The Value of High-Dose Systemic Chemotherapy and Intrathecal Therapy for Central Nervous System Prophylaxis in Different Risk Groups of Adult Acute Lymphoblastic Leukemia

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Although central nervous system (CNS) leukemic relapse is frequent in adult acute lymphocytic leukemia (ALL), the need for prophylaxis in different risk groups for CNS relapse, the value of high-dose systemic and intrathecal (IT) chemotherapy, and the timing of prophylaxis are not well defined. This analysis was conducted to investigate these questions and to assess the value of a risk-oriented CNS prophylaxis approach. We analyzed the incidence of CNS leukemia after initiation of therapy in patients treated on 4 consecutive trials for adult ALL including different CNS prophylactic modalities. The treatment groups included (1) the program preceding the vincristine-Adriamycin-dexamethasone (VAD) regimen, with no CNS prophylaxis; (2) the VAD regimen with prophylaxis using high-dose systemic chemotherapy; (3) the modified VAD program with high-dose systemic chemotherapy to all patients and IT chemotherapy for high-risk patients after achieving complete remission; and (4) the hyperCVAD program with early high-dose systemic and IT chemotherapy starting during induction to all patients, with more IT injections (16IT) administered to the high-risk group for CNS relapse compared with the low-risk group (4IT). A total of 391 patients were included, 73 of whom were treated with preVAD, 112 with VAD, 114 with modified VAD, and 92 with hyperCVAD. The overall CNS relapse rates were 31%, 18%, 17%, and 3%, respectively for the 4 groups (P < .001). For the high-risk group for CNS relapse, they were 42%, 26%, 20%, and 2%, respectively (P < .001). The differences in CNS relapse rates in the low-risk group were not statistically significant. At 3 years, the overall CNS leukemia event-free rates were 48%, 76%, 76%, and 98%, respectively (P < .001); in the high-risk group, the CNS event-free rates were 38%, 66%, 75%, and 98%, respectively (P < .001); however, there was no difference in the low-risk group. We conclude that (1) high-dose systemic chemotherapy is a useful prophylactic measure; (2) early IT chemotherapy is necessary to reduce the incidence of CNS leukemia overall and in the high-risk group; and (3) a risk-oriented approach is appropriate to tailor the intensity of CNS prophylaxis.

To investigate the value of different CNS prophylactic approaches for CNS relapse in adult ALL, we reviewed our experience using different alternatives in consecutive ALL treatment programs and assessed the use of a risk-oriented approach to guide the need and intensity of CNS prophylaxis.

PATIENTS AND METHODS

Study group. Since 1979, 391 consecutive patients with newly diagnosed, untreated ALL referred to the M.D. Anderson Cancer Center have been treated with 4 consecutive treatment protocols. To be eligible for these protocols, patients had to be older than 15 years of age and have a confirmed diagnosis of ALL, as previously described. There were no other exclusion criteria. Informed consent was obtained according to institutional guidelines.

Therapy. The treatment protocols were as follows. ADOAP-OAP/AMSAL-OAP (referred as preVAD). From 1979 to 1982, 73 patients received induction with 55 mg/m^2 adriamycin on day 1, 90 mg/m^2/day ara-C by continuous infusion (CI) for 7 days, 2 mg vincristine on day 1, and 100 mg/d prednisone for 5 days (ADOAP) or 30 mg/m^2/day amrubicin for 7 days, 70 mg/m^2/day ara-C CI for 7 days, 2 mg vincristine on day 1, and 100 mg/d prednisone for 5 days (AMSAL-OAP). Patients achieving a complete remission (CR) then received 3 consolidation courses with the same...
agents, followed by maintenance either with a sequence of 3 cycles of IVADOP, 3 cycles of OAP, and 3 cycles of prednisone, vincristine, methotrexate, and 6-mercaptopurine (POMP) or with 9 courses of AMSA-OAP followed by 3 courses of POMP. No specific CNS prophylaxis was used. The program has been previously detailed.27

VAD.26 From 1982 to 1988, 112 patients were treated with this regimen. Induction consisted of VAD (0.4 mg/d vincristine for 4 days, 12 mg/m²/d adriamycin for 4 days, and 40 mg/d/m² dexamethasone for 4 days on days 1 through 4, 9 through 12, and 17 through 20), followed by a second course with the same drugs with the addition of 1 g/m² cyclophosphamide on day 1 (C-VAD). This was followed by four weekly courses of 40 to 160 mg/m² methotrexate on day 1 and 20,000 U/L asparaginase on day 2. Patients then received intensification with adriamycin (60 mg/m² on day 1) and high-dose ara-C (3 g/m² every 12 hours for 6 doses), followed by three courses of M-DOMP (400 mg/m² methotrexate on day 1, with escalation in consecutive courses to up to 1,600 mg/m², if tolerated, 60 mg/m²/d adriamycin on day 15, 2 mg vincristine on day 15, 75 mg/m² 6-mercaptopurine administered orally on days 15 through 19, and 120 mg prednisone administered orally on days 15 through 19). Patients then received late intensification with AdOAP (20 mg/m² adriamycin administered intravenously [IV] on day 1, 2 mg vincristine on day 1, 30 mg/m²/d ara-C I.V for 7 days, and 100 mg/d prednisone for 5 days). Patients younger than 50 years of age received instead CBV (1.5 g/m²/d cyclophosphamide on days 1 through 4, 300 mg/m² BCNU on day 1, 250 mg/m²/d VP-16 for 3 days), followed by autologous bone marrow infusion. After intensification with AdOAP or CBV, patients received three more courses of M-DOMP. The whole cycle was then repeated two more times to complete the protocol, with the exception of the CBV/autologous bone marrow transplant part. CNS prophylaxis consisted of high-dose systemic chemotherapy (ara-C and methotrexate) for all patients, as outlined above. The detailed regimen has been previously published.26

Modified VAD.26 This study included 114 patients from 1988 through 1992. Induction chemotherapy included two courses of C-VAD, followed by consolidation with methotrexate and L-asparaginase, as with the VAD program. Early intensification with adriamycin and high-dose ara-C was also similar but included 100 mg/d solumedrol for 5 days. This was followed by 2 additional courses of CVAD and maintenance with interferon-alpha (IFN-alpha) 5 x 10⁶ IU/m²/d, 150 mg/d 6-mercaptopurine, and 20 mg/m²/d methotrexate for 3 months. The entire cycle was then repeated two more times. CNS prophylaxis included the high-dose systemic chemotherapy for all patients. In addition, high-risk patients received IT therapy starting at CR with 100 mg/wk ara-C for 8 doses, then every 2 weeks for 8 doses, and then monthly for 6 doses, for a total of 22 treatments.

Intensive short-term induction-consolidation therapy (hyper-CVAD).29 Ninety-two patients have been included in this ongoing study that started in 1992. Induction consists of 8 alternating cycles with (1) hyperCVAD (300 mg/m² cyclophosphamide every 12 hours for 6 doses on days 1 through 3, 2 mg vincristine on days 4 and 11, 50 mg/m² adriamycin on day 4, and 40 mg/d dexamethasone on days 4 through 4 and 11 through 14); and (2) 1 g/m² methotrexate over 24 hours on day 1 with citrovorum rescue and 3 g/m² ara-C every 12 hours for 4 doses. Treatment with 10 µg/kg granulocyte colony-stimulating factor (G-CSF) was started on day 4 of each cycle and was continued until recovery. Maintenance after the 8 courses was administered with 150 mg/d 6-mercaptopurine and 20 mg/m²/d methotrexate for 2 years. CNS prophylaxis consisted of high-dose systemic chemotherapy plus 12 mg methotrexate IT on day 2 and 100 mg ara-C IT on day 7 of every cycle. Patients at low risk received a total of 4 IT treatments, and those at high risk received 16 IT treatments.

Specific CNS prophylaxis therefore evolved from no prophylaxis (preVAD) to high-dose systemic chemotherapy for all patients (VAD); high-dose systemic chemotherapy plus, in those at high-risk for CNS relapse, IT chemotherapy after achieving CR (modified VAD); and high-dose systemic chemotherapy with early IT chemotherapy in all patients, with doses tailored according to risk (hyper-CVAD; Table 1). No patient received radiotherapy for CNS prophylaxis.

Risk categories. The risk of CNS recurrence was estimated as previously described.30 Patients with high risk for CNS relapse included those with (1) high serum lactic dehydrogenase levels (LDH, >600 U/L); normal, 166 to 225 U/L) or (2) high proliferative index (>14% cells in S + G2M compartment). Patients with none of these features were considered to be at low risk. All patients with mature B-cell ALL had at least one of these high-risk features. High-risk for systemic relapse was defined by (1) high white blood cell (WBC) counts (>5 x 10⁹/L), (2) Philadelphia-positive or B-cell ALL, or (3) more than one course to achieve CR.30

Definitions and endpoints. CR was defined at 5% or less blasts in a normocellular or hypercellular bone marrow, with normal peripheral counts and differential, including granulocyte count greater than 1,500/µL and a platelet count greater than 100 x 10⁹/µL, for at least 1 month. CNS relapse was defined as the presence of leukemic blasts in a cytospin preparation of cerebrospinal fluid or elevated and abnormal cerebrospinal fluid counts with CNS signs and symptoms. When blasts were present in the CSF together with high numbers of red blood cells, they were not considered to be representative of CNS disease if the patient had blasts in the peripheral blood. In the preVAD, VAD, and modified VAD protocols, all patients underwent a CSF examination at the time CR was achieved unless they had signs or symptoms of CNS disease requiring an earlier exam. In the hyperCVAD group, all patients underwent a CSF study on day 2 of therapy according to the treatment plan. Of the 6 patients with CNS disease at diagnosis as shown by CSF examination in this group, only 1 had symptoms of CNS disease. All patients with cranial nerve palsies had blasts present as shown by the CSF fluid examination.

The goal of the study was to define the impact of CNS prophylaxis in reducing the incidence of CNS leukemia. Therefore, patients with CNS disease at presentation were excluded from this analysis. All cases of CNS relapse, whether as the only site of relapse or concomi-
RESULTS

The CR rates of the four study groups were 64% for the preVAD group, 82% for the VAD group, 69% for the modified VAD, and 91% for the hyperCVAD. The 3 year event-free survival rates were 10%, 26%, 14%, and 48%, respectively. The number of patients at risk for CNS disease during each phase of the disease are shown in Table 2. Because the CR and event-free survival rates were greater in the hyperCVAD group, the proportion of patients at risk after achieving CR was significantly greater in this group. Of 391 patients included in the 4 treatment protocols, 17 (4%) had evidence of CNS leukemia at diagnosis and were therefore excluded from this analysis (1 preVAD, 5 VAD, 5 modified VAD, and 6 hyperCVAD). The characteristics of the evaluable patients are shown in Table 3. There is a trend towards a higher median age and a percentage of patients older than age 50 years in the latter studies. There was also a trend for a higher incidence of CNS disease in the hyperCVAD program.

Incidence of CNS disease. The incidence of CNS disease by prophylactic regimen is shown in Table 4. There has been a progressive reduction in the incidence of CNS leukemia during induction, in CR, concomitant with and after bone marrow relapse with consecutive regimens, with the highest incidence occurring in the preVAD regimen and the lowest incidence occurring in the hyperCVAD program. The most significant difference is seen in patients with CNS disease while in CR. Only 3 patients in the preVAD and 3 in the VAD groups had a CNS relapse after the bone marrow relapse (5 to 26 weeks after the bone marrow relapse) and none in the modified VAD or hyperCVAD groups had a CNS relapse after the bone marrow relapse.

Because the duration of follow-up has been different for the protocols analyzed, the greater incidence of CNS leukemia in the earlier patients could reflect only a more prolonged time at risk. Therefore, we calculated the event-free survival by regimen at equal follow-up times. The first comparison was between patients not receiving CNS prophylaxis (preVAD) and those receiving high-dose systemic chemotherapy as the only prophylactic intervention equal to all risk groups (VAD). This intervention increased the overall 5-year CNS event-free rate from 42% in the former to 75% in the later (P = .005). The improvement was significant in the high-risk group but marginal in the low-risk group. In the high-risk population, the 5-year CNS event-free rate was 28% in the preVAD and 67% in the VAD groups (P = .02), whereas in the low-risk group, the figures were 65% and 85%, respectively (P = .05).

When differential prophylaxis was introduced according to risk for CNS relapse as in the modified VAD regimen, the overall 5-year CNS event-free rate was again significantly better than with no prophylaxis (73% v 75% with VAD and 42% with preVAD, P = .005; Fig 1A). However,
the high-risk group benefited significantly more than did the low-risk group. In the high-risk population, the 5-year CNS event-free rate was 70%, compared with 67% for VAD and 28% for preVAD (P < .001; Fig 1B). In contrast, there was no significant difference in the low-risk patients (70%, 85%, and 65%, respectively; P = .13; Fig 1C). This finding suggested that IT therapy starting at CR added little benefit to reduction of CNS leukemia among high-risk patients.

When CNS prophylaxis was implemented with induction therapy (hyperCVAD) and tailored to the risk group, further improvement was shown. The overall 3-year CNS event-free rate improved to 92%, which was significantly better
than that for the previous regimens \((P < .001; \text{Fig 1A})\). This was again due to a major benefit among high-risk patients, whose rate improved to 98% \((P < .001; \text{Fig 1B})\). For the low-risk group, no statistically significant benefit could be documented \((3\text{-year CNS event-free rate, 78%; } P = .24; \text{Fig 1C})\). Patients in the earlier protocols have been observed for a longer time. However, among all patients in the three earlier groups, there has been only one CNS event after 36 months, which was in a patient in the preVAD group. When the 6 patients with CNS disease after bone marrow relapse were excluded from the analysis, the results were similar (data not shown). The CNS leukemia-free survival at 3 years for the high-risk group were 33%, 70%, 70%, and 98% \((P = .04)\).

Outcome of patients after CNS disease. Patients who developed CNS disease after the start of therapy had a poor prognosis. Their median survival periods were as follows: for the preVAD group, 50 weeks \((\text{range, 5 to 372 weeks})\); for the VAD group, 61 weeks \((\text{range, 14 to 468+ weeks})\); for the modified VAD, 82 weeks \((\text{range, 7 to 224 weeks})\); and for hyperCVAD, 33 weeks \((\text{range, 5 to 141+ weeks})\). The 3-year survival rates were 13%, 25%, 10%, and 32%, respectively \((P = .855)\).

DISCUSSION

Our study is one of few addressing the need, nature, and extent of CNS prophylaxis in adult ALL. It is also the only one to implement a risk-oriented CNS prophylactic approach.

The first question is whether CNS prophylaxis is needed in adults with ALL. This question was answered by the study of Omura et al.,\(^7\) which randomized 62 adult patients with ALL who achieved CR after induction chemotherapy to receive no CNS prophylaxis \((n = 34)\) or to receive cranial irradiation and IT methotrexate \((n = 28)\). The 3-year CNS-relapse rate was 45% and 20%, respectively \((P < .01)\), but this did not result in improved survival.

In our analysis, we further refined this knowledge. The first study group analyzed in the current report treated with preVAD had the highest incidence of CNS leukemia, whereas the other groups with different modalities of prophylaxis had marked reductions in the incidence, confirming the need for CNS prophylaxis.

The value of high-dose systemic chemotherapy was confirmed in the comparison of preVAD to VAD. Systemic high-dose chemotherapy reduced the overall incidence of CNS leukemia from 31% in the preVAD to 19% in the VAD regimen. IT chemotherapy starting at CR did not substantially reduce the occurrence of CNS relapse among high-risk patients, as suggested by the comparison of VAD and modified VAD. The CNS even-free rate at 3 years was increased from 67% to 75%. When CNS prophylaxis \((\text{IT} + \text{HD chemotherapy})\) was implemented early with induction therapy, the incidence decreased to only 2% \((P < .001)\). Therefore, CNS prophylaxis starting with induction chemotherapy is beneficial for high-risk patients. However, the difference may be explained, at least partially, by the different intensity of the systemic chemotherapy. Cranial radiotherapy was not used in any of our studies, except for radiation to the base of the skull for patients with cranial nerve involvement.

The best timing for CNS prophylaxis is controversial. Omura et al.\(^7\) introduced prophylaxis after patients achieved CR. However, others have suggested that earlier intervention is needed.\(^33\) In our analysis, patients in the VAD and modified VAD regimens received prophylaxis \((\text{high-dose systemic chemotherapy or IT chemotherapy})\) after achieving CR and little benefit was derived in high-risk patients. The hyperCVAD introduced IT chemotherapy early in the induction course. This early intervention appears to be most effective, because the incidence of CNS leukemia, both overall and in the high-risk population, was lowest in the hyperCVAD regimen \((3\% \text{ and } 2\%, \text{respectively})\). Moreover, evidence of CNS leukemia appearing early during induction chemotherapy was almost eliminated with this approach (Table 4). Consequently, it is reasonable to recommend initiation of prophylaxis early during induction chemotherapy. One potential disadvantage is the conunination of CSF with peripheral blood and blasts, which may confuse the interpretation of the results.

Because of the toxicity of CNS prophylaxis, it is desirable to identify those patients who would benefit most from this therapy and minimize the exposure to those at lower risk. Several risk factors have been identified to be associated with CNS relapse in children, including high WBC counts, T-cell or B-cell disease, young age, thrombocytopenia, lymphadenopathy, hepatomegaly, or splenomegaly.\(^34-36\) In adults, a multivariate analysis identified \((1)\) high serum LDH levels and \((2)\) high proliferative index \((\text{ie, } S + G2M compartment \geq 14\%)\) as the most significant factors to predict for CNS leukemia.\(^30\) Patients without any of these features had a 4% incidence of CNS leukemia at 1 year compared with 13% to 29% for those with one of these features and 56% for patients with both features.\(^30\) In our present analysis, two therapeutic modalities had a risk-oriented approach following this model: the modified VAD program, which used IT chemotherapy only among high-risk patients, and the hyperCVAD program, which included IT chemotherapy for both low- and high-risk patients but for only 4 doses in the former and 16 in the latter. This approach proved useful, because the incidence of CNS leukemia decreased most significantly in the high-risk group to 20% and 2%, respectively, which compares favorably to that in low-risk patients. The two programs with no differentiation between low- and high-risk prophylaxis \((\text{preVAD and VAD})\) had significantly higher incidence in the high-risk group. The fact that there has been no statistically significant improvement with more aggressive prophylaxis in the low-risk group is probably due to an already low incidence without prophylaxis that would require a larger population to document small changes in incidence.

Our studies have shown the leukemic cell proliferative index to be a significant factor predictive for risk of CNS disease. By itself, it identifies 11% of patients with CNS disease \((\text{ie, with a normal LDH level})\). However, because of the limited availability of this measurement, we are currently...
working on the development of an alternate predictive model for risk of CNS disease in which this measurement is not included.

We conclude that the use of CNS prophylaxis can decrease the incidence of CNS leukemia in adult patients with ALL. Although high-dose systemic chemotherapy was effective in reducing the incidence of CNS leukemia, IT chemotherapy added to the benefit and should probably be included early during remission induction. Finally, the use of a risk-oriented approach may be useful to guide the intensity of CNS prophylaxis.

REFERENCES

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