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ORIGINAL ARTICLE

Minimally early morbidity in children with acute myeloid leukemia and hyperleukocytosis treated with prompt chemotherapy without leukapheresis

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KEYWORDS
acute myeloid leukemia;
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Background/Purpose: Patients with acute myeloid leukemia (AML) and hyperleukocytosis, defined as an initial white blood cell (WBC) count of $\geq 100 \times 10^9$/L, are often treated with leukapheresis. In this study, we have reported our experience of treating AML without leukapheresis.

Methods: From November 1, 1995, to May 31, 2012, there were 74 children (≤18 years old) with *de novo* AML other than acute promyelocytic leukemia. Seventeen patients had an initial WBC count $\geq 100 \times 10^9$/L. Prompt chemotherapy was started within hours whereas leukapheresis was not performed.

Results: The median age of the 17 patients with hyperleukocytosis was 7.4 years (range: 0–16 years), and the median initial WBC count was 177×10^9/L (range: 117–635 $\times 10^9$/L). The median time between admission and initiation of chemotherapy was 4.5 hours (range: 2–72 hours) in patients with hyperleukocytosis, whereas it was 13 hours (range: 2–120 hours) in those without hyperleukocytosis. Seven patients (7/17, 41%) had one or more early complications before or during the first 2 weeks of chemotherapy. Fifteen of the 16 patients who received prompt chemotherapy achieved complete remission (93.8%), comparable with those without hyperleukocytosis (98.2%; $p = 0.33$).

Conflicts of interest: The authors have no conflicts of interest relevant to this article.

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Conclusion: Children with AML and hyperleukocytosis, treated with prompt chemotherapy without leukapheresis, had minimal early morbidities.
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Introduction

Patients with acute myeloid leukemia (AML) and hyperleukocytosis, defined as an initial white blood cell (WBC) count of $\geq 100 \times 10^9$/L, are at a high risk of early morbidity and mortality.[1] Early complications are attributed to leukostasis, a phenomenon associated with sludging of leukemic blasts in the microcirculation and adhesive interactions with capillary endothelium, especially affecting the brain and lung.[2] Intracranial hemorrhage and respiratory distress are the main causes of early mortality.

Leukapheresis is often applied for patients with hyperleukocytosis to rapidly decrease their WBC count. Some studies of adult patients have demonstrated that leukapheresis decreases early mortality but does not impact long-term outcome. Few studies have focused on the management of pediatric AML with hyperleukocytosis. Moreover, there is still no evidence that leukapheresis should be the standard procedure for the initial treatment of hyperleukocytosis. In pediatric patients, there are also disadvantages of applying leukapheresis. The placement of the large central venous catheter is more difficult to perform in pediatric patients and may cause bleeding or infections. Moreover, further thrombocytopenia and unstable blood pressure may occur during leukapheresis. Therefore, we performed a prospective, single-center, multiyear study to investigate the application of prompt chemotherapy, instead of leukapheresis, as the initial management for children with AML and hyperleukocytosis.

Materials and methods

Study design and patients

At Mackay Memorial Hospital (MMH), Taipei, Taiwan, there were 74 patients under the age of 18 years with *de novo* AML other than acute promyelocytic leukemia who were treated with two consecutive protocols, namely, MMH-AML-96 and Taiwan Pediatric Oncology Group (TPOG)-AML-97A, from November 1, 1995, to May 31, 2012.[3,4] Seventeen patients had an initial WBC count $\geq 100 \times 10^9$/L. One patient, who was deeply comatose due to severe multifocal cerebral hemorrhage at presentation and did not receive chemotherapy, was excluded from complete remission (CR) analysis.

Diagnosis

The diagnosis of AML and its subtypes was based on the French–American–British (FAB) classification.[5–7] Immunophenotyping and cytogenetic studies were performed in all patients. Molecular genetic testing, including reverse transcriptase-polymerase chain reaction assays and Southern blot analysis, was performed in all patients as previously described.[8] In recent years, fluorescence *in situ* hybridization was applied in the detection of mixed lineage leukemia (MLL) gene rearrangement.

Treatment

At initial presentation, all patients immediately received intravenous fluid hydration. Rasburicase (recombinant urate oxidase) was used to treat hyperuricemia, if present. Instead of leukapheresis, prompt induction chemotherapy was given to all patients after a rapid initial diagnosis of AML by leukemic cell morphology, cytochemical stain, and/or immunophenotyping. The regimens of induction chemotherapy in both the MMH-AML-96 and TPOG-AML-97A protocol were identically Ara-C (100 mg/m^2/day $\times$ 7) plus idarubicin (9 mg/m^2/day $\times$ 3). If CR was not achieved after one cycle of induction therapy, another one cycle of induction therapy with the same regimen was given. If CR could not be achieved after two cycles, second-line treatment including mitoxantrone (8 mg/m^2/day $\times$ 5) and etoposide (100 mg/m^2/day $\times$ 5) was given.

Initial outcomes

The CR was defined as less than 5% blasts in total nucleated cells in bone marrow aspirate with a regeneration of normal cell lines at the end of remission induction. Early complications and death were defined as events occurring before or during the first 2 weeks of chemotherapy.[9] Early complications were further classified into neurological symptoms, respiratory distress, bleeding events, renal insufficiency, and bacterial sepsis.

Statistical analysis

Comparisons of age, WBC count at diagnosis, and duration from admission to initiation of treatment of the AML patients with and without hyperleukocytosis were performed using the *t* test. Other characteristics of the patients based on univariate analysis were performed by the χ^2 test. A p value < 0.05 was taken to be significant.

Results

The characteristics of the patients with or without hyperleukocytosis are summarized in Table 1. The median age of the patients with hyperleukocytosis was 7.4 years (range: 0–16 years), and the median initial WBC count was 177 $\times$ 10^9/L (range: 117–635 $\times$ 10^9/L). The most frequent FAB subtypes were M4 and M5 (in 5 patients each), followed by M1 and M2 (in 3 patients each), and M0 (1 patient). Four patients had MLL gene rearrangements, one inv(16)/*CBFβ-MYH11*, one monosomy 7, one trisomy 8, one complex karyotype, and nine normal karyotype. The abnormalities of the *MLL* gene included t(9;11)/*MLL-AF9* in two patients,

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