53rd ASH® Annual Meeting and Exposition
December 10-13, 2011
Abstracts, Program, & Personal Scheduler

-Author name in bold denotes the presenting author
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denotes an abstract that is clinically relevant

293 Rituximab Maintenance In Patients with Chronic Lymphocytic Leukemia (CLL) After Upfront Treatment with Rituximab Plus Fludarabine, Cyclophosphamide, and Mitoxantrone (R-FCM): Final Results of a Multicenter Phase II Trial On Behalf of the Spanish CLL Study Group (GELLC)

Program: Oral and Poster Abstracts
Type: Oral
Session: 642. CLL - Therapy, excluding Transplantation: First line therapy

Monday, December 12, 2011: 7:00 AM
Ballroom 20BC (San Diego Convention Center)

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The effectiveness of rituximab, fludarabine, cyclophosphamide, and mitoxantrone (R-FCM) followed by rituximab maintenance in the treatment of CLL has been investigated in a phase II clinical trial that includes two treatment parts. First, patients were given induction therapy with R-FCM up to 6 cycles, achieving an overall response (OR) rate of 93% and a CR rate of 82% (46% MRD-negative CR) (Bosch et al. J Clin Oncol 27:4578-4584, 2009). Patients achieving CR or PR with the initial part of the treatment received rituximab maintenance. Here we present the final results of the treatment maintenance part, initiated three months after concluding R-FCM, and consisting of rituximab 375 mg/m^2 every three months for two years (up to 8 cycles). Sixty-four patients (median age 60 years, 70% male) receiving > 4 cycles of maintenance therapy were evaluated for response, including bone marrow (BM) examination and MRD assessment by four-color flow cytometry of peripheral blood and BM. Patients in whom rituximab maintenance was prematurely interrupted (≤ 4 cycles) due to toxicity were considered as failures. Median number of cycles of maintenance administered was 8 (range, 1 to 8) and 76% of patients completed the entire planned treatment. Treatment was delayed due to insufficient hematological recovery in 9 cycles (2%) and to non-hematological toxicity in 4 cycles (0.8%). Neutropenia was observed in 31.3% of cycles (grade 3&4 in 8.5%), thrombocytopenia in 4.6%, and anemia in 1.2%. At the end of the maintenance therapy, 45% of patients had low IgA serum levels, 37% low IgG, and 66% low IgM. Sixteen patients experienced grade 3&4 infectious episodes, including 9 pneumonia, 2 febrile neutropenia, 1 appendicitis, 1 myositis, 1 herpes zoster, and 1 cerebral abscess. Two patients died, one due to multifocal leukoencephalopathy and the other due to hemophagocytic syndrome. Infectious episodes grade 3&4 were observed in 19.5% of cycles with neutropenia 3&4, but in only 3% of cycles with neutropenia inferior to grade 3 (p<0.001). In contrast, no relationship was observed between infectious events and the presence of low levels of immunoglobulins or diminished CD4+ T lymphocyte counts. After rituximab maintenance, 40.6% of patients were in MRD-negative CR, 40.6% in CR, 7.9% in PR, and 10.9% failed to treatment. Failures were due to disease progression (two patients), severe neutropenia (three patients), infectious toxicity (one patient) and death (one patient). Among 35 patients in MRD-negative CR after R-FCM induction, 22 maintained the MRD-negative status at the end of maintenance treatment, 9 (25.7%) switched from MRD-negative to MRD-positive, and 4 failed to treatment (Table 1). Median time to conversion from negative to positive MRD was 45.4 months, significantly longer than that observed in patients treated with FCM only (45.4 vs. 16.4 months; p=0.011) (Bosch et al. Clin Can Res 14:155-161,2008) (Figure 1). Moreover, among 21 patients that achieved MRD-positive CR with the initial R-FCM treatment, 2 (9.5%) became MRD-negative upon rituximab maintenance, 17(81%) continued in MRD-positive CR, 2 achieved PR, and 2 failed to maintenance therapy. Among the 8 patients in PR, 4 patients achieved CR (2 MRD-negative and 2 MRD-positive), 3 patients continued in PR, and one patient progressed (Table I). Three-year progression-free survival was 94% (95% CI 88-100%). Compared to the FCM series, maintenance with rituximab significantly prolonged the time to next treatment in patients that after the initial treatment with R-FCM were in MRD-positive CR (44.1 vs. 54.5 months, p=0.049) or PR (6.5 vs. 54.4 months, p=0.001). In conclusion, treatment maintenance with rituximab after R-FCM in patients with CLL is feasible and might improve patients' outcome, particularly those who do not attain a MRD-negative CR after the initial, upfront therapy. However, its toxicity is not negligible. Further, ongoing studies should help to clarify the role of maintenance therapy with rituximab in the management of patients with CLL.

		RESPONSE TO RITUXIMAB MAINTENANCE			
		CR MRD(-)	CR MRD(+)	PR	Failure
RESPONSE TO R-FCM ***(N=64)***	CR MRD (-) *(N= 35)*	22	9	-	4
	CR MRD (+) *(N= 21)*	2	15	2	2
	PR *(N= 8)*	2	2	3	1

Disclosures: Bosch: *Hoffman La Roche:* Consultancy, Honoraria, Membership on an entity's Board of Directors or advisory committees. **Off Label Use:** Rituximab is currently not approved as maintenance therapy for patients with

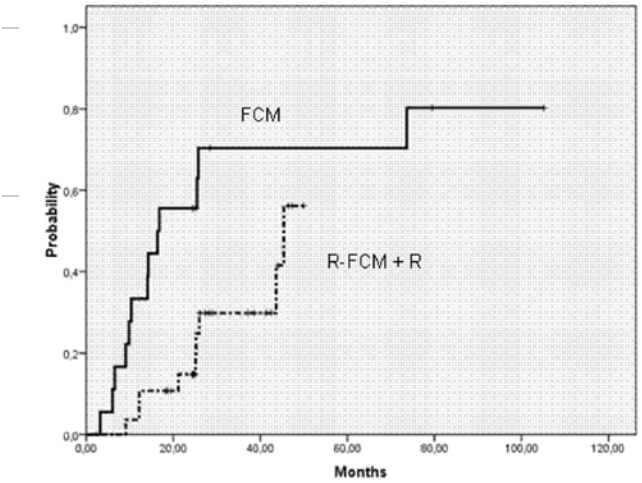

Figure 1. Probability of conversion from MRD-negative to MRD-positive

chronic lymphocytic leukemia.

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