (range 1–3). However no dose reductions were necessary in those patients. Grade I–II fever was seen in five patients (FUO) and resolved promptly with antibiotics. Regarding non-haematological toxicity: grade II gastrointestinal toxicity was seen in two patients.