Inefficacy of clarithromycin in advanced multiple myeloma: a definitive report

Fifty-one patients with relapsed or resistant multiple myeloma received clarithromycin p.o. at the dose of 500 mg b.i.d. Thirteen patients did not complete the planned therapeutic program of 12 weeks due to side effects or progression. Among the 38 evaluable patients, objective or minor responses occurred in one and two patients, respectively. Our data do not support the use of clarithromycin for the treatment of advanced multiple myeloma.

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Clarithromycin (CTM) is a macrolide which, in addition to its antibiotic activity, also exerts biological effects that could have relevance in regulating tumor growth of some neoplastic diseases.[1,2] In fact, observational studies have suggested that CTM treatment may improve survival in patients affected by non-small cell lung cancer[3] and may reduce the incidence of secondary tumors in AIDS.[4] A few clinical trials have also explored the potential therapeutic efficacy of CTM in multiple myeloma (MM), achieving, however, conflicting results.[5-7]

We used CTM to treat 51 patients with relapsed or resistant MM (Table 1). CTM (KLACID, Abbott) was given at the fixed dose of 500 mg b.i.d for a planned program of at least 12 weeks. Pamidronate was concomitantly administered to 23 patients. The first ten treated subjects received dexamethasone (4 mg i.m. b.i.w) during CTM treatment, according to the original schedule.[5] The remaining patients were given CTM alone.

Six patients interrupted the study early because of gastrointestinal side effects (diarrhea, nausea, vomiting, abdominal pain). Two of the subjects developed severe lung infection under treatment, which was fatal in one case. Five additional patients showed rapidly progressive disease and 2 of them died while receiving CTM. Of the 38 evaluable patients, 33 showed no response or progressive disease and stopped the treatment after the planned 12 weeks.

A reduction of M-component occurred in 5 patients (Table 2). Both patients with M-component decrease > 50% had received steroids during CTM therapy. One of them showed a focal progression of skeletal disease requiring local radiotherapy during CTM therapy. A reduction of M-component > 25% was observed in 2 other patients who received CTM alone. In a fifth anemic subject, a lower decrease of the paraprotein was associated with interruption of transfusional support. Freedom from progression in these patients lasted 2 to 19 months using adjusted, reduced doses (500-1000 mg/d for 2 weeks every month). No significant decrease of marrow plasma cell infiltration or improvement of bone lesions was observed.

Previous results on the use of CTM in MM have been contradictory. Durie *et al.* obtained 15 significant responses (50%), lasting up to 13 months, in 30 MM patients receiving CTM at the dose of 500 mg b.i.d, on alternate weeks, associated with dexamethasone (4-8 mg for 2 days for *flare reaction*).[5] (*Durie BGM, personal communication*). Continuous q.d. weekly dose escalation up to 1000 mg b.i.d. was performed in non-responders. Two following studies, however, have not confirmed such preliminary, promising results. In fact, Stewart *et al.* did not report any significant response among 20 evaluable MM patients in various phases of disease treated with CTM alone at the dose of 500 mg administered orally twice daily on a 2 weeks on, 1 week off schedule.[6] Likewise, Moreau *et al.* found no response in 35 patients receiving CTM without steroids as a continuous course of 500 to 1000 mg for 4-20 weeks (median 8 weeks).[7] More recently, the combination of CTM with dexamethasone and thalidomide has been reported to provide impressive results (up to 93% of significant responses) in patients with heavily treated MM.[8,9]

Our study (the largest one so far performed on this topic) indicates that CTM therapy is frequently poorly tolerated and not effective in the large majority of patients with advanced MM. Indeed, according to conventional criteria, we observed only 1 objective response and 2 minor responses. It is not clear whether the different schedule, the increased dose in non-responders, the adjunct of steroids and that of pamidronate in all patients, as well as the inclusion of subjects with less advanced disease, could justify the difference between the results obtained by Durie *et al.* and those found in our and other studies. It has been suggested that the *efficacy* of CTM therapy could be due to the concomitant administration of dexamethasone, rather than to the antibiotic itself.[6] CTM shows an unusual *steroid sparing* effect which enhances multiple activities of exogenous steroids.[10] It is of note that our only two patients with reduction of M-component > 50%, had also received low dose steroids in combination with CTM. Both these patients had relapsed after previous treatments including high dose dexamethasone and this fact remains quite intriguing. The possible effect on ery-

Table 1. Clinical and laboratory characteristics of myeloma patients treated with clarithromycin.

N. patients: 51
Median age: 67 (range 49-83)
Sex: 30 males, 21 females
Durie and Salmon clinical stage: 32 III A, 4 III B, 15 IIA
Median Hb: 10.3 g/dL (range 6.3-14.7)
Median serum m-component: 3.9 g/dL (range 1.5-8)
Median marrow plasma cells: 54% (range 2-100%)
Hypercalcemia: 5/51
High β2-microglobulin (> 3 mg/L): 22/51
Ig Class: 28 IgG,. 15 IgA, 7 light chain, 1 non-secreting
N. previous lines of chemotherapy: 2 to 6 (median 4, 12 patients had received autologous transplantation)
Status at treatment with CTM: #36 relapsed, 15 resistant
Mean time from diagnosis: #38 months (range 19-73).

Table 2. Clinical and laboratory characteristics of myeloma patients with M-component reduction after treatment with clarithromycin.

Sex	*Age*	*Ig class*	*M-component Pre/Post (g/dL)*	*BMPC Pre/Post (%)*	*Response duration (months)*	*DEX*	*PMD*
F*	66	IgGk	5.2/4.0	18/20	2	No	No
F*	52	IgAλ	2.1/1.3	22/20	5	No	Yes
M§	57	IgAk	2.2/1.9	n.d.	13	No	No
M°	57	IgAk	3.1/0.4	40/31	17	Yes	No
M^	57	IgGλ	3.2/0.7	3/2	19	Yes	No

**Concomitant secondary myelodysplastic syndrome; §Disappearance of transfusion dependency; °Concomitant local radiotherapy; ^Relapse after autologous transplantation. Abbreviations: BMPC:bone marrow plasma cells; DEX:dexamethasone 4 mg b.i.w.; PMD:pamidronate 60-90 mg i.v. every 4 weeks.*

thropoiesis observed in one of our patients is only speculative, since we have no formal evidence that this phenomenon was really due to administration of CTM.

Our conclusion is that the use of CTM in MM patients with progressive disease cannot be recommended.

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Relapse of chronic myeloid leukemia in lymphoid crisis after allogeneic bone marrow transplantation in chronic phase with a busulfan plus cyclophosphamide regimen

We report 3 cases of atypical relapse of chronic myeloid leukemia (CML) that presented with a sudden increase of lymphoid blasts, without preceding signs of chronic phase relapse, and viral infections after allogeneic bone marrow transplantation following conditioning with a busulfan plus cyclophosphamide regimen for treatment of CML in chronic phase.

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The leukemic cells of the 3 patients at relapse expressed CD10, CD19, CD34 and HLA-DR, and were negative for peroxidase.

The first case was a 39-year old male. Monthly follow-up of the peripheral blood count and a bone marrow aspirate every 6 months were normal for 18 months after a first bone marrow transplant (Table 1).One month later (19 months post-BMT), the white blood cell count (WBC) had risen to 23.3 × 10^9/L with 77% atypical cells. Chemotherapy and subsequent donor lymphocyte infusion from the bone marrow donor produced no effect. He received an allogeneic peripheral blood stem cell transplant conditioning with total bosy irradiation (TBI) (12 Gy) and etoposide 60 mg/kg, but he died of veno-occlusive disease 83 days after the second transplant.

The second case, a 31-year old woman, showed normal blood counts for 38 months after BMT. When she came to our clinic after a 2-month interval, her WBC was 34.5 × 10^9/L with 55% atypical cells. She achieved complete remission after an allogeneic transplant with CA/CY/TBI. However, she relapsed with CML in lymphoid crisis 6 months after the second transplantation. Although chemotherapy and donor lymphocyte infusion induced temporary remission of leukemia as well as chronic graft-versus-host disease (GVHD) in the skin and liver, she died of acute respiratory distress syndrome 14 months after the second transplant.

In the third case, a 19-year old man, the fluorescence *in situ* hybridization (FISH) analysis of BM cells obtained every 6 months post-BMT showed essentially all cells to be of donor origin. Relapse of CML was not detected for 39 months after BMT. One month later, the patient suddenly developed severe bone pain in the right tibia. Bone marrow examination revealed hypercellularity with atypical cells occupying 96% of nucleated cells. The patient underwent allogeneic PBSCT conditioned with CA/CY/TBI. He developed grade II acute GVHD a month after transplantation, and was in molecular remission until 11 months after the second transplantation. The patient relapsed again 12 months after transplantation, and died of refractory disease within a month.

Although a recent report showed that approximately one-third of CML patients relapsing in advanced phase were transplanted while in chronic phase, this paper did not distinguish relapse into myeloid or lymphoid blast crisis.[2] Relapse with lymphoid crisis does not seem so uncommon after BMT, but reports in the literature are scarce. To our knowledge, only 3 cases have been described.[1,3,4]

This atypical form of relapse may be ascribed to the conditioning regimen we used for allografting. Between April 1986 and May 2000, 30 consecutive patients with chronic phase CML were treated with allogeneic transplantation at our facility (Table 2). We have used the Bu/CY regimen for patients with CML in chronic phase since 1989 based on accumulated evidence that the regimen is as potent as CY/TBI in eliminating CML cells.[5,6] Among 16 patients transplanted during the last 11 years, three patients (19%) relapsed with lymphoid crisis of CML. In contrast, there was no advanced phase relapse among 14 CML patients who were transplanted during the same period after condition-