Acute lymphoblastic leukemia in the elderly. A twelve-year retrospective, single center study

Acute myeloid leukemia in elderly patients is a well-studied disease, while only a few studies on acute lymphoid leukemia (ALL) in elderly patients have been reported and their results are not encouraging. The aims of the present study were to review the characteristics of acute lymphoblastic leukemia developing in patients aged over 65 years old during a twelve-year period at our Institution and to analyze the clinical and laboratory characteristics.

Sir,

Between June, 1986 and June, 1998, 119 new cases of acute lymphoblastic leukemia (ALL) were diagnosed in patients aged over 14 years old, consecutively admitted to our Hematology Division. Among these, 37 patients (31%) were aged over 65 years.

On the basis of their performance status, and after evaluation of cardiac, respiratory, renal and liver function, the patients were enrolled in one of the protocols used in our Hematology Department at the time of the diagnosis of ALL. Patients with a relevant concomitant internal disease at diagnosis were excluded from intensive treatment and managed with more conservative therapy.

Of the 25 patients treated with intensive chemotherapy (group 1), 11 (30.5%) were treated according to Magrath’s protocol,3 in 5 patients, with a L3 morphology, the treatment included cyclophosphamide. Twelve patients (32%) presented with a poor performance status or with inadequate function of one or more organs. For these patients (group 2) the induction therapy consisted of weekly administration of vincristine (1.5 mg/m²) and methylprednisolone (40 mg/m²/day) for six weeks.

After the induction and consolidation phases, all the patients who achieved CR, underwent the same maintenance therapy of monthly administration of vincristine, prednisone, 6-mercaptopurine and methotrexate.

Cytogenetic studies were carried out in 20 patients: 13 (65%) had chromosomal abnormalities, the most frequent of which were Philadelphia and hyperploid set, found in four patients each (Table 1). Molecular biology studies found the p190 rearrangement in one other patient in whom the cytogenetic study failed.

Thirty-three patients (89%) had, at diagnosis, a lumbar puncture to study the cerebrospinal fluid (CSF): leukemic meningeosis was diagnosed in only one patient.

Overall we observed 25 complete remissions (CR) (67%), 9 deaths during induction (24%) and 3 cases of resistant disease (8%). The overall median duration of the CR was 10 months (2-76). The overall median survival was 7 months (0.3-82), but in patients who reached CR it was 14 months (2.8-82.3) and 1.4 months (0.3-7) in those who died during induction or who were resistant (Table 1).

Nine patients (24%) died within 60 days of diagnosis because of the following complications: 7 patients had acute toxicity from chemotherapy (cardiac and gastrointestinal), 1 patient had acute pancreatitis, 1 patient had Gram-negative septic shock.

The overall median duration of hospitalization was 39 days (10-80). Of the patients treated with aggressive chemotherapy, 20 patients (80%) reached a CR, 4 (16%) died of toxicity before the completion of the induction treatment, and 1 (4%) was resistant. The median duration of CR was 13 months (2.5-76) and the median survival of the patients in CR was 15.5 months (3-82). The median overall survival was 14 months (1.9-82).

Seven patients (28%) manifested signs of acute toxicity from chemotherapy in one or more organs (3 gastrointestinal, 3 cardiac, 1 neurologic, 1 hepatic). The median duration of hospitalization was 45.5 days (28-80).

Among patients managed with palliative therapy, CR was reached in 5 cases (42%) after a median of 28 days from the onset of treatment,
5 patients (42%) died during induction therapy after a median of 16 days of treatment, and 2 (16%) were resistant. The median duration of CR was 4 months (1.5-10) and the median survival in CR was 5 months (2.8-19). The median overall survival was 2.6 months (0.3-19).

Signs of toxicity were observed in 4 patients (36%) (2 gastrointestinal, 1 cardiac, and 1 neurologic).

The median duration of hospitalization was 28.5 days (10-60).

Comparing the 2 groups of patients (aggressive treatment vs palliative management) a significant difference was found in: the median duration time to reach CR (42 days in group 1 vs 28 days in group 2, p<0.001); the median CR duration (13 months in group 1 vs 4 months in group 2, p<0.02); the median overall survival (15 months in group 1 vs 2.6 months in group 2, p<0.008); and the median duration of hospitalization (45.5 days in group 1 vs 28.5 days in group 2, p<0.0001).

The 7-year Kaplan-Meier curve shows a median overall survival of 8%.

Induction treatment produced a higher CR rate and longer survival duration in the group treated intensively than in that managed with palliative therapy. However, the CR duration and survival in these patients was short; in fact the majority of them relapsed within a few months.

As also reported by other authors, the cumulative toxicity of chemotherapy is one of the main factors that influence these results, because it may worsen the clinical condition of the patients, in particular impairing cardiac function and requiring the overall chemotherapy dosage to be reduced, especially during the post-remission and maintenance phases. To overcome the limits of toxicity and improve the dose-intensity, some authors have suggested using less toxic chemotherapeutic agents. Indeed, while in the past Bassan and Delannoy used idarubicin rather than daunorubicin because of the former’s less toxic cardiovascular and hepatic effects, further improvement can be reached using a new formulation of a drug with proven efficacy, such as liposomal daunorubicin, that has already been used successfully in elderly acute myeloid leukemia. Further studies are needed to demonstrate the efficacy of less toxic drugs in patients with low performance status in order to improve their prognosis.

Livio Pagano, Luca Mele, Ida Casorelli, Luana Fianchi, Annalaura Di Febo, Giuseppe Leone
Istituto di Semeiotica Medica, Università Cattolica del Sacro Cuore, Rome, Italy

Key words
Acute lymphoblastic leukemia; elderly patients; intensive chemotherapy.

Funding
This work was supported in part by a grant from MURST 60% (Università Cattolica S. Cuore, Roma).

Correspondence
Livio Pagano, M.D., Istituto di Semeiotica Medica, Università Cattolica del Sacro Cuore, largo Francesco Vito 1, 00168 Rome, Italy. Fax: international +39.06. 3051343 – E-mail: lpagano@rm.unicatt.it
Unsuccessful treatment of resistant thrombotic thrombocytopenic purpura with prostacyclin

Prostacyclin has been suggested as a useful agent for patients with thrombotic thrombocytopenic purpura (TTP) refractory to plasma-exchange. We report our unsuccessful experience with iloprost instead of the ascorbic acid.

Sir,

Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by thrombocytopenia, microangiopathic hemolytic anemia and, less commonly, fever, fluctuating neurologic abnormalities and renal impairment. The underlying pathology is disseminated thrombotic occlusion of the microcirculation secondary to an abnormal interaction between vascular endothelium and platelets. However, so far, the etiology remains elusive. The primary process might involve endothelial damage with release of ultra large von Willebrand factor (ULWF multimers), impaired fibrinolytic activity and reduced vascular prostacyclin production. Recently, two clinical studies reported the presence of inhibitory antibodies to ULWF-cleaving protease. Plasma-exchange is the first line treatment of TTP; this treatment works by removing ULWF, inhibitory antibody and supplying normal protease. The procedure is effective in over 70% of patients. For refractory cases there is no standardized treatment. Some reports suggest the effectiveness of vincristine, intravenous γ-globulin (Ig) and splenectomy. Au et al. recently reported a favorable outcome with prostacycin in a patient with TTP diagnosed during immunosuppression with tacrolimus for mismatched liver transplantation.

Ilprost, a long-acting PGI₂ analog, inhibits endothelial reactivity and platelet aggregation. We describe our unfavorable experience with iloprost in a patient with TTP resistant to plasma-exchange, vincristine and high-dose IgG.

A 42-year old woman was admitted to our hospital because of asthenia and purpura. Physical examination was negative except for purpura. Laboratory studies revealed severe anemia (Hb: 6.1 g/dL), schistocytes, thrombocytopenia and hepatic failure. Immunosuppression with tacrolimus for mismatched liver transplantation was followed by relapse. After 37 plasmapheresis procedures, we started therapy with iloprost instead of the association of acetylsalicylic acid and dipyridamole. Following the experience of Au et al., iloprost was given as an eight-hour continuous infusion at the dosage of 50 µg/day for ten days. Stable, complete remission was obtained but any attempt to discontinue plasma-exchange was followed by relapse.

After 37 plasmapheresis procedures, we started therapy with iloprost instead of the association of acetylsalicylic acid and dipyridamole. Following the experience of Au et al., iloprost was given as an eight-hour continuous infusion at the dosage of 50 µg/day for ten days. Stable, complete remission was obtained but any attempt to discontinue plasma-exchange was followed by relapse.