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Outcome of treatment with Hyper-CVAD regimen in Chinese patients with acute lymphocytic leukemia

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Abstract

Modern intensive chemotherapy regimens have improved the prognosis for adult patients with acute lymphocytic leukemia (ALL). With these regimens, the complete response (CR) rates are approximately 75% and long-term disease-free survival (DFS) rates are about 20–35%. For patients with high-risk ALL, DFS rates are only 20% or less. Hyper-CVAD regimen is effective in ALL and aggressive non-Hodgkin lymphomas (NHL) with increased CR rates and DFS rates. Between June 2002 and October 2006, 53 consecutive adult patients with newly diagnosed adult ALL were treated with Hyper-CVAD regimen for six to eight cycles. The alternating courses were given every 3–4 weeks or earlier if count recovery occurred. CR rates of 73.6% were achieved in 39 patients, the estimated 2-year survival rate was 82.9% and the estimated 2-year event-free survival (EFS) rate was 87.3%. Side effects were as expected, mostly attributed to myelosuppression. Analysis of prognostic factors suggested that some previously well-established poor prognostic factors such as the degree of leukocytosis and central nervous system (CNS) or testicular involvement were less important with this dose-intensive regimen. However, patients with mediastinal disease had lower CR rates ($P < 0.05$), with the presence of hepatomegaly and $t(9;22)$ abnormalities had poor survival ($P < 0.05$). Compared with other established adult ALL regimens, Hyper-CVAD regimen was associated with significantly better CR rates, overall survival and EFS rates. The long-term follow-up results of Hyper-CVAD were favorable.

Keywords: Hyper-CVAD regimen; Acute lymphocytic leukemia; Treatment; Remission

1. Introduction

With modern intensive chemotherapy regimens, prognosis in childhood acute lymphocytic leukemia (ALL) has improved significantly, where complete remission (CR) rates exceed 90% and cure rates are approximately 80%. Adult ALL therapy has been modeled after pediatric regimens, but the results have been more modest. With current regimens analogous to those in childhood ALL, CR rates are approximately 75% and long-term disease-free survival (DFS) rates only about 20–35% [1–4]. Prognosis is associated with host and disease characteristics including age, performance status, degree of leukocytosis, leukemic-cell immunophenotype and karyotype, the rapidity of leukemic-cell clearance and achievement of CR [5,6]. Patients are divided by these features into low-risk, standard-risk and high-risk. Patients with low-risk or standard-risk are expected long-term DFS rates more than 30–50%, but only 20% or less in patients with high-risk.

Murphy et al. [7] designed a short-term, dose-intensive and dose-dense Hyper-CVAD regimen. It consisted of alternating A cycles (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) and B cycles (high dose methotrexate and cytarabine). The therapy was developed for childhood Burkitt's lymphoma, and was effective in ALL and aggressive non-Hodgkin lymphomas (NHL), which with increased CR rates and DFS rates [8–16]. But such regimen had induced significant myelosuppression-associated morbidity and mortality. Granulocyte colony-stimulating

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factor (G-CSF) was effective in supportive care in chemotherapy, reducing the incidence and severity of neutropenia, febrile neutropenia and preventing treatment delays or dose reduction. In this report we summarized the results of Hyper-CVAD regimen as front-line therapy for 53 Chinese patients with ALL.

2. Patients and methods

2.1. Patients

Fifty-three consecutive adult patients with newly diagnosed ALL were entered into this retrospective study between June 2002 and October 2006. Eligibility criteria were as follows (1) age at least 15 years and (2) absence of other active malignancy and expected consequent death within 12 months. No exclusions were made because of performance status; cardiac, hepatic, or renal function; or concomitant active infection. ALL was diagnosed based on bone marrow morphology, immunophenotype, and karyotype. Pretreatment evaluation included history and physical examination; complete blood counts and differential; serum chemistries, including liver and renal function; bone marrow aspiration for morphologic analysis and staining; cytogenetic analysis; and immunophenotyping.

2.2. Therapy

Hyper-CVAD regimen comprised A cycles and B cycles [14]. Patients received the dose-intensive chemotherapy for six to eight cycles, A cycles (courses 1, 3, 5, and 7) alternating with B cycles (courses 2, 4, 6, and 8), with maintenance therapy. The alternating courses were given every 3–4 weeks or earlier if count recovery occurred (at least 14 days apart).

2.2.1. A cycles

Cyclophosphamide 300 mg/m^2 intravenously (IV) over 3 h every 12 h for six doses on days 1 through 3, with mesna 600 mg/m^2 daily continuous infusion starting with cyclophosphamide and ending 12 h after the last dose; vincristine 2 mg IV on days 4 and 11; doxorubicin 50 mg/m^2 IV over 24 h on day 4; and dexamethasone 40 mg daily on days 1 through 4 and 11 through 14.

2.2.2. B cycles

Methotrexate (MTX) 200 mg/m^2 IV over 2 h followed by 800 mg/m^2 IV over 24 h on day 1; calcium leucovorin was given at a dose of 50 mg intravenously starting 12 h after the completion of MTX and continued at a dose of 15 mg IV every 6 h for eight doses; cytarabine 3 g/m^2 (1 g/m^2 in patients aged 60 or older) over 2 h every 12 h on days 2 and 3.

2.2.3. Guidelines for dose adjustment [14]

Standard dose reductions were as follows: (1) cytarabine was reduced to 1 g/m^2 for age older than 60 years, creatinine level greater than 2 mg/dL; (2) Vincristine was reduced to 1 mg if the total bilirubin level was greater than 2 g/dL; (3) Doxorubicin dose was reduced by 25% if the bilirubin level was 2–3 g/dL, by 50% if it was 3–4 g/dL, and by 75% if it was greater than 4 g/dL; (4) MTX dose was reduced by 25% when creatinine levels were 1.5–2 mg/dL and by 50% when levels were higher.

2.2.4. CNS prophylaxis

Patients were categorized according to their expected risk of central nervous system (CNS) disease, based on a previous multivariate analysis for prognostic factors for CNS leukemia. Patients were considered at high-risk for CNS disease if the lactate dehydrogenase (LDH) level was greater than 600 U/L or the proliferative index (percent S + G_2M) was more than 14%, at low-risk if neither was elevated, or at unknown-risk if the measurements were not available [14]. Patients with mature B-cell ALL were included in the CNS high-risk category. CNS prophylaxis was given with MTX 15 mg/m^2 intrathecal therapy (IT) on day 2 and cytarabine 50 mg/m^2 IT on day 8 of each cycle for 16 IT treatments in high-risk patients, four IT treatments in low-risk patients, and eight IT treatments in unknown-risk patients. Patients at low-risk or unknown-risk for CNS disease received their four or eight IT treatments on days 2 and 8 of the first two or four cycles of therapy. If there was CNS involvement, IT therapy was augmented to three times weekly (including planned IT days 2 and 8 if course given) until cerebrospinal fluid (CSF) cell count normalized and cytology was negative for malignant cells. The program was then resumed for prophylaxis until completion of chemotherapy. No prophylactic cranial irradiation was administered.

2.2.5. Supportive care

Hematologic profiles were obtained at least biweekly during induction and consolidations. G-CSF was given starting 24 h after the end of chemotherapy (i.e., on day 5 of A cycles and day 4 of B cycles). The dose of G-CSF was decided according to the level of absolute neutrophil count (ANC), 5 μg/kg daily for the patients with ANC more than 1×10^9/L, and 10 μg/kg daily for less than 1×10^9/L. None of the patients were given antibiotic prophylaxis. Red blood cells transfusions were given for symptomatic and/or hemoglobin < 60 g/L, and platelet transfusions for platelets $\leq 10 \times 10^9$/L or if with hemorrhage.

2.2.6. Maintenance phase

The patients with L3 morphologic subtype who had *t*(8;14), *t*(2;8) or t(8;22) abnormalities (Burkitt's-type ALL) did not receive maintenance therapy. All the other patients received maintenance therapy with mercaptopurine (6-MP), MTX, vincristine, and prednisone for until 2 years. 6-MP was given 50 mg orally three times daily (on an empty stomach), MTX 20 mg/m^2 orally weekly, vincristine 2 mg IV monthly, and prednisone 200 mg daily ×5 monthly with vincristine.