Effects of clarithromycin on oral mucositis in bone marrow transplant recipients

In an open-label prospective study to investigate the effects of clarithromycin on oral mucositis in bone marrow transplant (BMT) recipients, one group of patients received clarithromycin from day –7 until engraftment. The number of patients with severe mucositis in the control group was significantly higher than that in the clarithromycin group ($p<0.05$).

Mucositis, as a result of high dose chemotherapy with or without radiotherapy, occurs in 90% of bone marrow transplant (BMT) recipients, and is associated with significant morbidity and mortality.[1] The mainstay treatment of mucositis has been symptomatic, using non-steroidal anti-inflammatory drugs and narcotic analgesics. Although various agents have been tested to alleviate the severity of mucositis, none has been universally recognized as the prophylaxis of choice for mucositis.

Macrolides such as erythromycin, clarithromycin, azithromycin, and roxithromycin were demonstrated to have immunomodulatory activities.[2] The use of clarithromycin is associated with decreased inflammatory responses in Guinea pigs using a surgical trauma model[3] and in patients after mastectomy.[4] Recently, we have also shown that the administration of clarithromycin led to a decrease in mucositis in mice using a cyclophosphamide-induced mucositis model.[5] In this study, we investigated the potential beneficial effects of clarithromycin on oral mucositis in BMT recipients.

The study was performed as an open-label prospective randomized trial, which examined the effect of clarithromycin on oral mucositis in BMT recipients. Seventy patients (aged 17 or above) who underwent BMT at the Queen Mary Hospital in Hong Kong during a 15-month period (October 1996 to February 1998) were included in this study. The 70 patients were randomly divided into 2 subgroups by computer. In addition to the antimicrobial regimen described in a published paper,[6] half the patients were given oral clarithromycin 500 mg b.i.d. (or iv clarithromycin 500 mg q12h if oral medication could not be tolerated) from day -7 to day -2, and the treatment was continued with 250 mg b.i.d. (or iv clarithromycin 250 mg q12h if oral medication could not be tolerated) until engraftment.

All patients were monitored for 60 days after BMT. Hospitalized patients were assessed daily and out-patients at least once weekly for treatment-related toxicity and graft-versus-host disease (GVHD). Fever, neutropenic fever, engraftment, risk groups of the underlying diseases, conditioning toxicity including oral mucosal changes and acute GVHD were defined and graded according to criteria in published papers.[6-8]

The characteristics and outcome of BMT recipients who did or did not receive clarithromycin were compared. The chi-squared test was used for categorical variables and the unpaired Student's t-test was used for continuous variables. $p<0.05$ was considered as statistically significant.

The characteristics and conditioning toxicity of BMT recipients who did or did not receive clarithromycin are summarized in Tables 1 and 2, respectively. The number of patients with grade 2 mucositis in the control group was significantly higher than that in the clarithromycin group ($p<0.05$). There was no statistically significant differences between the characteristics, incidence of antimicrobial prophylaxis-related toxicities and other conditioning toxicities, day of engraftment, incidence of infections, duration of fever, neutropenic fever, use of intravenous antibiotics, amphotericin B, total parenteral nutrition and growth factors, number of patients requiring a change from oral to intravenous medication, and incidence and severity of acute GVHD of BMT recipients in the two groups.

The use of clarithromycin was not associated with increased toxic effects of the antimicrobial prophylaxis and conditioning regimen. Although the major side effects of clarithromycin have been reported to be hypersensitivity reactions, antibiotic-associated diarrhea, and hepatotoxicity, there was no significant increase in the incidence of skin rash, diarrhea, or liver function derangement in patients who received clarithromycin as com-

Table 1. Characteristics of BMT recipients who did or did not receive clarithromycin.

Characteristics	*Clarithromycin group (n=35)*	*Control group (n=35)*	*p value*
Age, (years) median (range)	34 (17-63)	40 (20-51)	NS
Sex: male:female	21:14	22:13	NS
Diagnosis, number (%)			
AML	5 (14)	12 (33)	NS
ALL	6 (17)	2 (6)	
CML	8 (23)	8 (23)	
Lymphoma	8 (23)	10 (29)	
Ca. breast	3 (8)	1 (3)	
SAA	2 (6)	0 (0)	
NPC	0 (0)	1 (3)	
Multiple myeloma	2 (6)	0 (0)	
MPD	1 (3)	0 (0)	
MDS-RAEB	0 (0)	1 (3)	
Stage of disease, number (%)			
Early	9 (26)	10 (29)	NS
Late	26 (74)	25 (71)	
Type of transplant, number (%)			
Allogeneic	21 (60)	20 (57)	NS
Autologous	12 (34)	11 (31)	
MUD	2 (6)	3 (9)	
Syngeneic	0 (0)	1 (3)	
HLA match, number (%)			
Matched	30 (86)	34 (97)	NS
Unmatched	5 (14)	1 (3)	
Conditioning, number (%)			
No TBI	40 (57)	40 (57)	NS
Cy-BCNU-VP16	7 (20)	6 (17)	
Cp-VP16-Cy	3 (8)	1 (3)	
Bu-Cy	7 (20)	9 (25)	
Cy-ATG	2 (6)	0 (0)	
BCNU-VP16-Ara C-Mel	1 (3)	2 (6)	
Mel	0 (0)	1 (3)	
Bu-Mel	0 (0)	1 (3)	
TBI	30 (43)	30 (43)	
Cy + TBI	7 (20)	2 (6)	
Mel + TBI	2 (6)	0 (0)	
Bu-Cy + TBI	5 (14)	12 (34)	
VP16-Cy + TBI	1 (3)	1 (3)	
GVHD prophylaxis, number (%)			
None	12 (34)	12 (34)	NS
Sh-Mtx + CSP	22 (63)	23 (66)	
CSP	1 (3)	0 (0)	

BMT: bone marrow transplant, AML: acute myeloid leukemia, ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukemia, Ca breast: carcinoma of the breast, SAA: severe aplastic anemia, NPC: nasopharyngeal carcinoma, MPD: myeloproliferative disease, MDS: myelodysplastic syndrome, RAEB: refractory anaemia with excess blasts, MUD: matched unrelated donor, TBI: total body irradiation, Cy: cyclophosphamide, BCNU: carmustine, VP16: etoposide, Cp: carboplatin, Bu: busulphan, ATG: anti-thymocyte globulin, Ara C: cytosine arabinoside, Mel: melphalan, GVHD: graft-versus-host disease, Sh-Mtx: short methotrexate, CSP: cyclosporine, NS: not significant.

Table 2. Conditioning toxicities of BMT recipients who did or did not receive clarithromycin.

Conditioning toxicities	Clarithromycin group (n=35)	Control group (n=35)	p value
Cardiac, number (%)			
Grade 0	35 (100)	35 (100)	NS
Grade 1	0 (0)	0 (0)	
Central nervous system, number (%)			
Grade 0	34 (97)	34 (97)	NS
Grade 1	1 (3)	1 (3)	
Gut, number (%)			
Grade 0	31 (89)	30 (86)	NS
Grade 1	4 (11)	5 (14)	
Oral, number (%)			
Grade 0-1	17 (49)	9 (26)	<0.05
Grade 2	18 (51)	26 (74)	
Liver, number (%)			
Grade 0	34 (97)	32 (91)	NS
Grade 1	1 (3)	3 (9)	
Lung, number (%)			
Grade 0	35 (100)	31 (89)	NS
Grade 1	0 (0)	4 (11)	
Kidney, number (%)			
Grade 0	32 (91)	32 (91)	
Grade 1	3 (9)	3 (9)	
Bladder, number (%)			
Grade 0	33 (94)	35 (100)	
Grade 1	2 (6)	0 (0)	

BMT: bone marrow transplant, NS: not significant.

pared to those who did not.

Clarithromycin was demonstrated to have marginal benefit on oral mucositis in BMT recipients in the present study. This is in line with the findings of a recently published report, which showed that patients receiving roxithromycin and ciprofloxacin as an antibiotic prophylaxis regimen developed significantly less severe mucositis than those who received norfloxacin, although the authors thought that the difference was probably due to the poorer clinical status of patients in the norfloxacin group.[9]

We speculate that the beneficial effect of clarithromycin on mucositis is mainly because of its action on macrophages. The macrophages (albeit in small numbers) present in the submucosa are extremely important in clearing up the debris due to epithelial cell damage by chemo-radiotherapy. It is known that macrolides can augment monocyte-macrophage differentiation and improve the phagocytic function of macrophages.[10] This would improve the repair of damaged mucosa through enhanced residual host tissue macrophage number and function. Furthermore, the antimicrobial effect of clarithromycin may also contribute by reducing secondary infection associated with mucosal breakdown.

The present observation has prompted further clinical trials using other members of the macrolide family, especially those with higher concentrations in macrophages such as azithromycin and roxithromycin, as well as a combination of macrolides and other agents shown to have immunomodulatory effects on mucositis.

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