High dose methylprednisolone and rituximab is an effective therapy in advanced refractory chronic lymphocytic leukemia resistant to fludarabine therapy

The combination of high dose methylprednisolone and rituximab induces superior overall (93%) and complete (14%) response rates compared to high dose methylprednisolone alone (overall 43%, complete remission 0%) in heavily pre-treated chronic lymphocytic leukemia patients with advanced disease. Despite its efficacy the combination is not easily manageable because of the high rate of opportunistic infections.

Dungarwalla M, Evans SO, Riley U, Catovsky D, Dearden CE, and Matutes E. High dose methylprednisolone and rituximab is an effective therapy in advanced refractory chronic lymphocytic leukemia resistant to fludarabine therapy. Haematologica 2008 Mar; 93(3):475-476. doi: 10.3324/haematol.11903

Patients with chronic lymphocytic leukemia (CLL) who are refractory to fludarabine containing regimens currently have a poor prognosis. Identifying effective combinations in these patients has been a focus of clinical investigation. High dose methylprednisolone (HDMP) either alone or in combination with cytotoxic agents has been evaluated in advanced refractory CLL in two studies.[1,2] These have demonstrated that HDMP can induce responses in refractory CLL patients including those with del(17p), bulky lymphadenopathy or refractory cytopenias who are unsuitable for single agent alemtuzumab therapy. We describe the response rate and outcome in 14 heavily pre-treated CLL patients treated with a combination of HDMP and the anti-CD20 monoclonal antibody, rituximab (HDMP-R). Although we have previously documented the efficacy of HDMP in refractory CLL, there are no reports on its combination with rituximab.

All patients had advanced CLL and were under treatment at the Royal Marsden Hospital. Eight out of 14 patients were male, the median age was 62.5 years (range 30-71) and 12 patients had bulky lymphadenopathy. Nine patients had Binet stage C and the remainder were stage B. All 14 patients were heavily pre-treated (2-5 prior therapies), with a median disease duration of 54 months (range 24-240). Thirteen patients (93%) had previously received fludarabine and 5 patients had prior exposure to rituximab (Table 1). A historical control group treated with HDMP alone[2] also consisted of 14 heavily pre-treated (2-4 prior therapies) patients with Binet stage C or bulky stage B disease. Ten out of 14 patients had previously received fludarabine.

HDMP was given intravenously at a dose of 1 gm/m^2 daily for 5 days in combination with 375 mg/m^2 of rituximab on day 1 of a 28 day cycle. Patients received a maximum of 6 cycles of treatment. All patients were given a proton pump inhibitor, cotrimoxazole and low dose oral antifungal prophylaxis with fluconazole. Acyclovir was used in those with a previous history of herpetic infection. Disease status was assessed by full blood count, bone marrow aspirate and trephine biopsy, and CT scan of the thorax, abdomen and pelvis before starting therapy. FISH analysis was performed to detect del(17p), del(11q23) and del(13q14).

Response to treatment was assessed using the criteria recommended by the NCI working group.[3] In addition, detailed immunohistochemistry of bone marrow trephine biopsies was considered.

Progression-free survival (PFS) and overall survival (OS) were calculated by the Kaplan-Meier method. The χ^2 test was used to compare response rates with HDMP-R and our previous cohort of patients treated with HDMP alone.[2] Responses were seen in 13/14 (93%). Two patients achieved a CR and another a nodular PR

Table 1. Patients' characteristics.

Patient	*Sex*	*Age*	*Disease duration/ months*	*N. of prior Rx*	*Previous treatments*	*Prognostic markers*	*Stage*	*Bulky LN*	*Auto-immune*
1	F	66	108	4	CBL, F, F-R, Alemtuzumab	del(11q23) del(13q14)	C	Y	PRCA
2	M	55	84	2	F, Splenectomy		C	N	AIHA
3	M	31	48	2	FC, FCM-R	del(11q23)	B	Y	N
4	F	55	132	4	CBL/Mel/C, F, FCR, Alemtuzumab	del(13q14)	C	Y	AIHA/ PRCA
5	M	43	84	2	Cyclo/Pred, Rituximab	del(11q23) del(13q14)	C	Y	AIHA
6	F	70	60	3	CBL, F, FC	del(11q23)	C	Y	N
7	M	70	240	5	CBL/vin/Epi/cis, FCM, Splenectomy, Alemtuzumab x2	del(13q14)	B	Y	N
8	M	70	36	2	CBL, F		C	Y	N
9	F	58	60	2	CBL, FC	del(11q23) del(13q14)	C	Y	N
10	M	64	40	2	CBL, FCM		B	Y	N
11	F	71	44	2	CBL, F		C	N	N
12	F	69	24	2	CBL, F		B	Y	N
13	M	61	36	3	Splenectomy, FC, Alemtuzumab	del(13q14)	C	Y	AIHA
14	M	30	48	3	CHOP, FCM-R, allo SCT	del(17p)	B	Y	N

CBL: chlorambucil; F: fludarabine; F-R: fludarabine + rituximab; FC: fludarabine + cyclophosphamide; FCM: fludarabine + cyclophosphamide + mitozanthrone; FCM-R: fludarabine + cyclophosphamide + mitozanthrone + rituximab; Mel: melphalan; C: cyclophosphamide; Epi: epirubicin; Vin: vincristine; Cis: cisplatin; CHOP: cyclophosphamide + daunorubicin + vincristine + prednisolone; Allo SCT; allogeneic stem cell transplant; AIHA: autoimmune hemolytic anemia; PRCA: pure red cell aplasia.

Table 2. Progression-free and overall survival, toxicity and cause of death

Patient	*Response*	*PFS (months)*	*OS (months)*	*Toxicity*	*Delays in treatment*	*N. cycles*	*Cause of death*
1	PR	6	18*§	N	N	6	Alive
2	CR	18	31§	*Cunninghamella betholatiae* infection	N	6	Gram negative septicemia
3	CR	24	24	Septicemia requiring IV antibiotics and admission	Y	6	Pulmonary aspergillosis
4	PR	4	4	*Aspergillus fumigatus, Candida albicans* septicemia	N	4	Pulmonary candidiasis, Enterococcal septicemia
5	PR	3	3*	*Candida tropicalis* septicemia	Y	3	Alive
6	Nodular PR	18	18*	N	N	6	Alive
7	PR	6	6*	N	N	6	Alive
8	PR	4	26*§	N	N	6	Alive
9	PR	2	2*	*Varicella zoster* Virus infection	Y	6	Alive
10	PR	7	20§	N	N	6	Richter's transformation
11	PR	9	9	Biliary septicemia	N	2	Cholangio-carcinoma
12	PR	7	18§	High blood sugars	Y	2	Progressive disease
13	PR	5	13§	2 x admissions with pneumonia, adenovirus infection	Y	3	Pulmonary *Candida guilliermondii*, aspergillosis
14	No	–	3	N	N	4	Richter's transformation

**Alive; §progressed.*

(Table 2). All 5 patients with del(11q23) achieved good responses. The single patient with del(17p) did not respond. Median progression free survival was 7 months (range 2-24). Median survival was 20 months.

In comparison, only 6/14 (43%) treated with HDMP alone responded, with no complete remissions. The median progression free survival was eight months.[2]

The most common and serious side effect observed was infection. Three patients developed fungal infections during or soon after treatment, and a further 2 patients went on to develop fungal infections while in remission or after further treatment. Two patients developed opportunistic viral infections. Patient #12 developed secondary diabetes. Eight patients (59%) completed 6 cycles of treatment. Treatment delays due to toxicity were observed in 5/14 (36%). Eight patients died (59%).

In this study we report the results of HDMP-R in 14 heavily pre-treated CLL patients. A comparison with historical controls treated with HDMP alone[2] has shown that the combination of HDMP-R is more effective ($p<0.01$). Despite its efficacy, only 59% of patients treated with HDMP-R completed 6 cycles. The combination is not therefore easily manageable. Although HDMP-R causes little or no myelosuppression, the addition of rituximab may make these patients more prone to opportunistic infections. However, heavily pre-treated CLL patients have an increased susceptibility to infection intrinsic to the disease[4] and this is a small series of patients so conclusions should be made with caution. Due to the high incidence of aspergillus and candida infection, it may be more appropriate to use itraconazole or posaconazole rather than fluconazole as primary prophylaxis in these patients.[5,6] Steroids induce apoptosis by a number of mechanisms[7-10] while rituximab sensitizes leukemia cells to apoptosis by downmodulating expression of the anti-apoptotic protein bcl-2. Therefore, it is possible that rituximab sensitizes CLL B cells to steroid induced apoptosis enhancing the effectiveness of HDMP in refractory CLL.

Moez Dungarwalla, Steve O. Evans, Unell Riley, Daniel Catovsky, Clare E. Dearden, and Estella Matutes

Haemato-oncology Unit, The Royal Marsden Hospital, Sutton, Surrey, United Kingdom

Correspondence: Moez Dungarwalla, The Royal Marsden Hospital, Sutton, Surrey, United Kingdom.
E-mail: fareedaj@hotmail.com

References

1. Thornton PD, Matutes E, Bosanquet AG, Lakhani AK, Grech H, Ropner JE, et al. High dose methylprednisolone can induce remissions in CLL patients with p53 abnormalities. Ann Hematol 2003;82:759-65.
2. Thornton PD, Hamblin M, Treleaven JG, Matutes E, Lakhani AK, Catovsky D. High dose methylprednisolone in refractory chronic lymphocytic leukaemia. Leuk Lymphoma 1999;4:167-70.
3. Cheson BD, Bennett JM, Grever M, Kay N, Keating MJ, O'Brien S, et al. National Cancer Institute sponsored Working Group guidelines for chronic lymphocytic leukaemia: revised guidelines for diagnosis and treatment. Blood 1996;87:4990-7.
4. Molica S. Infections in chronic lymphocytic leukaemia: risk factors and impact on survival and treatment. Leuk Lymphoma 1994;13:203-14.
5. Glasmacher A, Prentice A, Gorschlüter M, Engelhart S, Hahn C, Djulbegovic B, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for haematological malignancies: evidence from a meta-analysis of 3,597 patients. J Clin Oncol 2003;21:4615-26.
6. Cornely OA, Maertens J, Winston DJ, Perfect J, Ullmann AJ, Walsh TJ, et al. Posaconazole vs Fluconazole or Itraconazole prophylaxis in patients with neutropenia. N Engl J Med 2007;356:348-59.
7. McConkey DJ, Chandra J. Protease activation and glucocorticoid induced apoptosis in chronic lymphocytic leukaemia. Leuk Lymphoma 1999;33:421-31.
8. Mori N, Yamate J, Stassen AP, Oka S, Okumoto M, Tsubura A, et al. Modulations of glucocorticoid-induced apoptosis linked to the p53 deletion and to the apoptosis susceptibility gene Rapop1 (Radiation induced apoptosis 1). Oncogene 1999;18:4282-5.
9. Smets LA, Salomons G, Van den Berg J. Glucocorticoid induced apoptosis in leukaemia. Adv Exp Med Biol 1999; 457:607-14.
10. Riccardi C. Glucocorticoid hormones in the regulation of cell death. Pharmacol Exp 2000;55:165-9.