In the same study the authors remarked on the possibility of pamidronate improving survival in MM patients, probably by reducing IL-6 production. Other authors have also shown that in vitro pamidronate inhibits the production of IL-6 and induces apoptosis of myeloma cells. Recently, Dhodapkar et al. reported on 2 MM patients whose disease stabilized well with monthly cycles of intravenous pamidronate. Thus, they conclude that this therapy directed at the myeloma microenvironment might alter the natural history of myeloma delaying the requirement for chemotherapy.

We report here the case history of a patient with MM evolved from a MGUS, whose myeloma clone after treatment with monthly cycles of pamidronate showed a transient response.

Case Report
A 32-year-old man came to our attention in July 1996 with an IgG κ monoclonal component incidentally detected one month earlier during a routine control. The serum level of IgG was 21 g/L. Blood counts, serum calcium, creatinine, urea, LDH, β₂-microglobulin, and CRP were within normal limits. Bence Jones proteinuria was undetectable. The patient was asymptomatic and the physical examination yielded no significant findings. Skeleton survey did not show lytic lesions or osteoporosis. A bone biopsy revealed 20% bone marrow plasma cells (BMPC) without atypical morphologic features.

One year later, the disease progressed with an increase of the M-component (MC) up to 32 g/L and of the BMPC up to 40%. The other clinical or laboratory parameters remained stable and no lytic lesions were detected radiologically. Pamidronate was begun at the dosage of 90 mg, in a 3-hour i.v. infusion, every month. No chemotherapeutic agents or corticosteroids were associated. After 6 months of pamidronate treatment a reduction of the percentage of BMPC to 20% and of the MC to 26 g/L was observed (Figure 1). Treatment was continued for further 6 months. Clinical and hematologic examinations performed 6 months later, after a total of 12 cycles, showed a return to the initial hematologic condition (BMPC 40%, MC 37 g/L) (Figure 1). A chemotherapy program with the VAD protocol was started and the patient is presently under treatment.

The case described here gives further evidence of the anti-myeloma effect of pamidronate. In fact, albeit transiently, bisphosphonate treatment improved the hematologic condition with a significant decrease of BM PC and of the M C. Further controlled trials are needed to confirm these isolated case reports, and to define how such therapy can integrate cytotoxic treatment in the management of myeloma patients.

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Keywords
Multiple myeloma, bisphosphonates, IL-6

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References

A paradoxical side-effect of antiaggregating treatment with ticlopidine: the Moschowitz syndrome

Sir,
Ticlopidine is a widely used antiplatelet drug that achieves its antiaggregating activity by irreversibly blocking platelet ADP receptor. The effect requires 3-5 days to become manifest and persists for several days after treatment has been stopped. Neutropenia is a well recognized hematologic
adverse effect of ticlopidine therapy occurring in about 2% of patients² and being the main reason for monitoring white blood cell count. In contrast, thrombocytopenia has been only occasionally found in major clinical studies,¹,² but medical literature recently reported a dangerous association between ticlopidine and thrombotic thrombocytopenic purpura (TTP).³,⁴

We report here two additional cases of ticlopidine-related TTP (Table 1).

A 54-year old male was hospitalized because of jaundice, abdominal pain, cutaneous purpura and disorientation; he had been taking ticlopidine (500 mg/day) for 3 weeks because of a myocardial infarction. His history included multiple drug allergies and a Steven-Johnson syndrome secondary to aspirin taking. The diagnosis of TTP was supported by thrombocytopenia (10³–10⁹/L), hemolytic anemia (Hb 88 g/L), presence of schistocytes on peripheral blood smears, renal failure and normal values of both prothrombin and partial thromboplastin times. Ticlopidine was withdrawn at once, the patient was started on steroids, red cells transfusion and four daily plasma-exchanges (with reinfusion of fresh frozen plasma) with a rapid improvement in his clinical condition and laboratory parameters.

The second patient was a 61-year old male treated with ticlopidine (500 mg/day–250 mg/day) after a transient ischemic attack; his history revealed allergy to penicillin. On the 14th day of ticlopidine treatment, the patient suffered from fever, asthenia, headache, vomiting, dysarthria, right hemiplegia, hemianesthesia and an epileptic seizure. Laboratory tests showed severe thrombocytopenia (6×10⁹/L), leukocytosis (1.02×10⁹/L), worsening hemolytic anemia (Hb 107–60 g/L), presence of schistocytes on a blood smear, and renal failure. When the diagnosis of TTP was made, ticlopidine was withdrawn and the clinical and laboratory conditions improved after high dose methylprednisolone, intravenous dipyridamole, red cells transfusions, and six daily plasma-exchanges with fresh frozen plasma replacement.

TTP is a rare but life-threatening disease caused by microvascular thrombi, mainly composed of platelets and high-molecular weight von Willebrand’s factor (vWF),⁵ that are probably triggered by anti-vWF-cleaving metalloprotease antibodies.⁶ The clinical pictures of our patients are pathognomonic for a causal-relationship between ticlopidine and the development of TTP; how ticlopidine causes TTP is, however, uncertain.

The history of drug allergies and the time exposure to ticlopidine appear to be consistent with a harmful immune mechanism. After the initial report by Page et al.,³ 60 cases of ticlopidine-related TTP were recently reviewed⁴ but other anecdotal cases have been reported.⁷ On the other hand, ticlopidine appears to be beneficial in preventing TTP relapses⁸ and a patient with TTP who received ticlopidine was even uneventfully re-exposed to the drug.⁹

The true incidence of this dangerous side-effect of ticlopidine might still be underestimated; for example, the retrospective analysis of patients treated with ticlopidine following coronary stenting (EPISTENT study) showed a 0.02% incidence of TTP.¹⁰ The recognition of ticlopidine-related TTP may also be difficult because of the underlying thrombotic symptoms for which ticlopidine is administered. It is mandatory to monitor platelet count in all patients treated with ticlopidine.

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Key words
Ticlopidine, platelets, thrombotic thrombocytopenic purpura, anti-platelet drugs

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Flow cytometry of cell suspensions from lymph nodes: immunophenotype, DNA content and proliferative rate are strongly correlated with histopathology diagnosis

Sir,
A proposed REAL classification has reinforced the role of immunophenotyping in the diagnosis of lymphomas. Immunophenotyping is performed with immunohistochemical staining, but the availability of flow cytometry (FCM) offers an alternative method. Despite the loss of tissue architecture and potential lack of tumor representation, FCM has been reported to be effective, especially in B-cell NHL. On the other hand, DNA content and cell cycle analyses have been studied mainly with regard to their clinical impact. In this study lymph nodes were analyzed by FCM with a multiparameter approach which involved firstly, surface immunophenotyping and secondly, analysis of DNA content, S-Phase Fraction (SPF) and BCL2 expression, in order to evaluate their contribution to diagnosis.

Cell suspensions were prepared in an automated device, MedIMachine (Dako, Denmark), and incubated with the following fluorochrome or phycoerythrin labeled monoclonal antibodies (Mabs): CD5, CD19, CD4, CD8, CD3, CD7, anti-κ, anti-λ, CD10 and CD23. Cells were immediately analyzed in a FACScan (Becton Dickinson, San José, CA, USA). One aliquot was resuspended in 1 mL of cold methanol 70% briefly stored at –20º, and then incubated with fluorescein labeled MAb against BCL2 protein. Cells were treated with RNase and 20 µL of propidium iodide was added. DNA ploidy and cell cycle were analyzed using MODFIT software.

Results of surface B and T cell markers of 12 samples are given in Table 1. In 4 samples a B-cell neoplasm was confirmed since CD19 positive cells accounted for more than 50% of the total population and the D value of k/l analyses was 0.83-0.97. In samples #1 and 11 a T-cell NHL was initially suspected, based on an abnormal asynchronous expression of CD3, CD5 and CD7. Results of the second step are as follows: among four cases of B-cell NHL, DNA content analysis disclosed aneuploid peaks only in case #4 (Figure 1A) and BCL2 expression was higher than 50% in 3 cases. Extremely helpful information was obtained in cases 1 and 11, since a high SPF was found. In six cases with immunophenotype, SPF and BCL2 un conclusive for diagnosis, when gating on the largest population, we could detect hyperploid peaks in two cases (Figure 1B). Anatomic

Table 1. Surface markers’ expression, Bcl2 and S phase.

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<th>Sample</th>
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