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Fludarabine, cyclophosphamide, mitoxantrone plus rituximab (FCM-R) in frontline CLL <70 Years

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ABSTRACT

Randomized trials demonstrated the superiority of chemoimmunotherapy over chemotherapy in the frontline treatment of CLL. Based on favorable experience with the addition of mitoxantrone (M) to fludarabine (F) plus cyclophosphamide (C), we designed a pilot study testing the combination of FCM plus rituximab (R). Thirty patients with previously untreated, symptomatic CLL, <70 years, and beta-2-microglobulin <twice upper limit of normal were evaluated. Treatment consisted of F 25 mg/m^2/day on days 2–4, C 250 mg/m^2/day on days 2–4, M 6 mg/m^2 on day 2, and R 375 mg/m^2 on day 1. For cycles 2–6, FCM started day 1 together with R 500 mg/m^2. Pegfilgrastim was administered with each cycle. Cycles were repeated every 4–6 weeks. Complete remission (CR) was achieved in 83% of 30 patients, nodular partial response in 10%, and partial response in 3%. The overall response rate was 96%. Sixteen of 24 CR patients (67%) achieved a flow cytometry response with <1% marrow CD5/CD19-positive cells and 13 of 21 CR patients (62%) were MRD-negative by molecular evaluation for clonal IgV_H. With a median follow up of 38.5 months, the median time to treatment failure (TTF) has not been reached. A comparison with a historical group of FCR-treated patients showed no significant differences with respect to response and toxicities. FCM-R is highly active in patients < 70 years with favorable beta-2-microglobulin levels and previously untreated CLL. Outcome does not differ from FCR-treated patients.

1. Introduction

Commensurate to the discovery that CLL is not of a uniformly indolent nature, but can take a remarkably heterogeneous clinical course with short survival time in some patients, treatment has evolved from single-agent alkylator therapy, to purine nucleoside analogs, to combination therapies with alkylators and nucleoside analogs (e.g. fludarabine plus cyclophosphamide, FC), and eventually addition of monoclonal antibodies to chemotherapy (e.g. FC plus rituximab in "FCR") [1]. Single institution phase II studies suggested that FCR (or similar chemoimmunotherapy regimens) improves outcome in both frontline and relapsed patients over chemotherapy alone [2,3]. In fact, recently conducted large randomized phase III studies in both settings confirmed significantly higher response rates and progression-free survival (PFS) for FCR compared with FC [4,5]. Furthermore, the rate of patients achieving molecular responses or low-level minimal residual disease (MRD) is higher, too, and has been associated with improved PFS [6]. On the other hand, overall survival has not been impacted. Although these studies suggest that chemoimmunotherapy should become standard therapy in CLL, they are not curative. Hence efforts are ongoing to optimize combination therapy in CLL. Mitoxantrone was shown in vitro to trigger apoptosis in CLL cells and exhibit synergistic activity in combination with nucleoside analogs and alkylators [7]. Combining mitoxantrone with FC (FCM), Bosch et al. in two separate studies demonstrated high response rates with durable response durations in relapsed/refractory and previously untreated patients, respectively [8,9]. Responses included eradication of minimal residual disease in up to a third. Given the additional lead from the chemoimmunotherapy experience, we designed a clinical study combining FCR with mitoxantrone (FCM-R) for previously untreated, symptomatic patients with CLL. The objective was to assess clinical, flow cytometry, and molecular response rates and to compare these with a historical control of FCR-treated patients.

2. Patients and methods

2.1. Study group

Patients <70 years and beta-2-microglobulin levels ≤2× the upper limit of normal (ULN) with untreated CLL and NCI-Working Group indications for therapy were eligible to participate in the study. Patients were excluded for ECOG performance status of ≥3,

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active hepatitis B, and either symptomatic heart disease (NYHA ≥3) or a left ventricular ejection fraction (as measured by either multigated cardiac acquisition scan [MUGA] or echocardiography) of <40%. All patients signed informed consent according to institutional guidelines. The study was approved by the Institutional Review Board (IRB) of the University of Texas MD Anderson Cancer Center and was conducted in accordance with the basic principles of the Declaration of Helsinki.

2.2. Treatment plan

Fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 were administered on days 2–4 of course 1 and on days 1–3 of courses 2–6. Mitoxantrone 6 mg/m^2 was given on day 2 of course 1 and then on day 1 of courses 2–6. Rituximab 375 mg/m^2 was given on day 1 of course 1 and at a dose of 500 mg/m^2 on days 1 of all subsequent courses. Prior to rituximab, patients received oral acetaminophen 650 mg and diphenhydramine 25–50 mg. Before chemotherapy, patients received intravenous ondansetron 24 mg. At the discretion of the treating physician, patients received prophylaxis for *Pneumocystis jiroveci* (*carinii*) pneumonia with trimethoprim/sulfamethoxazole or equivalent and antiviral prophylaxis with valacyclovir or equivalent for the duration of therapy. Pegfilgrastim was given routinely following the last day of each treatment cycle. Use of other hematopoietic growth factors was permitted throughout therapy as felt necessary for optimal supportive care. Courses were administered every 4–6 weeks as permitted by neutrophil and platelet recovery and/or resolution of toxicities. Patients who achieved a stable partial response or who had continued response after their first 3 courses could receive up to a total of 6 courses. Patients with no response or progressive disease after 1–3 courses were considered as having failed therapy and were taken off treatment and observed for progression and survival.

Monitoring of patients consisted of CBC with differential every 1–2 weeks as long as on therapy and during 6 monthly follow-up visits thereafter as long as on study. Physical examination and serum chemistries including creatinine, transaminases and total bilirubin were repeated before each treatment course. Dose adjustments were made for any ≥grade 3 treatment-related toxicity (based on National Cancer Institutes Common Toxicity Criteria [http://ctep.cancer.gov/reporting/ctc.html]) during the preceding course. For patients with pretreatment platelet counts $\geq 100 \times 10^9$/L and/or ANC $\geq 1 \times 10^9$/L, the platelet count was required to be $\geq 60 \times 10^9$/L and/or ANC $\geq 1 \times 10^9$/L prior to continuation. For patients with pretreatment platelet counts $<100 \times 10^9$/L or ANC $<1 \times 10^9$/L at the start of therapy, blood counts were required to have recovered to within 20% of pretreatment levels prior to starting the next course. Dose level-1 was fludarabine 20 mg/m^2 daily for 3 days and cyclophosphamide 200 mg/m^2 daily for 3 days without any change in the dose of mitoxantrone. Dose level-2 included a reduction of the mitoxantrone dose to 4.5 mg/m^2. There were no dose adjustments for rituximab.

2.3. Response assessment

Patients were evaluated for response according to 1996 NCIWG criteria after their third and sixth course with physical examination, CBC with differential and bone marrow biopsy and aspiration including immunophenotyping and, in some cases, IgV_H molecular studies [10]. Immunophenotyping was performed based on standard two-color flow cytometry. Molecular monitoring for residual disease was performed using a polymerase chain reaction (PCR)-based ligase assay for patient-specific clonal IgV_H as described elsewhere [3].

2.4. Statistical analysis

The objective of the study was to determine the clinical, flow cytometry, and molecular response rate in previously untreated patients with symptomatic CLL, age <70 years, and beta-2-microglobulin levels <2× ULN when adding mitoxantrone to the FCR combination. A previous phase II clinical trial of FCR resulted in an overall response rate at 6 months of approximately 95% [2]. When measuring flow cytometry for CD5/CD19 at 3 and 6 months it was shown that those patients who achieved <1% CD5/CD19-positive cells had better survival than those whose expression was ≥1%. It was therefore concluded that obtaining expression of CD5/CD19 by flow cytometry at 3 months was a useful tool for early assessment of survival. The method of Thall, Simon, and Estey was used to perform interim efficacy (CD5/CD19 expression at 3 months and safety monitoring (≥grade 3 neutropenia) [11]. Monitoring for efficacy and safety started once the first 10 patients had been enrolled and was then conducted continuously. Historical data were based on 189 previously untreated patients who were treated with FCR on the previous phase II trial [2]. In this study 34.4% of the patients had CD5/CD19 expression <1% at 3 months and 74.6% had ≥grade 3 neutropenia. The study aimed to achieve an increase in patients with favorable flow cytometry (CD5/CD19 < 1%) to 50%, an increase of approximately 15%, while not allowing the ≥grade 3 neutropenia rate to increase. As this study was designed as a pilot study, not more than 30 patients were included.

Descriptive statistics were used to summarize patient characteristics and response data. Duration of response and progression-free survival were estimated according to Kaplan–Meier method. Time intervals were measured from the first day of treatment until progression or relapse.

3. Results

3.1. Patient characteristics

Patient characteristics are summarized in Table 1. A total of 31 patients have been registered of whom 30 patients are evaluable. One patient decided to come off study because of uncertainty whether the health insurance plan would cover the costs of treatment. As per eligibility requirements, all patients had serum beta-2-microglobulin levels less than twice the upper limit of normal, i.e. <4 mg/L. Only a minority of patients presented with advanced clinical stage as their treatment indication and in most cases treatment was initiated based on a rapid lymphocyte doubling time and/or worsening and significant B-symptoms. Fourteen of 30 patients had >20% CD38-positive CD5-positive B cells in the marrow. In 17 of 26 patients ZAP-70 immunostaining of marrow lymphoctes was positive, and in 12 of 18 patients IgV_H mutational analysis revealed <2% deviation from germline consistent with unmutated IgV_H. A fluorescence in situ hybridization (FISH) panel demonstrated deletions of 17p and 11q in 2 (7%) and 3 (10%) patients, respectively.

3.2. Response

CR was achieved in 25 patients (83%), nPR in 3 patients (10%), and PR in 1 patient (3%) for an OR rate of 96%. Neither of the 2 patients with abnormalities of chromosome 17p achieved a response, whereas one patient with an 11q23 deletion achieved CR. Response by IgV_H mutation status, ZAP-70 staining, and beta-2-microglobulin levels is shown in Table 2. Since the majority of patients achieved a major response (CR/nPR), no significant differences could be observed based on the pretreatment characteristics. No deaths occurred on study. Only 1 patient showed progression