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Letter to the Editor: A Phase II study of the combination of rituximab and granulocyte macrophage colony stimulating factor as treatment of patients with chronic lymphocytic leukemia

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Rituximab monotherapy has been associated with lower response rates in CLL when compared to other CD20 positive lymphoproliferative disorders, such as follicular lymphoma¹. It has been hypothesized that the low level of expression of surface CD20 on CLL cells could be contributing to the inferior efficacy of rituximab monotherapy in this disease. Pre-clinical data, subsequently not reproduced in the in vivo setting^{2,3}, indicate that the administration of GM-CSF to patients with CLL may enhance the effectiveness of rituximab by increasing the level of expression of surface CD20 antigen and potentiating rituximab- induced antibody-dependent cell-mediated cytotoxicity (ADCC) against CLL cells.^{3,4,6} Moreover, encouraging clinical data have been reported in patient with follicular lymphoma^{5,6}. We, therefore, conducted a phase II trial assessing safety and efficacy of the combination of GM-CSF and rituximab in CLL and present here the results.

A total of 130 patients with CLL were treated in this multi-center phase II trial of the CLL Research Consortium between 10/2004 and 1/2007. Baseline characteristics are shown in Table 1. To be eligible for this study, patients were required to be at least 18 years or older, have adequate performance status, and renal and hepatic function. The study included 3 groups: 1) patients age 70 years or older with indication for treatment according to 1996 National Cancer Institute-Working Group (NCI-WG) guidelines, who refused or were deemed unsuitable for chemoimmunotherapy; 2) patients with previously untreated B-cell CLL with Rai stage 0-II disease, deemed at moderate/high risk for progression based on high beta-2 microglobulin ($\geq 3\text{mg/dL}$) or moderate constitutional symptoms without

standard indications for therapy initiation 3) patients with relapsed CLL. Among these, 52% had received a fludarabine-containing regimen and 14% were fludarabine-refractory.

The treatment consisted of recombinant human GM-CSF (sargramostim, Genzyme Corp., Cambridge, MA) given at the fixed dose of 250 mcg subcutaneously on day 1, 3 and 5 of each week for eight consecutive weeks. This dose was chosen based on the ongoing experience at that time in vaccine and immunotherapy trials. Rituximab was given at a standard dose of 375 mg/m² intravenously on day 4 and continued weekly for 4 consecutive weeks. Two doses of GM-CSF were administered prior to the first dose of rituximab and GM-CSF was continued for four weeks after completion of rituximab to better allow increased surface expression of CD20 and ADCC potentiation. All patients received one course of therapy and the patients that achieved a response according to NCI-WG guidelines could be offered a second course of treatment. The primary objectives of this study were toxicity and efficacy. The efficacy of the combination was measured as overall response rate (ORR) and the sample size was established to be significant for each separate group. Toxicity was assessed using the NCI Common Terminology Criteria for Adverse Events (CTCAE) v3.0. FcγRIIA, RIIIA and RIIB expression prior to treatment were measured as previously described⁷ and correlated with response.⁵

One hundred-twenty seven patients were included in the final efficacy analysis, 39 in group 1, 38 in group 2 and 50 in group 3. Responses consisted of complete response (CR) in 10 patients (8%), nodular partial response (nPR) in 11 patients (9%) and partial response (PR) in 56 (44%), for an overall response rate (ORR) of 61%. The ORR was significantly higher in untreated patients with no indications for therapy (group 2, 82%) compared to elderly untreated patients with indications for therapy (group 1, 59%)(p=0.05) and to patients with relapsed disease (group 3, 46%)(p=0.01). After a median follow up of 79 (1-97) months, median Progression Free survival (PFS) was 15 (range, 2-83) months for patients in group 1 and 9 months (range, 1-86) for patients in group 3 (Figure 1A). Median PFS was longer for patients in group 2 (25 months, range 3-97) compared to group 1 (p=0.006) or group 3 (p=0.003). Time to next treatment was calculated for patients in group 2 and was 34 months (range, 1-110). Median Overall Survival (OS) has not been reached for patients in group 1 and 2 and is 86 months for patients in group 3. The estimated proportion of patients alive at 7 years is 87% in group 2, higher compared to group 1 (67%, p=0.01) and group 3 (54%, p<0.001)(Figure 1B). Three patients discontinued treatment within the first week: two due to severe (grade 3) bone pain following GM-CSF administration. One patient had a severe infusion reaction within minutes of the start of rituximab and refused further administration. The most common toxicity was mild (grade 1-2) erythema and pain at injection site of GM-CSF in 40% of patients. Grade 3-4 hematological toxicities were observed only in 2 previously treated patients. Only six grade 3-4 infectious episodes occurred during treatment, four of them in previously treated patients (group 3). FcγRIIA, RIIIA and RIIB polymorphisms were measured prior to treatment in the first 75 patients. No difference was observed in terms of ORR and PFS according to polymorphism expression, in agreement with data reported by Byrd et al.⁸

In this phase II study the combination of rituximab and GM-CSF was well tolerated and easily administered in the outpatient setting. The most common toxicity related to the use of

GM-CSF was mild pain or erythema at the injection site. Grade 3-4 toxicities, such as myelosuppression and infections, mostly related to the use of rituximab, were rare and occurred mostly in previously treated patients. With the limits of an inter-study comparison, when compared to previously published studies, response rates and response duration obtained in this study suggest improved efficacy of the combination of rituximab with GM-CSF with respect to single agent rituximab. A phase II trial of the Minnie Pearl Cancer Research Network investigated the efficacy of rituximab in CLL as a single agent in the frontline setting⁹. In this study rituximab was administered as a 4-week induction scheme, followed by maintenance. Median age was 66 years, ORR was 51% and PFS was 18.6 months. When compared with our results in group 1, similar ORR and response duration were observed, despite older median age and shorter duration of rituximab administration in our study. The activity of the combination of rituximab and GM-CSF in patients in group 2 (early intervention in moderate/high risk patients) is difficult to evaluate, due to the lack of comparable studies. Our group previously published the experience with rituximab single agent as an early intervention in patients with early stage CLL and a beta-2-microglobulin (B2M) higher than 2 mg/dL¹⁰. Given the difference in median values of B2M (3 vs 2) definitive comparisons cannot be performed between the 2 studies. However, both experiences showed similarly high ORR and PFS of 2 years. Of interest, Zent and colleagues reported that when added to rituximab and alemtuzumab, GM-CSF failed to produce benefit in the early treatment of patients with high-risk CLL.¹¹

In regard to patients with relapse/recurrent disease, two studies investigated the efficacy of rituximab as a single agent. A German multicenter study included 12 patients, treated with 4 weeks infusions of rituximab, followed by monthly maintenance for up to 2 years¹². The best response was PR and it was reported in 30% of patients, with a median duration of 6.7 months. The Nordic multicenter study used a similar scheme. ORR was 30%, with no CR and a median duration of response of 12.5 weeks.

In conclusion based on our experience, GM-CSF can be easily administered in combination with rituximab to patients with CLL. Patients were able to self-administer GM-CSF daily and the toxicity profile of this combination was favorable. ORR and PFS are encouraging and may support further trials evaluating this combination with established and upcoming treatment modalities. In our study, the efficacy of the combination of rituximab and GM-CSF may have been limited by previous cytotoxic therapies and their long-term toxicity on the immune system. In the future with a more widespread use of novel targeted agents, additional treatment strategies to potentiate the activity of anti-CD20 monoclonal antibodies, such as the one described in this report, may result more effective.

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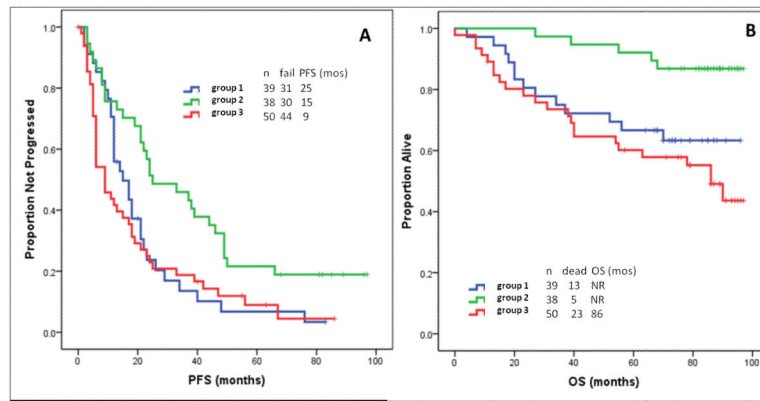


Figure 1.

A. Median Progression Free Survival (PFS) was longer for patients in group 2 (25 months) compared to group 1 (15 months, $p=0.006$) or group 3 (9 months, $p=0.003$); relapses were 31/39 in group 1, 30/38 in group 2 and 44/50 in group 3. B. Median OS was not reached in group 1 and 2, and is 86 months in group 3; the estimated proportion of patients alive at 7 years is higher for patients in group 2 (87%) compared to group 1 (67%, $p=0.01$) and group 3 (54%, $p<0.001$).

Table 1

Patient pretreatment characteristics

	Median [range], number (%)		
	Group 1 (n=40)	Group 2 (n=40)	Group 3 (n=50)
Age, years	73 [70-83]	56.5 [34-70]	68 [41-84]
Previous treatments	0	0	2 [1-8]
B2M level, mg/L	3.9 [1.5-7.2]	2 [1.1-5]	2.8 [1.5-8.3]
Rai stage 0-II	25 (63%)	40 (100%)	36 (72%)
III-IV	15 (37%)	0 (0%)	14 (28%)
CD38 positive (>30%)	13/35 (37%)	11 (28%)	24/43 (56%)
ZAP70 positive (>20%)	14/22 (64%)	14/25 (56%)	12/16 (75%)
IgHV mutation (<98%)	16/38 (42%)	20/34 (59%)	16/41 (39%)
FISH 17p deletion	5/34 (15%)	0/37 (0%)	8/38 (21%)
11q deletion	2/34 (5%)	2/37 (5%)	2/38 (5%)
Trisomy 12	7/34 (21%)	9/37 (24%)	7/38 (18%)
negative	7/34 (21%)	12/37 (32%)	11/38 (29%)
13q deletion	13/34 (38%)	14/37 (39%)	10/38 (27%)

B2M, beta-2-microglobulin; *IgHV*, immunoglobulin heavy chain variable gene; FISH, fluorescence in situ hybridization.