Aberrant Expression of CD13 Identifies a Subgroup of Standard-Risk Adult Acute Lymphoblastic Leukemia With Inferior Survival

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Abstract

Acute lymphoblastic leukemia in adults (aALL) is divided into standard-risk (SR) and high-risk (HR) subgroups with different treatment algorithms. The SR-aALL subgroup contains many patients with short survival that should be treated as HR. The retrospective analysis of flow cytometric data of 81 patients with SR-aALL found that those with aberrant expression of CD13 had shorter survival, and such patients should be considered for more aggressive treatment.

Background: The standard-risk (SR) subgroup of acute lymphoblastic leukemia in adults (aALL) is a heterogeneous category, with a 20% to 40% relapse rate and a wide range of relapse-free survival (RFS) and overall survival (OS). There is a need to identify at the outset those patients with SR-aALL who are likely to have shorter RFS and OS, so they can be treated more aggressively. **Patients and Methods:** Flow cytometric data of 81 patients with SR-aALL treated with a standardized protocol were retrospectively analyzed. Thirty-two patients (40%) relapsed; the median RFS and OS were 12.5 months (range, 1-136 months) and 30 months (range, 3-235 months), respectively. Twenty-six patients survived $\geq$ 48 months. **Results:** Expression of myeloid antigen CD13, using the conventional $\geq$ 20% threshold and a lower $\geq$ 5% threshold, was seen in 17 (29%) of 59 and 29 (49%) of 59 patients, respectively, whereas dual expression of CD13 and CD33 was seen in 8 patients. CD13 positivity at $\geq$ 20% and $\geq$ 5% threshold was associated with a shorter RFS ($P = .0158$ and $P < .0001$, respectively) and OS ($P = .0072$ and $P < .0001$, respectively). Dual expression of CD13 (at $\geq$ 5% or $\geq$ 20% threshold) and CD33 was associated with inferior OS ($P = .0038$ and $P = .0032$, respectively) and RFS ($P = .0705$ and $P = .2516$, respectively). For $\geq$ 20% and $\geq$ 5% threshold of positivity, 16 of 42 and 28 of 42 who survived $<$ 48 months were positive, compared with 1 of 17 and 1 of 17 who survived $\geq$ 48 months ($P = .0133$ and $P < .0001$, respectively). **Conclusion:** Aberrant expression of CD13 in $\geq$ 5% of blasts of patients with SR-aALL is an adverse prognostic factor, delineating a subgroup of patients with SR-aALL that should be considered for more aggressive treatment.

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Introduction

Acute lymphoblastic leukemia in adults (aALL) is a heterogeneous disease, presenting with variable tumor load, exhibiting diverse genetic abnormalities, and showing variable response rates and survival. Proven prognostic factors[1] include age, sex,[2,3] white blood cell (WBC) count at presentation,[3-5] presence of central nervous system disease,[6] morphology,[7] cytogenetic profile,[8-10] molecular genetic profile,[11-16] immunophenotype,[17-32] response to the first cycle of induction chemotherapy,[3,33] and presence of minimal residual disease, assessed by molecular[16,34] or immunophenotypic techniques.[35] Of these, age, WBC count at presentation, cytogenetic profile, molecular genetic profile, immunophenotype, and response to initial chemotherapy continue to be significant prognostic factors, and variable combinations of these factors are used for risk stratification of patients with aALL,[3,4,36,37] who are typically divided into standard-risk (SR) and high-risk (HR) subgroups with different treatment algorithms.

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Immunophenotyping[17-32] is a proven prognostic factor in patients with aALL. Expression of CD34 has been associated with induction failure.[38] It has been correlated with superior overall survival (OS) and event-free survival (EFS) by some investigators[18] but not by others.[38] Adult patients with B-cell acute lymphoblastic leukemia (B-ALL) expressing CD10 have had superior disease-free survival.[20,23] In one study, patients with aALL expressing CD20 and presenting with high WBC count ($\geq 30 \times 10^9$ cells/L) had higher incidence of relapse and shorter EFS, but those with lower WBC counts ($< 30 \times 10^9$ cells/L) did not.[25] In another study,[28] CD20 expression was associated with shorter EFS and OS, irrespective of the WBC count, and was an independent factor in multivariate analysis. Expression of myeloid antigens CD13, CD33, or CD117 has been associated with inferior complete remission (CR) rate[17] and survival by some investigators[26,32,39] but not by others.[18,24,31] In adult patients with T-cell acute lymphoblastic leukemia (T-ALL), expression of CD13 or CD33 was associated with lower CR rate in univariate analysis but not in multivariate analysis, and there was no correlation with EFS.[26] Another study of adult patients with T-ALL found inferior CR rate using multivariate analysis in patients expressing CD33.[30] Patient cohorts studied in these publications included either patients with unstratified aALL or adult patients with T-ALL or B-ALL but not both.

Patients with HR-aALL are managed aggressively with chemotherapy and stem cell transplantation (SCT), whereas patients with SR-aALL are generally offered chemotherapy but no SCT. However, patients with SR-aALL are a heterogeneous group, with a 20% to 40% relapse rate,[40,41] and factors that could identify patients at risk of relapse would help in the planning of more aggressive therapies.

This study was a retrospective analysis of detailed immunophenotypic profile of patients with SR-aALL at a single institution who were treated with a standardized protocol. The study associated the immunophenotype with CR rate and survival.

Patients and Methods

Patients

All the patients with aALL diagnosed and treated between January 1989 and June 2010 at the Leukemia/Bone Marrow Transplant Program of British Columbia at the Vancouver General Hospital were included in the study. All patients followed an institution-specific protocol for initial and follow-up laboratory testing and multiagent chemotherapy (ALL89-1) with or without SCT. The initial laboratory testing included a complete blood count, bone marrow aspiration and biopsy for morphology, flow cytometric immunophenotyping complemented with immunohistochemistry as necessary, and genetic studies including conventional karyotyping, fluorescence in situ hybridization for *BCR/ABL* translocation, and molecular genetic studies for *BCR/ABL* fusion transcripts. The diagnosis of acute leukemia and its classification was based initially on the French-American-British system[42,43] and later on the World Health Organization scheme.[44,45] Those with incomplete data, those with reclassification of leukemia, and those who received nonstandard chemotherapy were excluded from the study. All the remaining patients were stratified into SR or HR groups as described,[4,36] with slight modification; the HR group had WBC counts $\geq 50 \times 10^9$ cells/L for B-ALL and $\geq 100 \times 10^9$ cells/L for T-ALL, or no CR after induction chemotherapy, or any of the following karyotypic abnormalities: t(9;22), t(1;19), t(4;11), or complex karyotype. The rest were stratified as SR. The SR group was further analyzed for association of clinical and laboratory features, immunophenotype, and survival.

Treatment

All the patients were treated with a consistent induction/consolidation/intensification and maintenance chemotherapy plan as per the hospital's in-house ALL-89 01 protocol. The induction regimen consisted of 2 phases. Phase I (days 1 to 28) consisted of daunorubicin 60 mg/m^2 intravenously (IV) on days 1, 2, and 3; vincristine 1.4 mg/m^2 (maximum dose, 2.0 mg) IV on days 1, 8, 15, and 22; L-asparaginase 10,000 units IV on days 17 to 28, and prednisone 60 mg/m^2/d in 2 divided doses orally (PO) on days 1 to 28. The L-asparaginase was deleted for patients older than 50 years and for those patients who were to receive SCT. Methotrexate 12 mg was given intrathecally as soon as platelets were $\geq 50 \times 10^9$ cells/L and no blasts were found on the blood film. Patients were evaluated for response on day 21 of phase I induction; those who achieved a complete morphologic remission proceeded to phase II induction. If persistent leukemia ($\geq$ 5% blasts) was present on the day 21 bone marrow, additional treatment was given with daunorubicin 60 mg/m^2 IV on days 22 and 23 and vincristine 1.4 mg/m^2 IV on days 28 and 35, and prednisone was continued at the same dose, 60 mg/m^2 PO daily, until day 42. Risk stratification as per the aforementioned criteria was completed by this time, and all patients with SR received further chemotherapy as detailed in the following paragraphs.

Phase II of the induction regimen began on day 29. It was postponed until WBC count $\geq 3.0 \times 10^9$ cells/L in patients with delayed hematologic recovery. It consisted of the following agents: cyclophosphamide 650 mg/m^2 IV on days 1, 14, and 28; cytarabine 75 mg/m^2 IV per day on days 1 to 4, 8 to 11, 15 to 18, and 22 to 25; 6-mercaptopurine 60 mg/m^2 PO on days 1 to 28; methotrexate 12mg intrathecally on days 1, 8, 15, and 22; leucovorin 5 mg PO on days 2 to 4, 9 to 11, 16 to 18, and 23 to 25. Patients who were not to receive allogeneic SCT would also receive cranial irradiation, 1800 cGy in 9 $\times$ 200-cGy fractions.

The consolidation regimen consisted of 5 phases. Phases I, II, IV, and V were identical and consisted of cytarabine 75 mg/m^2 IV on days 1 to 5 and teniposide 60 mg/m^2 IV on days 1 to 5. They were started 4 to 8 weeks after the previous phase or when the WBC count recovered to $\geq 3 \times 10^9$ cells/L. Phase III of the consolidation regimen was started 4 weeks after phase II or when the WBC count recovered to $\geq 3 \times 10^9$ cells/L. It consisted of intensification with dexamethasone 10 mg/m^2 PO on days 1 to 28; vincristine 1.5 mg/m^2 on days 1, 8, 15, and 22; daunorubicin 25 mg/m^2 on days 1, 8, 15, and 22; cyclophosphamide 650 mg/m^2 IV on day 29; cytarabine 75 mg/m^2 IV on days 31 to 34 and 38 to 41, and thioguanine 60 mg/m^2 PO on days 29 to 42.

Patients completing the 5 courses of consolidation proceeded to maintenance chemotherapy including 6-mercaptopurine 75 mg/m^2 PO per day and methotrexate 20 mg/m^2 PO once per week for a total of 2.5 years dated from completion of phase II induction. Doses were adjusted to maintain the absolute neutrophil count between 1.5 and 4.0 $\times 10^9$ cells/L.