Fludarabine, Cyclophosphamide and Rituximab (FCR) in First-Line Treatment of Patients with Chronic Lymphocytic Leukemia (CLL): Retrospective Analysis of Czech CLL Study Group

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Background: Combination of fludarabine, cyclophosphamide and rituximab (FCR) is currently considered the first-line treatment of choice in physically fit patients (pts) with chronic lymphocytic leukemia (CLL) based on the results of CLL-8 study (Hallek et al., 2008). Although higher dose of rituximab (500 mg/m^2 from 2nd cycle) was used in CLL-8 as well as landmark phase II study (Keating et al., 2005), it is purely empirical and ideal rituximab dosing remains unknown. Furthemore, there is a very limited amount of data regarding the use of FCR in real practice. Aims: to perform a retrospective efficacy and safety analysis of FCR regimen used as routine first-line treatment in CLL. Patients and Methods: Between October 2002 and May 2008, we treated 107 pts with active CLL (68% males, median age, 60 years [range, 27-75]) by FCR regimen as first-line therapy at five centers cooperating within Czech CLL Study Group. Diagnosis of CLL, indication for treatment and assessment of response to therapy followed NCI-WG criteria. Patients received standard doses of fludarabine (25mg/m^2 i.v. or 40mg/m^2 p.o. d1-3) and cyclophosphamide (250mg/m^2 i.v. or p.o. d1-3). Rituximab was administered i.v. on day 1 of each cycle at the dose of 375mg/m^2 in all cycles (n=87) or 500mg/m^2 from 2nd cycle (n=20). Treatment was repeated every 4 weeks. Antimicrobial prophylaxis and growth factors were not routinely used. Low/intermediate/high risk according to modified Rai staging was present in 1/72/27 %. IgVH mutation status and FISH aberrations were available in 85% and 79% of pts. IgVH genes were unmutated in 74%; according to hierarchical model, del 13q was present in 31%, trisomy 12 in 9%, del11q in 26% and del17p in 8%. Results: At the time of analysis (February 2009), the median observation time was 22.3 months (mo). Median number of FCR cycles was 5. The overall response rate/complete response rates were 92/47%. Median PFS was 30 mo; median overall survival (OS) was not reached. Patients with unmutated IgVH genes had significantly shorter PFS (p=0.0051). Small numbers of pts in each FISH aberration group precluded a meaningful statistical analysis. Four out of 7 pts with del 17p responded to FCR (1x CR, 3x PR). Patients treated with lower dose of rituximab (375mg/m^2) did not have significantly different ORR, CR and PFS from those treated with 500 mg/m^2 (p=0.79, p=0.24 and p=0.65). Grade III/IV neutropenia occured in 22/14% of cycles and thrombocytopenia grade III/IV in 5/3% of cycles. Serious infections occured in 1% of cycles only. G-CSF was administered in 54% and recombinant erythropoietin in 13% of pts. Conclusions: Treatment of CLL patiens in first line with fludarabine, cyclophosphamide and rituximab resulted in high number of overall and complete responses despite unfavourable prognostic factors present in the majority of pts. Toxicity was acceptable and manageable. Further studies are needed to address the question whether lower dose of rituximab (375mg/m^2) in FCR yields the same therapeutical efficacy as 500 mg/m^2. Supported by grant MSM 0021620808 from Ministry of Education and research project MZO 00179906 from Ministry of Health, Czech Republic.