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Guest Editorial

How to improve the treatment outcome in chronic lymphocytic leukemia?

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Despite improvements in the therapy of patients with chronic lymphocytic leukemia (CLL), the vast majority of patients cannot be cured with current treatment strategies. Purine nucleoside analog (PNA) therapy has had an important impact on the treatment of CLL in the last 20 years. The most widely used agent from this group of antileukemic drugs, fludarabine (FA), induces response in approximately 70% of previously untreated patients, with a minority achieving a complete response (CR). The advantage of PNA over alkylating agent, chlorambucil as the first-line therapy was confirmed in randomized clinical trials [1,2]. PNA combined with cyclophosphamide (CY) represents a significant advantage over a single agent in terms of an overall response (OR), CR and progression free survival (PFS) [3–6]. However, this approach is associated with a moderately higher toxicity, compared to PNA monotherapy.

Another important drug for CLL, bendamustine (Treanda), was synthesized as a bifunctional alkylating agent, comprised of an alkylating nitrogen mustard group and a purine-like benzimidazole ring. The safety and efficacy of this drug have recently been investigated in an open-label, randomized, comparative trial in previously untreated patients [7]. The OR rate and the CR rate were significantly higher and the duration of response was longer in patients treated with bendamustine than in patients treated with chlorambucil. However, no difference in the overall survival was observed in both groups. In March 2008 bendamustine was approved by the USA FDA for the treatment of CLL. Unfortunately, the efficacy of this agent, in relation to first-line therapies other than chlorambucil, has not been investigated.

Combinations of PNA with mitoxantrone, or mitoxantrone and CY, have also been investigated in previously untreated patients with CLL [7,8]. Bosch et al. evaluated FA combined with CY and mitoxantrone (FCM) as a frontline therapy in patients with CLL and showed extraordinary results. The OR rate was 90% and minimal residual disease (MRD)-negative CR was 26%. However, patients with 17p13.1 deletion failed to attain CR. Median response duration was 37 months. The treatment was well tolerated and severe (grade 3 or 4) neutropenia developed only in 10% of the patients, and major infections were reported only in 1% of cases. However, patients received prophylaxis with granulocyte colony-stimulating factor (G-CSF) for 7 days. These results indicate that FCM is a very active and safe regimen in patients with previously untreated CLL, and should be further investigated in combination with monoclonal antibodies (mAbs).

On the other hand, the results of recent clinical studies suggest that in patients with CLL anti-CD20 mAb, rituximab, in combination with PNA, can significantly improve the course of CLL. The report by Byrd et al. from the Cancer and Leukemia Group B (CALGB) suggested that adding rituximab to FA may produce an increase in the CR rate and possibly prolong PFS and OS in patients with previously untreated CLL [9]. In this randomized, phase II study, patients either received 6 monthly courses of FA concurrently with rituximab, followed by 4 weekly doses of rituximab for consolidation therapy 2 months later, or sequential FA alone followed by rituximab alone for consolidation 2 months later. In the concurrent regimen, the OR rate was 90% with 47% CR compared with 77% OR and 28% CR with the sequential regimen. Taking into account the observation that the combination of FA with CY may be more effective than FA alone, combined use of rituximab with FA and CY (R-FC protocol) was an attractive option, undertaken by the investigators from the MD Anderson Cancer Center. Keating et al. reported their results in 224 treatment-naive CLL patients treated with this regimen [10]. Treatment consisted of rituximab, FA and CY. The CR rate was 70% and OR rate was 95%. Two third of patients evaluated by flow cytometry had <1% CD5+/CD19+ cells in bone marrow after the therapy. Recently, the up-dated results have shown that median time to progression was 80 months [11]. In a multivariate analysis of patients receiving FA – basic therapy at this center – R-FC therapy was associated with a significantly superior overall survival ($p < 0.001$). The German CLL study group (GCLLSG) has confirmed high activity of the R-FC therapy in previously untreated patients with advanced CLL in a randomized, multicenter phase III trial [12]. In this study, 817 patients were randomly assigned to receive six courses of either FC of R-FC. At the time of the analysis (June 2008), the median observation time was 25.5 months. The OR rate was significantly higher in the R-FC arm (95%) compared to FC

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(88%, $p = 0.001$). The CR rate of the R-FC arm was 52% as compared to 27.0% in the FC arm ($p < 0.0001$). PFS was 76.6% at 2 years in the R-FC arm and 62.3% in the FC arm ($p < 0.0001$). There was a trend towards an increased OS rate in the R-FC arm (91% vs. 88% at 2 years, $p = 0.18$). These results indicate that R-FC regimen has the highest OR and CR rates, the longest response duration and the most favorable survival, when used as first-line therapy in CLL patients. Taken into account extraordinary antileukemic activity of R-FC regimen as front line treatment in CLL and favorable experience with the FCM regimen as first-line therapy in this disease, it was reasonable to design a combined protocol, in which mitoxantrone is added to R-FC or rituximab is added to FCM.

In this issue of *The Leukemia Research* Faderl et al. report the results of a pilot study, testing the four-drug regimen, in which rituximab was added to FCM (FCM-R) [13]. In this study OR was 96% and CR was 83%. Median time to treatment failure with a median follow up of 38.5 months was not reached. The efficiency and toxicity of this four-drug combination is almost identical to the standard R-FC immunochemotherapy used as the historical control. Despite the fact that this is not a randomized study, the comparison seems to be valuable, because both groups have similar demographics as well as clinical and laboratory characteristics. Moreover, both studies were performed in the same centre by the same investigators. Importantly, the results of FCM-R immunochemotherapy are also similar to the efficacy of FCM in the Bosch trial in terms of OR, CR and response duration [8]. It is worth noting, that myelotoxicity of the FCM-R was rather high. Despite of prophylactic use of pegfilgrastim, grade 3/4 neutropenia was seen in 67% of patients and fever of unknown origin in 40%. In contrast, in patients treated with FCM grade 3/4 neutropenia was only observed in 4% of cycles and infectious episodes, particularly fever of unknown origin, were recorded in 9% of cycles. It means that FCM-R is more myelosuppressive that FCM, despite similar doses of cytotoxic drugs in both regimens. Despite the fact that rituximab is not a myelotoxic drug, its addition to chemotherapy increases the frequency of severe neutropenia in CLL patients. Grade 3/4 neutropenia was also observed more frequently in patients treated with R-FC, than in patients treated only with FC, in large randomized studies comparing both regimens [12,14]. Fortunately, this increase in severe neutropenia did not translate into more frequent infections in these studies.

As could be expected, none of the two CLL patients with 17p abnormalities, responded to the therapy with FCM-R in the Faderl et al. study [13]. It should be noted, however, that of all biological factors identified, the 17p13.1 deletion is recognized as the most powerful predictor of poor response to conventional therapy and shortened survival in CLL [15]. Previous reports showed poor efficacy of FA and FA-based combinations in p53-defective patients [3,5]. Negative prognostic impact of 17p13.1 deletion is attributed to the loss of the *TP53* gene that encodes for p53 protein. Therefore, different treatment strategies, including drugs with different mechanisms of action, should be used for patients with 17p13.1 deletion. The results of the CAM 307 study may indicate that patients with 17p13.1 deletion can be initially treated with alemtuzumab [16]. In this randomized phase III trial, 11 patients with 17p13.1 deletion were treated with alemtuzumab and seven patients (64%) responded, with the median PFS of 10.7 months. Recently, a combination of alemtuzumab and methylprednisolone has been tested with promising results in 5 p53-defective poor-risk CLL patients [17]. In another study, a high proportion of previously untreated CLL patients with 17p13.1/*TP53* deletion responded to the combination of 2-CdA with CY (CC regimen). The response was seen in 80% of patients with a significant CR rate of 50% [18]. Moreover, a dose-finding phase I study with a novel p53-independent drug flavopiridol showed ORR of 42% in patients with 17p.13 deletion [19]. Also allogeneic stem-cell transplantation with reduced-intensity conditioning regimens appears to be highly active in this poor-risk group, but limited to fit patients with matched bone-marrow donor [20].

Several recent studies indicate that achieving eradication MRD is associated with prolonged DFS [8,10,21]. MRD negativity, evaluated by PCR-based ligase assay for patient-specific clonal IgVH, was achieved in 14 of 24 patients (61%) treated with FCM-R for whom PCR data were available [13]. Similar results were obtained in patients treated with FCM alone [8]. Among 44 patients in CR, 18 (41%) achieved MRD negative status. In this study MRD assessment was done using four-color flow cytometry and PCR in peripheral blood and/or bone marrow at the time of the response evaluation. Sixty-seven percent of the patients treated up-front with R-FC had less than 1% of CD5- and CD19-co-expressing cells in the Keating at al. study [10]. However, the sensitivity of this two-color flow cytometry method is lower than sensitivity of techniques used in patients treated with FCM or FCM-R.

Consolidation and maintenance therapy is a promising concept in lymphoid malignancies, which can further improve the response quality and duration in CLL patients. Alemtuzumab has been used as consolidation therapy for purging residual disease in patients previously treated with FA [22–24]. Montillo et al. [22] evaluated 34 patients with CLL who received alemtuzumab consolidation in an effort to improve the quality of their response to FA-based induction. The patients received alemtuzumab at a dose of 10 mg s.c. three times per week for 6 weeks. The CR rate improved from 35% after FA induction to 79.4% after alemtuzumab consolidation, including 19 patients (56%) who achieved MRD negativity. Consolidation treatment with alemtuzumab has been also evaluated in a randomized multicenter phase III trial of the German CLL study group [23,24]. Patients with CLL responding to initial therapy with FA alone or in combination with CY, were randomized for treatment with alemtuzumab at a dose of 30 mg three times per week, for a maximum of 12 weeks of observation. Of 21 evaluable patients, 11 were included into the alemtuzumab arm. The study was prematurely closed because of severe infections in 7 of 11 patients treated with alemtuzumab. At 6 months after randomization, all 11 patients on alemtuzumab were in remission, including three in CR and eight in PR, while seven patients in the observation arm were in remission including two in CR and five in PR. It should be noted that after the alemtuzumab treatment, five patients achieved molecular remission, while all patients in the control group showed MRD. Moreover, the patients treated with alemtuzumab had longer PFS. The above study has shown that consolidation treatment with alemtuzumab induces molecular remission and prolongation of DFS and probably OS. However, optimal dosing schedule with lower toxicity should be defined in future trials.

Recently, rituximab maintenance therapy has demonstrated benefits for patients with follicular lymphoma after CVP (cyclophosphamide/vincristine/prednisone) induction therapy and after rituximab-containing chemotherapy combinations at relapse [25,26]. Randomized trials in patients with mantle cell lymphoma have also demonstrated a benefit after rituximab maintenance following R-FCM (fludarabine/cyclophosphamide/mitoxantrone plus rituximab) chemoimmunotherapy but not after single-agent rituximab. Further studies are needed to characterize the benefits of rituximab and other agents in maintenance therapy for maintaining remission in patients with CLL.

At present, available therapies are only partially efficient in patients with CLL and there is an obvious need to develop better strategies and new, more specific and active drugs. For the last 20 years, significant progress in molecular and cellular biology has resulted in a better characterization and understanding of the biology and prognosis of CLL. These achievements provided new opportunities for the development of innovative, more effective therapies in this disease. Over the last few years, several new mAbs directed against lymphoid cells have been developed and