Current Approaches to Therapy for Childhood Lymphoblastic Leukemia: St. Jude Studies XI (1984–1988) and XII (1988)*

G. K. Rivera [1], D. K. Kalwinsky [1], J. Rodman [2], L. Kun [3], J. Mirro [1], Ching-Hon Pui [1], M. Abromowitch [1], J. Ochs [1], W. Furman [1], V. M. Santana [1], O. H. Hustu [3], J. Sandlund [1], and W. M. Crist [1]

A. Introduction

During the past decade, evidence from clinical trials for children with acute lymphoid leukemia (ALL) indicates that improved end results can be obtained by use of intensified early therapy [1–5]. Such improvement has been especially apparent for children judged to be at higher risk of relapse based on prognostic factor analysis. Risk assessment based upon the clinical features of patients at diagnosis (e.g., age, WBC count, and race) and the biologic features of their leukemic blast cells (e.g., immunophenotype and karyotype) has made it possible to modify therapy in rational ways. Additionally, alternative methods of irradiation for the treatment of preclinical CNS leukemia have been shown to be highly effective for children with non-B-cell ALL. Newer approaches to effective CNS prophylaxis include use of so-called, triple intrathecal (IT) chemotherapy [methotrexate (MTX), hydrocortisone, cytosine arabinoside (ara-C)] given early and throughout one or more years of treatment [6].

In the St. Jude Total XI study (1984–1988), intensive early treatment with seven agents is being used for remission induction; this phase of therapy is followed by consolidation with high-dose MTX. During continuation treatment, we are evaluating the use of pairs of effective antileukemic drugs alternated either weekly or every 6 weeks throughout the entire duration of therapy (120 weeks). The risk of relapse is assessed by a new system based on prognostic factor analysis of data obtained in the Total X study [7]. Age, WBC count, race, DNA index, and chromosome translocation were most predictive of relapse in our Total X Study [7] and, therefore, are being used to determine risk status in the Total XI study. A summary of the efficacy and toxicity of early therapy in the Total XI trial, and plans for our next study (Total XII), form the basis of this report.

B. Patients and Methods

Between March 1984 and May 1988, we treated 332 consecutive children with non-B-cell ALL according to the Total XI protocol. The diagnosis of ALL is based on morphologic evaluation of Wright-stained smears of bone marrow and negative marrow myeloperoxidase preparations (<3% positive blasts). CNS disease is defined as greater than five mononuclear cells/mm^3 on a CSF cell count and blasts seen on a cytospin preparation. Complete remission is defined as <5% marrow blasts and signs of recovery of normal hematopoiesis. Detailed immonologic marker studies including surface immunoglobulin (SIg) evaluation are performed on all cases to rule out B-cell ALL and to define other major

[1] Department of Hematology/Oncology*, [2] Pharmaceutical Division, and [3]Department of Radiation Oncology, St. Jude Children's Research Hospital; and the Departments of Pediatrics and Radiation Oncology, University of Tennessee, Memphis, College of Medicine, Memphis, Tennessee 38105, USA

* Supported by National Cancer Institute grants CA-21765 and CA-20180, and by the American Lebanese Syrian Associated Charities (ALSAC).

Table 1. Criteria for risk assignment in Total Therapy Study XI

Factor	Adverse feature	Estimated relative risk[a]
DNA index[b]	≤ 1.15	4.7
Race	Black	2.5
Chromosomal translocation	Present	2.2
Leukocyte count	$\geq 25 \times 10^9$/liter	1.9
Age	≤ 2 or ≥ 10 years	1.8

[a] Probability of relapse, at any time, in a child with a "worse" feature compared with that in a patient having the complementary feature

[b] Ratio of the modal DNA content of G_0/G_1-phase tumor versus normal cells

immunophenotypes (T, pre-B and common). All surface Ig-negative cases are included herein and detailed results of the immunologic studies will be summarized in a separate report. Flow cytometry to establish the ratio of the DNA content of leukemic versus normal cells (DNA index) and cytogenetic studies to determine the leukemic cell karyotype are successful in over 95% of cases. Results of these studies will be described separately.

The clinical and biologic features that determine risk assignment are shown in Table 1, together with the estimated relative risk of treatment failure for each factor, as determined by Cox regression model analysis of data from 431 patients treated from 1979 to 1983 in our preceding Total X study. We recently published two reports summarizing the results of Total X, including details of the risk model noted above and end results at a median follow-up time of 4 years [1, 7]. The five factors noted in Table 1 were most predictive of outcome in Total X and therefore were used for risk assignment in Total XI. The presence of any two of these features resulted in a worse-risk assignment; a WBC count of over 100×10^9/liter was sufficient by itself to confer a worse risk classification.

The details of therapy including drug schedule, dosage, and duration of administration are shown in Figs. 1 and 2. In brief, seven highly effective agents are used for induction treatment, given over 8 weeks; CNS prophylaxis with IT chemotherapy is started early in this phase of treatment. High-dose MTX (2 g/m^2 given intravenously over 2 h with 6 h of hydration and urinary alkalinization) is begun on day 43 and is repeated 1 week later. Leucovorin rescue is given at a dose of 30 mg/m^2 at 32, 44, and 48 h, followed by 5 mg/m^2 at 56 and 68 h. These doses are intended to achieve total reduced folate serum concentrations above MTX concentrations at 44 h and equimolar levels until MTX concentrations are less than 0.05 μmol/liter.

Three regimens were employed as continuation therapy. One-third of the better-risk patients receive conventional continuation treatment 1 (6-MP, MTX, vincristine, and prednisone) and two-thirds receive treatment 2, which is experimental and consists of drug pairs rotated weekly as shown in Fig. 2. Worse-risk patients are randomized unequally between experimental treatment 2 (two-thirds) and experimental treatment 3 (one-third). Relatively non-cross-resistant effective drug pairs with different toxicities are used and rotated either weekly (treatment 2) or every 6 weeks (treatment 3); this allows us to evaluate the effect of rapid versus slower rotation of drug pairs. Both treatments use the same drug pairs administered at identical doses. Further, this intensive continuation therapy is continued for the entire length of treatment rather than only during early therapy. Continuation therapy given is based on the patient's absolute phagocyte count (absolute number of

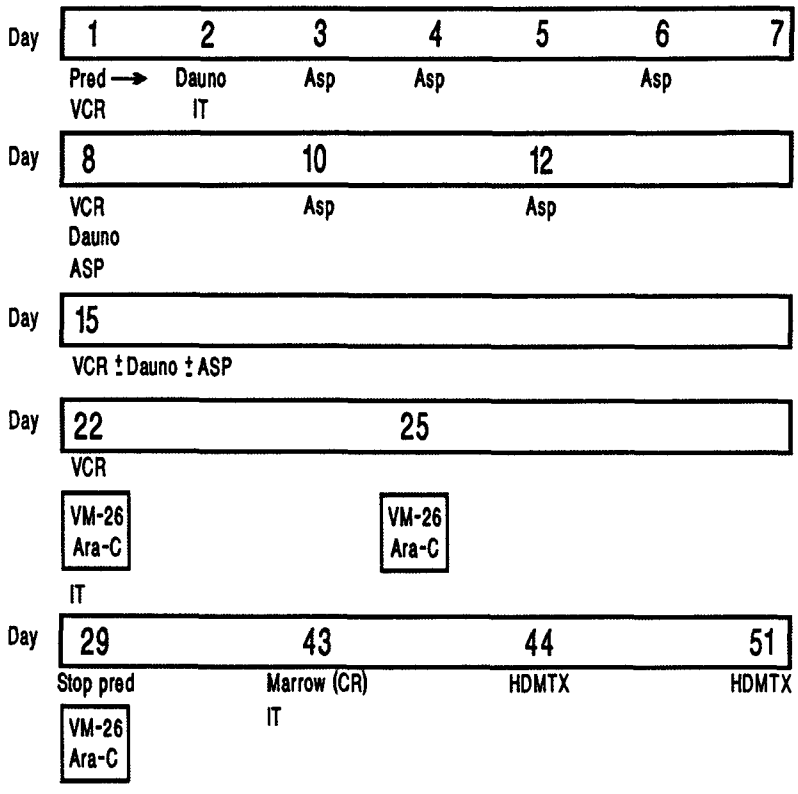

Fig. 1. Schema of early therapy, St. Jude Total Therapy Study XI. The induction phase continues until day 43; the remainder of therapy is considered a consolidation phase. *Pred*, prednisone (40 mg/m^2/day); *VCR*, vincristine (1.5 mg/m^2/week); *Dauno*, daunomycin (25 mg/m^2/week); *Asp*, L-asparaginase (10 000 U/m^2/dose i.m.); *VM-26*, teniposide (200 mg/m^2); *ara-C*, cytarabine (300 mg/m^2/dose), *IT*, intrathecal methotrexate (12 mg), hydrocortisone (24 mg), and ara-C (36 mg) (dosages of IT chemotherapy adjusted for children less than 3 years of age). *HDMTX*, high-dose methotrexate (2 g/m^2/dose) with leucovorin rescue

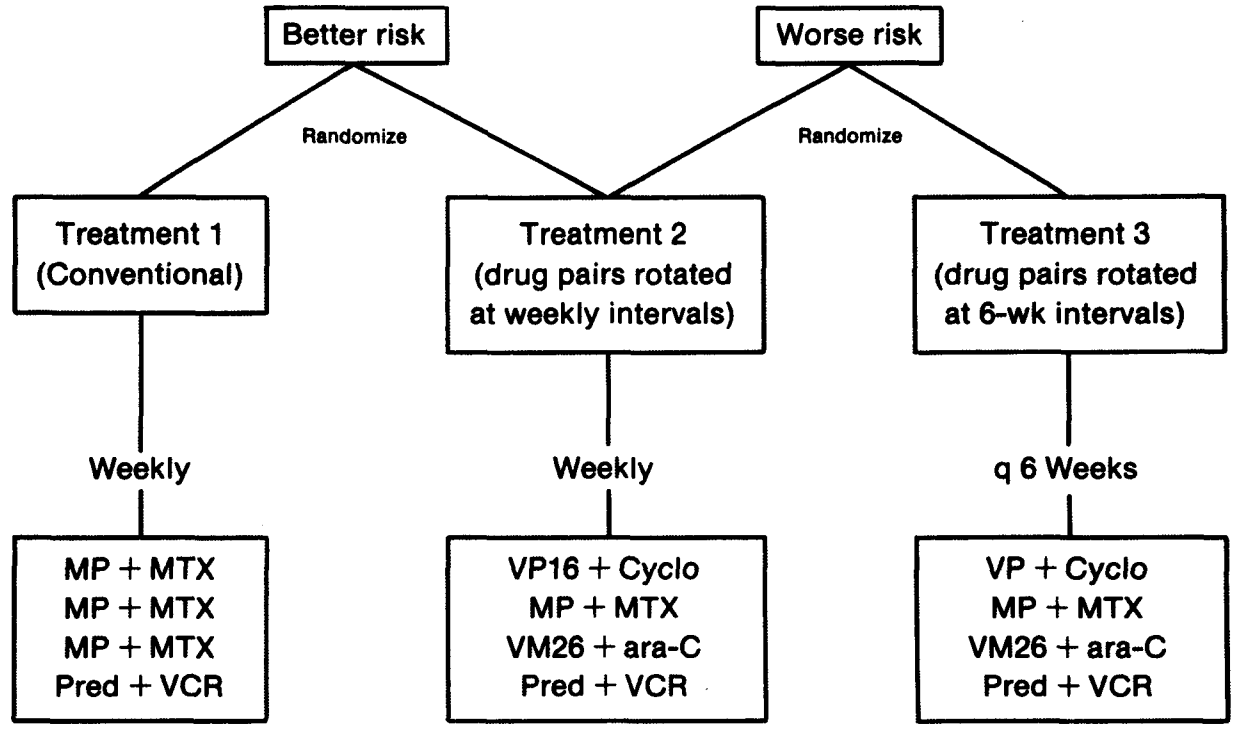

Fig. 2. Schema of continuation therapy, St. Jude Total Therapy Study XI. Dosage schedule and routes of administration; VP-16 (300 mg/m^2 i.v., once a week); cyclophosphamide (*CTX* 300 mg/m^2 i.v., once a week), Mercaptopurine (MP) (75 mg/m^2 p.o. daily $\times 7$), MTX (40 mg/m^2 i.m., once a week), VM-26 (150 mg/m^2 i.v., once a week), ara-C (300 mg/m^2 i.v., once a week), prednisone (40 mg/m^2 p.o. daily $\times 7$), VCR (1.5 mg/m^2 i.v., once a week)

early myeloid forms and segmented neutrophils plus monocytes). Full doses of chemotherapy are given if the absolute phagocyte count level exceeds 0.5×10^9/liter; otherwise doses are skipped and not delayed.

Central nervous system prophylaxis is continued for 1 year based on available data from studies of the Pediatric Oncology Group (ALinC 11, 12, 13), which suggest that such therapy is effective, especially for better-risk patients [6, 8]. Patients with CNS leukemia at diagnosis or those at worse risk also receive delayed cranial irradiation (2400 or 1800 cGy, respectively) after 1 year of remission. The results are sequentially analyzed and appropriate stopping rules are incorporated to avoid continuing the study unnecessarily.

C. Results

I. Patient Accrual and Risk Distribution

As of 1 May 1988, 335 patients had been enrolled in the Total XI study. Only three of these children were not evaluable (one refused therapy, two had incorrect diagnoses). Of 332 evaluable children, 107 (32%) were considered standard risk and 225 (68%) worse risk. Thirteen percent of the patients are black and 3.0% are infants (≤ 1 year of age). Twenty-five percent are over 10 years of age, but under 18 years. Seventeen percent have a WBC count greater than 100×10^9/liter. The proportion of worse-risk patients is much higher than we had anticipated largely due to an increased number of patients with chromosomal translocations, as compared with results in the Total X study. This circumstance resulted primarily from improvements in our cytogenetic techniques during the Total X study which led to better detection of subtle translocations in Total XI.

Ninety-seven percent (321/332) of our patients had successful immunologic marker studies and DNA indices performed on leukemic blast cells. Banded karyotypes were available for over 90% of the patients.

The toxicity encountered during the induction phase of therapy is summarized in Table 2. It can be seen that the major problems encountered were infectious in nature and developed during periods of neutropenia. A relatively increased rate of seizures noted early in the

Table 2. Toxic effects during induction therapy

No. of patients	335
No. evaluable	332
% receiving all planned treatment	85
Median No. (range) of inpatient days	10 (0–57)
% Patients with:	
VCR-induced toxicity	42
Asp-induced toxicity	22
VM-26-induced toxicity	4
Fever	75
Infections	51
Seizures	5
Early death	2
Median no. (range) of days when:	
APC $<0.5 \times 10^9$/liter	23 (0–56)
APC $<0.1 \times 10^9$/liter	8 (0–50)
Median No. of days to recover	
APC $>0.5 \times 10^9$/liter	40

VCR, vincristine; Asp, L-asparaginase; VM-26, teniposide; APC, absolute phagocyte count

course of Total XI was largely corrected by changing the schedule of intrathecal therapy during induction treatment.

II. Early Results of Therapy

The complete remission (CR) rate for all patients is 96% (318/332). Of the 318 patients attaining CR, 106 (99%) of 107 better-risk patients and 212 (94%)/225 worse-risk patients achieved CR. Of the 14 patients who did not attain initial remission (early failures), 6 had primary drug resistance and 8 died of chemotherapy-related toxicity. Since we revised the induction phase of chemotherapy, the tolerance to treatment has improved and, in fact, one-third of children receive the early phase of therapy as outpatients. Ninety-seven percent of the planned doses of induction treatment have been given and 85% of patients received all planned therapy (Table 2). Ninety-six percent of children have received the two courses of high-dose MTX consolidation in the "day hospital" setting.

Three hundred and eight patients have been randomized to receive continuation therapy as follows: better risk, treatment 1 ($n=37$); better risk, treatment 2 ($n=61$); worse risk, treatment 2 ($n=139$); worse risk, treatment 3 ($n=71$). Three patients were not randomized and received other therapies after CR induction. The tolerance to continuation treatment for each of the randomized treatment regimens has been excellent and most treatment is delivered in the outpatient setting. It is too early to report the durations of remission on the three treatment regimens of Study XI (the median follow-up time is only 2 years). However, event-free survival (EFS) is estimated to be significantly better than the result obtained in Total Therapy Study X.

D. Comments

These results indicate that a high remission induction rate (96%) can be obtained without undue toxicity in children with non-B ALL using a seven-drug induction regimen that features early administration of VM-26 and ara-C (at days 22, 25, and 26) and high-dose MTX (at days 44 and 51). The rationale for this treatment is that very early use of multiple effective agents may eradicate larger numbers of leukemic cells before the emergence of drug resistance, yielding improved end results with acceptable toxicity. Another notable feature of the Total XI treatment is use of intensification therapy, not only early but sustained throughout 120 weeks of continuation treatment. It is also of interest that CNS prophylaxis for one-third of patients who have had a lower risk of relapse does not include irradiation and that cranial irradiation for worse-risk patients or those with CNS disease at diagnosis is delayed for 1 year, permitting better tolerance to systemic therapy and sparing patients who relapse early in the bone marrow from the toxic effects of irradiation. The isolated CNS relapse rate in Study XI is currently $<2\%$, and all continuation therapy has been administered in an outpatient setting. The toxicity has been modest in all phases of treatment. We are encouraged by the comparatively low relapse rate in this study; at the time of the most recent analysis, duration of event-free survival was superior to that seen in the preceding clinical trial, although follow-up times are too short for Study XI for statistically meaningful evaluation.

From experience in Total XI, combined with that in studies of patients with ALL in relapse, we believe that the epidophyllotoxins VM-26 and VP-16 warrant further evaluation in clinical trials for children with newly diagnosed ALL. Information demonstrating that high-dose MTX may be more effective if systemic exposure is optimized [7, 9] indicates that such therapy may be especially effective for patients with better-risk ALL. Fixed dosing of each of these three agents results in a wide variation in systemic exposure among patients and

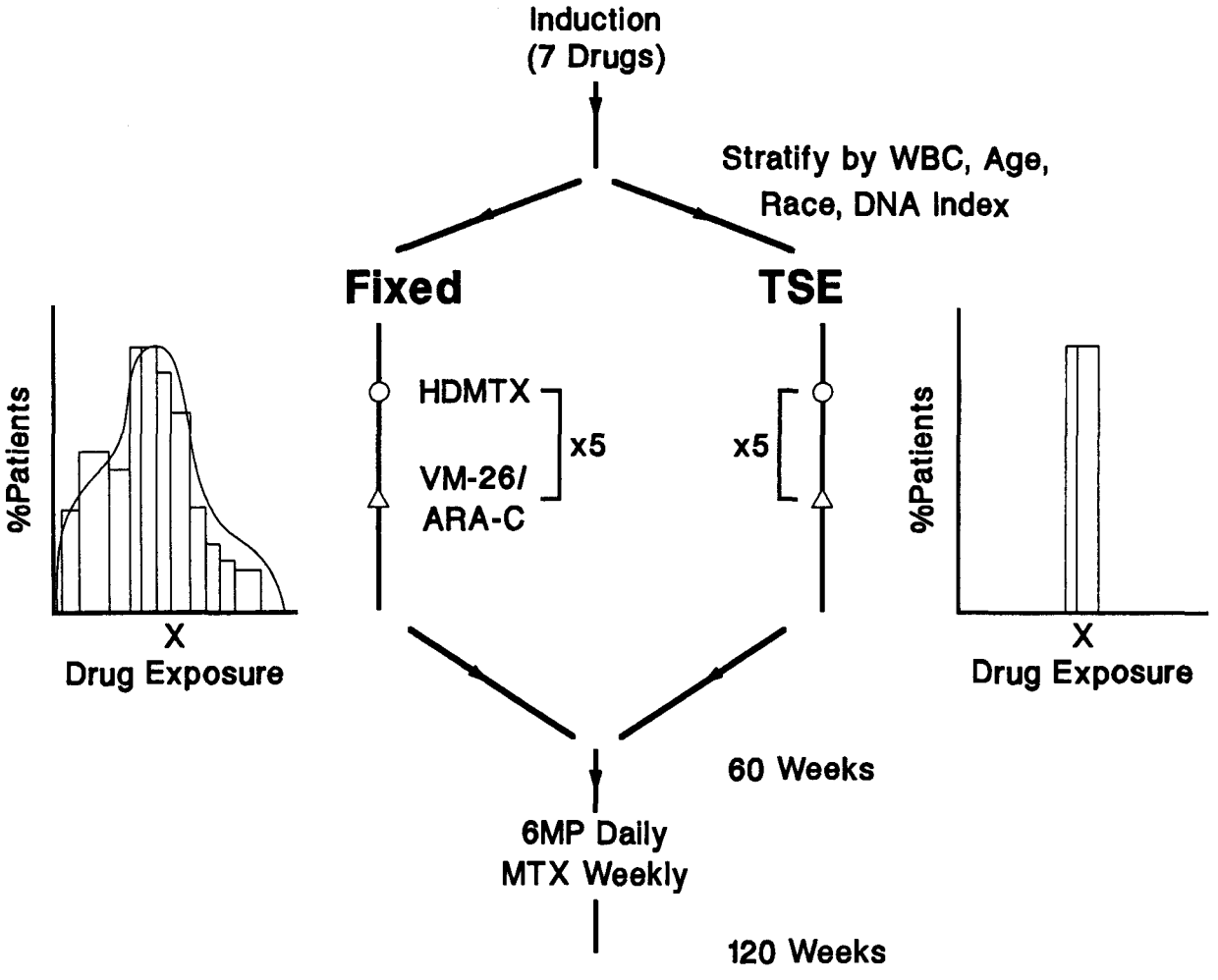

Fig. 3. Schema for planned Total XII study for children with non-B ALL showing general treatment plans and expected differences in systemic drug exposure between patient groups receiving fixed dosing versus those getting "modeled" drug delivery. *Fixed,* constant drug dosage; *TSE,* targeted systemic exposure

among successive courses administered to individual patients, and lower steady-state plasma drug concentrations may be associated with inferior treatment outcome [9, 10]. Our collective experience with the pharmacokinetic evaluation of each of these agents has permitted us to plan a study that will further test the potential of pharmacokinetically modeled therapy for improving the clinical outcome of children with non-B-cell ALL.

Therefore, in our Total XII study (Fig. 3), we will evaluate the impact of "modeled" administration of VM-26, ara-C, and high-dose MTX to maintain a narrow range of predetermined systemic exposure within one group of patients as compared with a fixed-dose approach in another group. Patients will be stratified by WBC count, age, race, and DNA index to assure prognostic uniformity of the groups being compared. Induction therapy will be given as in the Total XI study, and all biologic studies performed in Total XI will be repeated in Total XII. CNS prophylaxis will consist of periodic triple IT chemotherapy with CNS irradiation only in patients with high WBC levels. Periodic pulsed VM-26 and ara-C and high-dose MTX will be given to both groups using the aforementioned methods of drug administration, and 6-MP and IM MTX will be given between pulses during the first 60 weeks (Fig. 3). Thereafter, only the latter two drugs will be given (for 120 weeks). This research should provide data regarding the value of optimized systemic exposure to these effective agents as compared with the highly variable exposure seen with stan-

dard dosing. If significantly improved responses can be demonstrated in the former group, we will have obtained support for the concept that systemic exposure of leukemic cells to chemotherapy impacts favorably on cure rates in childhood ALL.

References

1. Dahl GV, Rivera GK, Look AT, Hustu HO, Kalwinsky DK, Abromowitch M, Mirro J, Ochs J, Murphy SB, Dodge RK, Pui C-H (1987) Teniposide plus cytarabine improves outcome in childhood acute lymphoblastic leukemia presenting with a leukocyte count $\geq 100 \times 10^9$/L. J Clin Oncol 5:1015–1021
2. Riehm H, Feickert H-J, Lampert F (1986) Acute lymphoblastic leukemia. In: Voute PA, Barrett A, Bloom J et al. (eds) UICC cancer in children: clinical management, 2nd edn. Springer, Berlin Heidelberg New York, pp 101–118
3. Steinherz PG, Gaynon P, Miller DR, Reaman G, Bleyer A, Finklestein J, Evans RG, Meyers P, Steinherz LJ, Sather H, Hammond D (1986) Improved disease-free survival of children with acute lymphoblastic leukemia at high risk for early relapse with the New York regimen – a new intensive therapy protocol: a report from the Children Cancer Study Group. J Clin Oncol 4:744–752
4. Clavell LA, Gelber RD, Cohen HJ, Hitchcock-Bryan S, Cassady JR, Tarbell NJ, Blattner SR, Tantravahi R, Leavitt P, Sallan SE (1986) Four-agent induction and intensive asparaginase therapy for treatment of childhood acute lymphoblastic leukemia. N Engl J Med 315:657–663
5. Rivera GK, Mauer AM (1987) Controversies in the management of childhood acute lymphoblastic leukemia: treatment intensification, CNS leukemia, and prognostic factors. Semin Hematol 24:12–26
6. Sullivan MP, Chen T, Dyment PG, Hvizdala E, Steuber CP (1982) Equivalence of intrathecal chemotherapy and radiotherapy as central nervous system prophylaxis in children with acute lymphatic leukemia: a pediatric oncology group study. Blood 60:948–958
7. Abromowitch M, Ochs J, Pui C-H, Fairclough D, Murphy SB, Rivera GK (1988) Efficacy of high-dose methotrexate in childhood acute lymphocytic leukemia: analysis by contemporary risk classifications. Blood 71:866–869
8. Pullen J, Boyett J, Frankel L, Iyer R, Van Eys J, Crist W, Harris M, Ravindranath Y, Sullivan M (1988) Extended triple intrathecal (T.I.T.) chemotherapy provides effective central nervous system (CNS) prophylaxis for both good and poor prognosis patients with non-T, non-B, acute lymphocytic leukemia (ALL); substitution of intermediate dose methotrexate (IDM for T.I.T. after consolidation provides less effective protection for the CNS). Proc ASCO 7:176 (abstr no 681)
9. Evans WE, Crom WR, Abromowitch M, Dodge R, Look AT, Bowman WP, George SL, Pui C-H (1986) Clinical pharmacodynamics of high-dose methotrexate in acute lymphocytic leukemia: identification of a relation between concentration and effect. N Engl J Med 314(8):471–477
10. Rodman JH, Abromowitch M, Sinkule JA, Hayes FA, Rivera GK, Evans WE (1987) Clinical pharmacodynamics of continuous infusion teniposide: systemic exposure as a determinant of response in a Phase I trial. J Clin Oncol 5:1007–1014