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Malignant Lymphomas

Early and late infectious consequences of adding rituximab to fludarabine and cyclophosphamide in patients with indolent lymphoid malignancies

Whether the addition of rituximab to fludarabine and cyclosphosphamide (FC) increases early or late infection risk remains poorly defined. This retrospective analysis of 160 patients treated with FC±rituximab found no evidence of increased infection among patients receiving FC+rituximab, providing some evidence of safety for the continued exploration of this regimen.

haematologica 2005; 90:700-702
(*http://www.haematologica.org/journal/2005/5/700.html*)

The combination of fludarabine and cyclophosphamide (FC) is highly effective against indolent lymphoid malignancies, but its use is associated with infectious toxicity related to transient myelosuppression and prolonged T-cell depletion.[1] The anti-CD20 antibody rituximab demonstrates significant *in vitro* synergy with fludarabine,[2] and in combination with FC (FCR) is associated with improved outcomes in patients with chronic lymphocytic leukemia (CLL) and indolent non-Hodgkin's lymphomas.[3,4] However, rituximab also effectively depletes peripheral B cells and causes variable suppression of serum immunoglobulins,[5] and may increase the frequency of severe neutropenia when administered with chemotherapy.[6] Therefore, there is significant concern surrounding a possible increased risk of infection with addition of rituximab to FC, particularly in pretreated and older patients with pre-existing risk factors for severe infections.[7] In order to explore this issue, we retrospectively analyzed infectious episodes during chemotherapy and in the first 12 months of remission among consecutive patients treated with FC (n=63; fludarabine 25 mg/m^2 i.v. days 1-3, cyclophosphamide 250 mg/m^2 i.v. days 1-3, repeated 4 weekly) or FCR (n=97; FC + ritux-

Table 1. Baseline characteristics of the FC and FCR cohorts. FC: fludarabine and cyclophosphamide; FCR: FC and rituximab.

Baseline characteristics	*FC cohort (N=63)*	*FCR cohort (n=97)*	*p value*
Age–median (range)	60 (36-80)	60 (30-89)	0.96
Male sex	42 (67%)	62 (64%)	0.62
No previous treatment	11 (17%)	24 (25%)	0.33
Relapsed or refractory disease	52 (83%)	73 (75%)	0.33
Pretreated patients	n=52	n=73	
Previous fludarabine use	17 (33%)	26 (36%)	0.85
Fludarabine refractory	1 (2%)	6 (8%)	0.24
Previous stem cell transplantation	4 (8%)	3 (4%)	0.45
Number of prior therapies median (range)	2 (1-10)	2 (1-9)	0.40
Chronic lymphocytic leukemia	21 (33%)	42 (43%)	0.32
Prolymphocytic leukemia	5 (8%)	1 (1%)	0.03
Follicular lymphoma	22 (35%)	32 (33%)	0.74
Mantle cell lymphoma	3 (5%)	8 (8%)	0.53
Marginal zone lymphoma	3 (5%)	3 (3%)	0.68
Waldenström's macroglobulinemia	9 (14%)	9 (9%)	0.32
"Low-grade" lymphoma, not specified	0 (0%)	2 (2%)	0.52
Months from diagnosis –median (range)	48 (0-324)	38 (0-196)	0.81
ECOG Performance Status –median (range)	1 (0-3)	1 (0-3)	0.26
Elevated serum LDH	11/61 (18%)	16/66 (24%)	0.74
International Prognostic Index –median (range)	2 (0-4)	2 (0-5)	0.51
Grade 3+ infection past 12 months	7 (11%)	17 (18%)	0.37
Asplenic	6 (9%)	6 (6%)	0.54
Median baseline ANC ($\times 10^9$/L) (range)	3.5 (0-26)	2.9 (0.6-11)	0.11
Median baseline IgG (g/L) (range)	5 (2-17)	7 (1-20)	0.12
Infection prophylaxis during therapy (% pts)[a]	17 (27%)	27 (28%)	0.95
PCP (bactrim/dapsone)	4 (6%)	14 (14%)	0.20
Antiviral (aciclovir/valaciclovir)	1 (2%)	10 (10%)	0.05
Antifungal (fluconazole/itraconazole)	5 (8%)	31 (32%)	<0.01
G-CSF use			
Median number of cycles (range)	4 (1-6)	4 (1-6)	0.35
Total evaluable cycles	214	355	

[a]*Patients who received hematopoietic growth factor or prophylactic antimicrobial agents for one or more cycles of chemotherapy were considered to have had infection prophylaxis for the purposes of comparative analyses.*

Table 2. Infections during chemotherapy and in first year of remission after completion of therapy. FC: fludarabine and cyclophosphamide; FCR: FC and rituximab.

Infections during chemotherapy	*FC cohort (% per cycle) N = 214*	*FCR cohort (% per cycle) N = 355*	*p*
All infections	33 (15%)	69 (19%)	0.26
Grade 3+ infections	17 (8%)	31 (9%)	0.88
Herpes infections virus[a]	3 (1%)	7 (2%)	0.75
Untreated disease	3/37 (8%)	17/108 (16%)	0.41
Relapsed/refractory disease	30/117 (17%)	52/247 (21%)	0.68
Chronic lymphocytic leukemia	15/76 (20%)	36/151 (24%)	0.61
Follicular lymphoma	10/72 (14%)	17/128 (13%)	1.00
Age 60+ years	18/100 (18%)	40/161 (25%)	0.23
Time to treatment >3 years	23/115 (20%)	37/166 (22%)	0.66
Performance status 2+	5/28 (18%)	22/77 (29%)	0.32
Neutrophil <2.0×10^9/L	8/25 (32%)	17/95 (18%)	0.16
High risk infection score[b]	17/71 (24%)	36/132 (27%)	0.74
No infection prophylaxis	24/161 (15%)	38/256 (15%)	1.0
No growth factor use	29/190 (15%)	36/249 (14%)	0.79
Grade 4 Neutropenia during therapy[c] (% cycles)	17%	19%	0.58

Infections during remission	*FC cohort (per pt-month) N = 336*	*FCR cohort (per pt-month) N = 637*	*p value*
All infections	25 (1/13)	47 (1/14)	1.0
Grade 3+ infections	4 (1/84)	17 (1/37)	0.17
Herpes virus infections[a]	7 (1/48)	8 (1/80)	0.41
Untreated disease	4/59 (1/15)	7/185 (1/26)	0.48
Relapsed/refractory disease	21/277 (1/13)	40/452 (1/11)	0.58
Chronic lymphocytic leukemia	8/115 (1/14)	20/249 (1/12)	0.83
Follicular lymphoma	10/125 (1/13)	19/267 (1/14)	0.84
Age 60+ years	9/146 (1/16)	25/287 (1/11)	0.45
Time to treatment >3 years	12/167 (1/14)	26/288 (1/11)	0.60
Performance status 2+	3/25 (1/8)	10/126 (1/13)	0.45
Neutrophil <2.0x10^9/L	3/41 (1/14)	11/167 (1/15)	1.0
High risk infection score[b]	7/101 (1/14)	22/230 (1/10)	0.53

[a]Defined as clinically diagnosed reactivation of Herpes simplex or Varicella zoster virus. [b]Three or more of : age >60 years, ≥3 previous therapies, previous fludarabine use, time to treatment >3 years, performance status ≥2, baseline neutrophils <2.0×10^9/L. [c]Nadir neutrophil counts recorded in 85% and 70% of FC and FCR cohorts, respectively.

imab 375 mg/m^2 day 1). Baseline demographic data, histological subtype, previous treatment history and infection risk factors were comparable in the two cohorts (Table 1). Infection prophylaxis differed significantly owing to differences in institutional protocols. Cytomegalovirus (CMV) monitoring by viral load was not routinely performed. A median of 4 (range 1-6) cycles of therapy was delivered in both cohorts; nadir blood counts were available in 85% and 70% of the FC and FCR cohorts respectively, with no significant difference in the rate of severe neutropenia (Table 2). A total of 569 cycles of chemotherapy were evaluable for infectious episodes. The risk of developing an infection during chemotherapy did not differ between the FC and FCR cohorts (15% vs 19%/cycle, p=0.26), with no difference in rates of grade 3+ infections (8% vs 9%/cycle, p=0.88) or clinically diagnosed reactivation of *Herpes simplex* (HSV) or *Varicella zoster* (VZV) viruses (1% vs 2%/cycle, p=0.75). Subset analysis by previous treatment, histological subtype, known risk-factors for infection, or infection score[7] did not identify any subgroup with an increased frequency of infections with the addition of rituximab (Table 2). Due to differences in prophylactic strategies between the FC and FCR cohorts (Table 1), further analyses restricted to patients not given antimicrobial prophylaxis or growth-factor support were performed. These again showed comparable infection rates (Table 2), indicating that the absence of increased infections in the FCR cohort was not due to differences in infection prophylaxis. With 973 patient-months of follow-up during the first year of ongoing remission, no significant differences in total infections, grade 3+ infections or herpes virus infections were observed (Table 2), despite a trend to increased late neutropenia in the FCR cohort during the first three months of remission (neutrophils <1.5×10^9/L at 12 weeks after completion of therapy, 14% for FC *vs* 31% for FCR, p=0.15). Immunoglobulin G (IgG) levels were assessed before and at a median of six months after chemotherapy in 59 patients, with 35% and 33% of the FC and FCR cohorts, respectively, showing a ≥20% reduction of IgG levels from baseline.

Despite over two-thirds of patients not receiving prophylaxis against *Pneumocystis jirovecii* (PCP) during therapy, only one case of suspected PCP was encountered. This patient had significant concurrent exposure to corticosteroids, a well-established risk factor for PCP during fludarabine treatment for which routine prophylaxis is recommended.[8,9] Other opportunistic infections recorded in the FCR cohort included one episode of CMV viremia in a heavily pretreated patient with multiple previous episodes of CMV reactivation, one episode of central nervous system toxoplasmosis and one episode of BK virus hemorrhagic cystitis. Among FCR patients not receiving antiviral prophylaxis, the risk of HSV or VZV reactivation was 2% during chemotherapy, and 1 per 86 patient-months during remission. No cases of significant fungal infection were recorded during either chemotherapy or follow-up among FCR patients treated without fungal prophylaxis.

Although early results from three randomized studies examining concurrent fludarabine and rituximab therapy are available and support our observation of no increased infections during therapy,[4,6,10] there are few data regarding the effect of rituximab addition on late infections. Due to the retrospective nature of our study, data on lymphocyte subsets following therapy were not available. Nevertheless, the individual lymphocytotoxicity of FC and rituximab are well established,[1,5] and our observation of no significant increase in late infections despite this risk of prolonged lymphopenia and possible increase in late neutropenia is important in providing some evidence of safety for continued exploration of FCR and related regimens.

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Funding: this study was supported in part by research funding from Schering AG inc.

Acknowledgments: the authors express their sincere thanks to Mr. Michael Bailey for statistical assistance.

Key words: opportunistic infection, purine analog, monoclonal antibody.

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Malignant Lymphomas

Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma

We assessed the impact of a reduced-dose (10 mg × 3/week for 4 weeks) schedule of alemtuzumab in 10 patients with pretreated cutaneous/peripheral T-cell lymphomas. The overall response rate was 60% (2 complete responses and 4 partial responses). In terms of infectious toxicity, cytomegalovirus reactivation occurred in 1 (10%) patient.

haematologica 2005; 90:702-703
(*http://www.haematologica.org/journal/2005/5/702.html*)

The natural history of peripheral T-cell lymphomas (PTCL) seems to be unaffected by the use of conventional or high-dose chemotherapy, and 5-year overall survival rates remain between 20-40%.[1-4] Recently, alemtuzumab (MabCampath), a humanized anti-CD52 monoclonal antibody, has been reported to induce remission in patients with cutaneous T-cell lymphoma[5] and with PTCLU (unspecified)[6] using conventional dosage schedules. Our study population comprised patients with pretreated PTCLU or mycosis fungoides (MF) treated between March 2003 and March 2004 satisfying these eligibility criteria: histologic diagnosis according to the REAL classification;[7] relapsed/refractory disease after at least two treatments; good performance status; age >18 years; normal renal, hepatic and cardiac function. The protocol was approved by the local Ethical Committee, and informed consent was obtained from all patients.

Alemtuzumab (Schering AG, Milan, Italy) was diluted in 100 mL of 0.9% normal saline and administered over 2 h as an intravenous infusion through a line containing a 0.22 µm filter. An escalating initial dosage regimen was used: 3 mg on day 1; 10 mg on day 3; followed by 10 mg, 3 times a week, for a maximum of 4 weeks. Patients received oral paracetamol, antihistamines, and betamethasone before each alemtuzumab infusion. Trimethoprim/sulphamethoxazole (twice daily, 2 times per week) and valaciclovir (500 mg twice daily) were administered from day 2 until at least 2 months after alemtuzumab discontinuation.

Polymerase chain reaction (PCR) analysis for cytomegalovirus (CMV) was performed until 2 months after discontinuation of alemtuzumab. Responses were evaluated according to International Workshop criteria.[8] All toxicities were assessed using WHO criteria.

Ten patients (8 males, 2 females; median age 65 years, range 49-76) satisfied the eligibility criteria. Of these, 6 had nodal PTCLU and 4 had MF. All MF patients were in stage T3 or T4, N0, M0 of the TNM classification.[9] All PTCLU patients were in stage III-IV according to the Ann Arbor system[10] (Table 1). Among PTCLU patients, 4 presented ≥4 involved nodal sites and 3 had ≥3 involved nodal sites with bulky disease. The median number of prior treatments was 3 (range, 2-4), and the median time from original diagnosis was 13 months (range, 6-15). The overall response rate (ORR) was 60%, with 2 (20%) patients achieving complete responses (CR), and with 4 (40%) obtaining partial response (PR). In the MF subset, the best response was PR (3/4, 75%). However, in the PTCLU subset, there were 2 (33%) CR which lasted 3 and 8 months as well as 1 (17%) PR. The median duration of response was 7 months