Central nervous system (CNS) infiltration in a case of promyelocytic leukemia

Sirs,

CNS infiltration is occasionally seen in acute myelogenous leukemia (AML); it is usually associated with those cases that present a monocytic component. Some investigators propose cranial irradiation for all AML patients not undergoing bone marrow transplantation, in order to prevent recurrence of the initial disease.1 We describe a case of acute promyelocytic leukemia (APL) in which a patient had a relapse in the CNS.

A 40-year-old male patient was admitted in April 1995, presenting hemorrhagic disorders. The coagulation screen demonstrated disseminated intravascular coagulation. Total blood counts showed: Hb 10.6 g/dL, platelets 22x10^9/L and WBC 33 x10^9/L (80% abnormal promyelocytes). The bone marrow was hypercellular with 95% anaplastic promyelocytes, myeloperoxidase and Sudan Black B positive. PAS and nonspecific esterases were negative. The immunophenotype on BM revealed CD13, CD33 and CD9 positive and HLA-DR, CD34, CD14, CD15, CD43, Tdt and CD61 negative.

Molecular study demonstrated PML/RAR-alpha rearrangement by RT-PCR analysis. An APL diagnosis was made and remission induction therapy consisting of ATRA (45 mg/m²/d) + ARA-C (100 mg/m²/12h) and intensification protocol with daunorubicin and cytarabine (Ara-C) were administered. A complete morphological, cytogenetic and molecular remission was achieved in June 1995. In December 1995 a BM relapse was presented with the same clinical and biological features as the initial one. He was treated with ATRA followed by chemotherapy and achieved a complete remission in February 1996.

One month later, headaches began and atypical promyelocytic cells were identified in the cerebrospinal fluid by morphological and cytochemical staining. The immunophenotype expressed CD13 (80%), CD33 (87%), CD9 (60%), showing absence of expression regarding HLA-DR and CD14. Blood film showed a leukoerythroblastotic picture, with Hb 11 g/dL, 222x10^9/L plts and WBC 8.8x10^9/L. Bone marrow smears showed a complete cytological remission but molecular studies determined the PML/RAR-a rearrangement in the bone marrow and cerebrospinal fluid.

The diagnosis of CNS involvement was made, and the patient was treated with intrathecal methotrexate + ARA-C, followed by allogenic BM transplantation. A sustained hematological improvement was observed but he had a BM relapse three months later. There was no response to treatment and the patient died five months after transplantation.

CNS involvement is an unusual form of relapse in APL and should be considered a very serious symptom.1,2 Neurological manifestations of acute myelogenous leukemia are usually presented with a high WBC count.3 Our patient showed a normal WBC count at the time of CNS relapse. Some reports recommend no prophylaxis for CNS disease in the non-monoblastic leukemias,4 but we think that screening lumbar punctures should be performed when CNS symptoms occur.

References


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Warfarin resistance induced by teicoplanin

Sirs,

Patients with a prosthetic heart valve require lifetime treatment with an oral anticoagulant, in order to decrease their high thrombotic risk, and their coagulant activity must be carefully monitored in order to avoid an intolerable increase of the hemorrhagic risk. Drug interaction is one of the main factors capable of altering this balance, leading to a re-evaluation of INR and an adjustment of warfarin dosage when another drug is added to patient therapy. We report a case of warfarin resistance induced by teicoplanin in a patient with a prosthetic valve and bacteremia.

A 60-year-old woman underwent mitral valve replacement with a prosthetic valve because of rheumatic endocarditis. Five weeks after cardiac surgery, the patient developed fever and was therefore admitted to our division. Multiple blood culture tested positive to methicillin-resistant staphylococcus aureus, and a treatment with rifampin 450 mg b.i.d. and teicoplanin 400 mg b.i.d. was initiated while the patient was taking digoxin, furosemide and 3.75 mg/day of warfarin, with an INR between 3.5 and 5. Three days after beginning antibiotic treatment, the INR began to decrease, and after three more days the prothrombin time was normal. The INR remained between 1.2 and 1.6 despite a progressive increase of the warfarin dose to 10, 15 and 20 mg/day and the interruption of rifampin treatment. Teicoplanin was suspended after 42 days of treatment, and INR gradually rose, reaching the target INR after 14 days of 10 mg/day of warfarin (Figure 1). The patient is now taking warfarin 5 and 2.5 mg on alternate days, with an adequate anticoagulation.

The antibiotic interference in warfarin treatment is mostly represented by an increase in its effect, while an inhibiting effect has been described for griseofulvin, rifampin, nafcillin and dicloxacillin only.1 In our cases, rifampin was considered primarily responsible for the warfarin resistance, but no significant modification of INR was found when the drug was suspended. Teicoplanin has never been reported to interfere with oral anticoagulation in clinical settings, and an experimental study detected no effect on warfarin metabolism.2 Teicoplanin is a vancomycin-related glycopeptide antibiotic: although no
patients with overt interaction have been described, previous studies have not definitely excluded a possible interference of vancomycin with oral anticoagulants. As with other drugs, the mechanism responsible for the teicoplanin-warfarin interaction in our patient is probably represented by an increase of warfarin clearance.1 In view of this report, we recommend strictly monitoring the INR value when administering teicoplanin to patients who are adequately anticoagulated.

References

Early autologous stem cell transplantation in Hodgkin disease in partial remission or in relapse

Sir,

With MOPP/ABVD like protocols, is possible to achieve a 70-80% cure rate in patients with different stages of Hodgkin’s disease (HD). Prognosis is still poor for patients who never achieve a complete remission (CR) or relapse within one year, or for patients who are in resistant relapse.1,2

The poor therapeutic results observed in such patients treated with standard chemotherapy suggested investigating the alternatives for intensive treatment, such as high-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT). Several HDC regimens like CBV (CPM + BCNU + VP16), BEAM (BCNU + VP16 + ARA-C and melphalan), BEAC (BCNU + VP16 + ARA-C + CPM), or CP + VP16 + TBI etc. are currently employed with HD patients. The cure rate is extremely low (10-15%) when HDC and ASCT are delayed, resulting in an increasing drug resistance. Better results are obtained if patients are grafted early on in the first relapse or in significant partial remission (sPR), with 30-50% of continuous CR.3,4

This report concerns 31 patients with HD in partial remission (PR) or in relapse, treated with BEAM (19 pts), CBV (8 pts) and high-dose sequential chemotherapy (HDSC) (4 pts), with bone marrow (ABMT) in 21 subjects (67.7%) and peripheral blood stem cell (PBSCT) rescue in 10 (32.3%). Twenty patients (64.5%) were treated in PR or significant PR (sPR>70%), 9 (29.1%) were treated in relapse and 2 in refractory disease. The histology presented nodular sclerosis in 21 pts (67.7%), mixed cellularity in 9 (29.1%) patients and lymphocyte depletion in 1 (3.1%). The median age was 28.5 years (16-53). Stage III-IV was present in 24 pts (77.4%) and IIB with bulky disease (mediastinal or subdiaphragmatic) was present in 7 patients. B-symptoms in 23 subjects (74.2%), bulky disease (>10 cm) in 19 (61.3%), extranodal disease in 12 (38.7%), LDH >500 UI/L in 20 (64.5%) patients, β2-microglobulin >2.5 mg/mL in 7 (22.6%) were the most frequent adverse prognostic factors at the time of diagnosis.

The CR rate was 71% (CR+PR>90.4%) and the median duration of CR was 15.2 months. No treatment-related deaths were reported, but Gram+ sepsis in 6 pts and grade 1 cardiotoxicity in 8 pts were documented. No difference in terms of response rate and median duration of CR was observed between the ABMT and PBSCT group. In the BSCT group, the median MNC reinfused was 3.2·10^9/kg; the median CD34+·CD38- cells was 28.8·10^4/kg and median CFU-GM was 135.5·10^3/kg. The median time to ≥0.5·10^9/L PMN following transplantations was 11 days in PBSC autografts and 13 days in the BM group. A platelet count ≥30·10^9/L was reached at day +9 for the PBSC group and at day +13 for the BM group. The median follow-up was at 17 months, and 24-months projected event-free survival from graft was 53% (Figure 1).

The knowledge that a survival rate at 5 years is about 30% in HD pts with more than three adverse prognostic factors, encouraged research regarding use of HDC and ASCT in the early phase of therapeutic approach, in the attempt of increasing survival and DFS. The treatment with several regimens of HDC followed by ABMT for relapsed or refractory HD achieved a response rate of about 50% with 20 to 30% of long-term DFS. Considering our group of patients (31), the median follow-up (17 months) and the median duration of CR (15.2 mths), our results confirm the possibility of achieving long-term EFS (53% at 24 months) and a high percentage of CR (71%) with ASCT in patients with advanced stage HD (77.4% of cases) and adverse prognostic factors (B-symptoms in 74.2%, bulky disease in 61.3%, elevated LDH in 64.5% of the cases).

ASCT has become a more and more frequent and safe procedure in HD patients and toxicity is very mild. This approach, in the early phase of a treatment plan, may be recommended for partial responders or early relapsing HD patients. More investigative research, including prospective randomized trials, are needed in order to assess the efficacy of HDC and ASCT in treating patients with HD in PR or in relapse.5-6

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Probable ticlopidine-induced severe aplastic anemia and cholestatic hepatitis
Sir,
Ticlopidine is a thienopyridine derivative with platelet-inhibitor capability used to reduce the risk of stroke. The most common adverse effects are mild and transitory: diarrhea, nausea, dyspepsia and rashes. More serious side effects are less frequent; they include: neutropenia, thrombocytopenia, purpura and cholestatic hepatitis, whose pathogenesis is not fully understood.1-4

A 67-year-old man with no history of liver or hematological disease was admitted to the hospital on February 12, 1996. He had been suffering for ten days from acholia, choluria, fever, weakness and painless jaundice. His medical antecedents included chronic auricular fibrillation, hiatal hernia and duodenal ulcer with gastrointestinal bleeding. Treatment on admission consisted of digoxin, ciprofloxacin (for the last 3 days), occasional metamophen and ticlopidine (250 mg po bid) for 69 days. The patient was markedlyicteric, with 39°C fever and crepitation at both pulmonary bases. He had no abdominal tenderness and no palpable gallbladder or lymph nodes. The urine was dark brown and the stool was light. On admission, WBC count was 0.6 × 10^9/L (90% lymphocytes), hemoglobin 13 g/dL, platelets 79 × 10^9/L, reticulocytes 0%, ALAT 24 iu/L (5-40), γGT 321 iu/L (5-53), alkaline phosphatase 512 iu/L, bilirubin 18 mg/dL (conjugated 10 mg/dL) and abdominal ultrasound showed hepatomegaly, but no evidence of biliary obstruction. Coagulation tests, renal functions, immunoglobulin level, complement, autoantibodies and sucrose hemolytic tests were normal; viral screening was negative for AHV, BHV, CHV, HIV, CMV, and EBV; the bacterial blood cultures and parasitic investigation were negative as well. A chest x-ray displayed a minor cardiomegaly. The trephine biopsy showed a pattern of severe aplastic anemia with very hypoplastic cellularity and an absence of granulocytes, erythroid and megakaryocytic cells, presenting mainly mononuclear cells. On day 3 his blood cell counts were: 0.3 × 10^9/L (0% neutrophils), 9.4 g/dL hemoglobin, platelets 16 × 10^9/L and 0% reticulocytes. Our diagnosis was very severe aplastic anemia and intrahepatic cholestasis, probably due to ticlopidine. We suspended ticlopidine and began with empirical broad-spectrum iv antibiotic, antifungal agents, G-CSF (Linogristm, Chugai-Rhone-Poulenc, 150 mg/m^2) infusion, transfusion and hydration. On the fifth day we started immunosuppressive therapy with ATG (Atgam® Upjohn, 15 mg/kg iv daily for 8 days). The clinical evolution was excellent: on the twelfth day WCB count was 5.7 × 10^9/L, platelets were 93 × 10^10/L, hemoglobin 9 g/dL, reticulocytes 32 × 10^10/L, bilirubin 3.7 mg/dL, alkaline phosphate 402 iu/L and γGT 268 iv/L. All the analyses were normal after three weeks and on the fourteenth day, the patient was discharged. Sixty days later his tests were clinically and biologically normal.

In our study, we describe one of the first cases of the association of ticlopidine and severe aplastic anemia in addition to intrahepatic cholestasis. We believe the combination of general supportive and specific therapy probably determined the positive clinical evolution, as spontaneous normalization is usually observed within three to five weeks after suppression of ticlopidine.4,5 We conclude that patients receiving ticlopidine should be monitored closely with a complete blood cell count and should be instructed to look for signs and symptoms of liver damage.

References

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Desferrioxamine in the treatment of myelodysplastic syndromes
Sir,
For many patients with myelodysplastic syndrome (MDS) refractory anemia is the main clinical problem. Unfortunately, only some patients benefit from treatment with hematopoietic growth factors.1-4 Unresponive individuals often have a high transfusion requirement and need iron chelation treatment. In some of these patients, desferrioxamine (DFO) has been reported to be effective not only as an iron-chelating agent but also in reducing the transfusion requirement.4,5 In the last few years, we have treated three MDS patients with DFO. All three patients presented isolated anemia (see Table 1). All patients received 30 mg/kg of DFO three days per week, by subcutaneous infusion over a 12-hour period via a disposable infusor. No other medication was given. On each transfusion day, transfusion (of red cell concentrate, RCC) was given if Hb was below 9 g/dL; the transfusion requirement was estimated using the following formula:4,5

\[
[(A \times BV) + (B \times 75) - (C \times BV)] \times 31
\]

where A = pre-transfusional Hb (g/dL) at start of a transfusion episode; B = number of RCCs supplied on that day; C = pre-transfusion Hb at a subsequent transfusion episode; BV = blood volume; 75 = mean Hb content (g) in one RCC; D = number of days between A and C; and 31 = 31 days/month. The results are summarized in Table 1. Patients 1 and 2 showed steady improvement as regards both transfusion requirement and Hb concentration, and no longer needed transfusion after 12 and 15 months of treatment respectively. Patient 3 continued to require transfusions after 20 months of treatment. Serum ferritin levels did not decrease in patients 1 and 2.

The results for patients #1 and #2 show a reduction in transfusion requirement following DFO treatment, in accordance with previous reports.1-4 These authors observed that the reduction in transfusion requirement correlated with the efficacy of iron chelation (as indicated by the reduction in the hepatic iron concentration), but not with the degree of attainment of normal iron stores.1 In our patients, improvement was observed
Despite the fact that serum ferritin levels did not decrease, although it must be noted that ferritin level alone is a poor guide to the extent of iron overload. Thus, the effects observed on the transfusion requirement may be independent of the normalization of iron stores, and depend only on the chelant properties of DFO. It would be of interest for future studies to investigate these possibilities.

Table 1. Results of DFO treatment in three MDS patients.

<table>
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<th>Patient</th>
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<tr>
<td>Treatment period (months)</td>
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<td>15</td>
<td>20</td>
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</table>

Hb: pre-transfusional Hb. Req: transfusion requirements. F: ferritin. pre and post: means for the three months before and after the treatment period.

In conclusion, we consider DFO treatment to be an attractive option for MDS sufferers who require regular transfusion. As has been reported previously, long periods of treatment seem to be necessary before any improvement is observed. In our opinion, DFO is most suitable for non-elderly patients who can easily manage self-administration of the drug.

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