Impact of pre-induction therapy leukapheresis on treatment outcome in adult acute myelogenous leukemia presenting with hyperleukocytosis

Received: 23 November 1999 / Accepted: 8 March 2000

Abstract  Acute myeloid leukemia (AML) presenting with hyperleukocytosis is generally of poor prognosis due to an increased early death rate and a lower response to initial chemotherapy. Between April 1985 and December 1995, all patients with newly diagnosed AML admitted to our institution with an initial white blood cell (WBC) count greater than 100 × 10^9/l were scheduled to undergo leukapheresis. This represented 53 patients (median age 59 years, range 16–78 years) who underwent from 1 to 4 sets of leukapheresis (median 1). The median initial WBC count was 160 × 10^9/l (range 100–480 × 10^9/l). Morphologic subtypes, according to the French–American–British classification, showed 3 M0, 16 M1, 6 M2, 10 M4, 16 M5, and 2 unclassified cases of AML. In 21 patients (40%), leukapheresis did not reduce their WBC counts significantly, while 32 patients (60%) achieved a WBC count of less than 100 × 10^9/l (median 71 × 10^9/l) after leukapheresis. Analysis of cell cycle was performed on bone marrow (BM) and peripheral blood leukemic cells before and after leukapheresis in three cases. In two of those cases, a recruitment of BM leukemic cells in the S phase was observed after leukapheresis. The median WBC count at the time of starting chemotherapy was 85 × 10^9/l (range 23–264 × 10^9/l). Complete remission was achieved in 55% (95% confidence interval 40–68%). Early death occurred in two cases. Median disease-free survival was 10 months, while median overall survival was 8 months. In this study, early death rate is lower than data previously published in the literature and almost all patients could receive chemotherapy. This might suggest a benefit of initial leukapheresis in the treatment of AML presenting with hyperleukocytosis.

Key words  Leukapheresis · Acute myelogenous leukemia · Leukostasis · Hyperleukocytic leukemia

Introduction

Successful remission induction therapy is essential to achieve long-term survival in patients with acute myeloid leukemia (AML). Induction therapy requires intensive cytotoxic chemotherapy with life-threatening morbidity and significant mortality (McCueley 1992). AML presenting with hyperleukocytosis is generally considered of poor prognosis due to an increased early death rate and a lower response to initial chemotherapy (Hug et al. 1983; Cuttner et al. 1983; Creutzig et al. 1987; Dutcher et al. 1987; Ventura et al. 1988; Porcu et al. 1997). Early death is particularly frequent when initial white blood cell (WBC) count is above 100 × 10^9/l due in large part to severe pulmonary and neurological complications arising from leukostasis (Dutcher et al. 1987). Indeed, the excessive number of leukocytes results in increased blood viscosity and may seriously affect the microcirculation in lungs, brain, and other organs by obstructing micro-channels or by forming micro-aggregates and white thrombi in small veins (Lichtman and Rowe 1982). Moreover, leukemic blasts may compete for oxygen in the microcirculation, and they may be invasive, damaging vessels walls (McKee and Collins 1974). Their rapid destruction in response to chemotherapy causes metabolic disturbances (lytic syndrome) with uric acid accumulation leading to obstructive uropathy or coagulation disorders (coagulopathy) with hemorrhages. Recommendations for care of these patients include adequate hydration, alkalinization, control of uric acid production with allopurinol, correction of possible...
fluid and electrolyte problems, avoidance of excessive transfusions, and a careful use of antileukemic drugs at the outset of therapy. Therapeutic leukapheresis has been proposed to mechanically lower the number of leukemic cells in peripheral blood (PB) in order to prevent the sometimes fatal complications in patients with hyperleukocytosis (Bunin and Pui 1985; Porcu et al. 1997). A possible effect by recruiting blast cells in the S phase has also been suggested, resulting in a higher sensitivity to subsequent chemotherapy regimens by increasing the cytotoxic effect of dependent-cell cycle drugs (Kotelnikov et al. 1987). However, there is still no convincing evidence that leukapheresis is essential in the immediate treatment of hyperleukocytosis, and the effectiveness of this technique remains in question.

Since 1985, our department policy was to perform systematically therapeutic leukapheresis in all patients with newly diagnosed AML presenting with a WBC count greater than $100 \times 10^9$/l in order to reduce the threat of complications from leukostasis. In this study, we examined the clinical and biological characteristics and the treatment outcome of 53 adult patients with hyperleukocytic AML, seen in our institution over a 10-year period, who underwent leukapheresis before intensive chemotherapy.

**Patients and methods**

**Patients**

According to our institution policy, all patients seen between April 1985 and December 1995 with newly diagnosed AML presenting with an initial WBC count greater than $100 \times 10^9$/l were systematically scheduled to undergo leukapheresis before initiation of intensive chemotherapy. Fifty-three AML patients fulfilling these criteria were registered. These patients represented 7% of newly diagnosed AML cases seen in our institution during this period. Diagnosis of AML was established on the basis of morphological and standard cytochemical examinations of bone marrow smears according to the French–American–British (FAB) criteria (Bennett et al. 1985). During leukapheresis and chemotherapy, all patients underwent daily biologic evaluations, including determination of the complete blood cell count and differential coagulation tests and serum electrolytes. Coagulopathy was defined as the presence of any two of the following abnormalities: prothrombine time less than 60%, fibrinogen less than 2 g/l, and fibrinogen degradation products greater than 10 mg/l. Lytic syndrome was defined as the presence of at least three of the following criteria: maximal phosphoremia > 1.4 mmol/l, maximal kaiemia > 4.8 mmol/l, minimal creatininemia < 2.1 mmol/l, maximal uricemia > 300 μmol/l, and creatininemia > 110 μmol/l.

**Leukapheresis**

Therapeutic leukapheresis was performed before chemotherapy administration using mostly discontinuous-flow automate instruments (Haemtectics, modèle 30 l). Continuous-flow automate instruments (IBM, modèle 2997 or Cobe-Spectra) were only used in some ambulatory patients. Blood cell counts were performed from 30 min to 1 h after each round of leukapheresis. The total number of rounds of leukapheresis in each patient depended on the evolution of WBC counts and on the severity of restricted physical activity, graded according to the World Health Organization (WHO) criteria. Overall, leukapheresis was performed daily until the achievement of WBC counts below $100 \times 10^9$/l or until an improvement of WHO performance status allowing initiation of induction chemotherapy.

**Cell cycle analysis**

Analysis of the cell cycle was performed in three cases on bone marrow (BM) and PB leukemic cells prior to the first leukapheresis and again 24 h after pheresis. Cell cycle studies were carried out by means of a standard method using the incorporation of bromodeoxyuridine (BrdU) in BM and PB cells isolated by Ficoll and detection of S-phase cells having incorporated BrdU into DNA using an indirect immunofluorescence method on cytosin slides (French et al. 1989).

**Chemotherapy received**

The 53 AML patients with hyperleukocytosis were treated according to age and year of diagnosis by five different chemotherapy protocols detailed in Table 1 (Archimbaud et al. 1994; Castaigne et al. 1996; Löwenberg et al. 1997; Keating et al. 1998; Löwenberg et al. 1998). Patients underwent one or two courses of induction chemotherapy including anthracycline in combination with cytosine arabinoside at a conventional dose ± mercaptopurine ± etoposide. Chemotherapy was begun 24–72 h after the last round of leukapheresis. One patient died before any chemotherapy could be given. Patients received standard supportive care during the neutropenic period. Once complete remission (CR) was achieved, patients received either no maintenance therapy, conventional maintenance therapy, or additional courses of myelosuppressive consolidation according to the protocol design in which they were included in. Three patients underwent autologous bone marrow transplantation (BMT) and one patient autologous BMT during early first CR.

**Evaluation of therapy**

CR was defined according to the CALGB criteria (Cheson et al. 1990) as less than 5% blasts in BM aspirates with evidence of maturation of cell lines and restoration of PB counts. Treatment failures were classified according to Preissler (1978) as non-response (resistant), including all patients with proven blastic regrowth following chemotherapy even if they died before blood count recovery, and other failures corresponding to patients who died while nonblastic of presumably treatment-related toxicity. Survival was defined as the time from diagnosis to death. Disease-free survival (DFS) was calculated from the first CR to the time of relapse or death from any cause. Hematological relapse was considered when more than 5% of blasts were seen in two BM aspirates obtained at 15-day intervals. Early death was defined as death occurring within the first week following the beginning of treatment.

**Statistical analysis**

Initial characteristics [age, gender, WHO performance status, weight loss > 5%, central nervous system leukemia, tumoral syndrome, hemoglobin level, WBC and platelet counts, blast and polymorphonuclear (PMN) cells percentages, hemostatic disorder, uric acid, creatinine, phosphoremia, kaiemia, calcaemia, FAB subtypes, percentage of blast cells] were analyzed for potential prognostic significance on treatment outcome. Quantitative variables were treated as dichotomous in the analysis. The cut-off points used were the approximate median value for age and hematological parameters and the upper limit of normal value for serum parameters. CR rates were compared using Yate’s corrected $\chi^2$, and 95% confidence intervals (CI) on pro-