The Ochsner Experience with Acute Lymphoblastic Leukemia in Childhood

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Pediatricians at Ochsner Clinic and Alton Ochsner Medical Foundation have treated children with acute lymphoblastic leukemia for the past 17 years with excellent results. Although a single institution, and small in comparison to the national cooperative groups, we have achieved results comparable to the most successful national groups. In collaboration with the Dana-Farber Cancer Institute in Boston, MA, we have pursued several themes of study, including the comparison of various drugs, doses, and schedules of administration in the context of an investigational window in previously untreated patients. Schedules and dosages of radiation for prevention of relapse of leukemia in the central nervous system have also been studied with interesting results.

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For 17 years, Ochsner Clinic and Alton Ochsner Medical Foundation have participated in clinical trials with the Dana-Farber Cancer Institute (DFCI) Childhood Acute Lymphoblastic Leukemia (ALL) Consortium. Serial results from the DFCI ALL Consortium are presented in Figure 1. These data demonstrate the tremendous progress in therapeutic outcomes achieved in the past 2 decades.

Earlier studies of new therapeutic options attempted to study patients who had been treated previously and already failed treatment. The DFCI ALL Consortium sought to demonstrate that such studies could be done—at little risk to the patient—during a window of treatment at the beginning of therapy. Following our groundbreaking approach, this concept has been used in various clinical trials and has now become an accepted way of beginning therapy in a variety of cancers, as long as this approach is felt not to pose an inordinate risk to the patient.

Pharmaceutical Studies

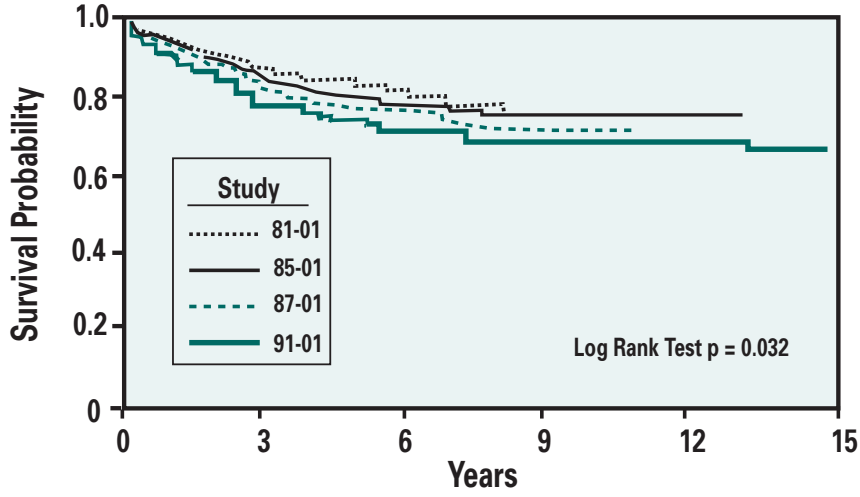
Within the concept of an investigational window, several themes have been pursued, including the comparison of various drugs, doses, and schedules of administration in previously untreated patients. Further study questions have been asked in later phases of treatment.

Methotrexate

In several studies, we have compared high-dose methotrexate at the beginning of a month of induction chemotherapy (followed by Leucovorin rescue) versus standard-dose methotrexate. In protocol 81-01, conducted from 1981 to 1985, patients were randomly assigned to receive high- or low-dose methotrexate on the first day of chemotherapy. Although toxicity was not a problem, by 1983 it appeared that there was no difference in outcome between the high-dose and lower-dose patients and the randomization was stopped. It became apparent during the following study (85-01), however, that patients who differed in their treatment (in 81-01) only by virtue of having received high-dose methotrexate on the first day of chemotherapy had outcomes statistically superior to those who had received the low-dose methotrexate (1). We reinstituted the randomization to methotrexate dosage in protocol 87-01, and our subsequent protocols have all used the higher dose of methotrexate (4 g/m^2).

6-mercaptopurine (6-MP)

Based upon the findings of other investigators that high-dose intravenous (IV) 6-mercaptopurine (6-MP) improved the outcome of patients with B-lineage ALL (2), protocol 91-01 randomized



Study	Time Interval 0 - 3	3 - 6	6 - 9	9 - 12	12 - 15	15 - 18	18-21
81-01	61/289	19/226	6/198	0/178	1/148	0/58	0/0
85-01	38/220	9/179	1/155	0/114	0/34	0/0	0/0
87-01	60/369	27/306	4/243	0/57	0/0	0/0	0/0
91-01	51/377	13/320	1/69	0/0	0/0	0/0	0/0

(# events/# at risk)

Figure 1: Event-free survival of patients registered on successive Dana-Farber Cancer Institute protocols, 1981-1995. Between (approximately) 1981 and 1985, protocol 81-01 registered 289 patients. Protocol 85-01 registered 220 patients from 1985 to 1987, protocol 87-01 registered 369 patients from 1987-1991, and protocol 91-01 registered 377 patients 1991-1995. These children all had acute lymphoblastic leukemia (ALL) or acute undifferentiated leukemia (AUL). [Courtesy of the Dana Farber Cancer Institute.]

patients to receive pulses of either high-dose IV 6-MP or standard-dose oral 6-MP during the first year of postremission therapy. Unfortunately, we did not observe an advantage in treatment with the use of high-dose IV 6-MP over standard, oral 6-MP. However, we also did not observe any severe toxicity such as that recently reported by others (3).

Prednisone vs. Dexamethasone

We have compared prednisone with various doses of dexamethasone, in induction and pulse therapy of both drugs, throughout the intensification and maintenance phases of chemotherapy. With the exception of protocol 91-01, which used 5-day pulses of dexamethasone, prednisone was used in 5-day pulses every 3 weeks following attainment of remission. Both of the steroids prednisone and dexamethasone have significant antileukemic activity, but dexamethasone was chosen for its enhanced central nervous system (CNS) penetration. Although the rate of CNS relapse was extremely low on protocol 91-01, it is not possible to attribute this result conclusively to the change in steroid form. However, a decrease in cognitive performance was observed in children entered on protocol 91-01, all of whom received dexamethasone as their postremission steroid (4).

Furthermore, both prednisone and dexamethasone are associated with significant skeletal toxicity (5). We have debated how to limit this toxicity but have not reached an agreement. Dexamethasone is felt to merit further study, however, and we plan to include it in the next protocol, which is being developed at this time.

Doxorubicin and Dexrazoxane

The drug doxorubicin has been used as a "fourth" induction drug for several years (6). Our current use, spanning the past 15 years, includes two doses of 30-mg/m^2 doxorubicin early in induction for all patients with ALL. Patients classified as high-risk (or very-high-risk) continue to receive doxorubicin during a period of intensification of treatment, reaching a target dose of 450 mg/m^2, 360 mg/m^2, or, now, 300 mg/m^2.

In protocol 91-01, high-risk patients were randomized to receive doxorubicin as a bolus or as a 24-hour infusion, in the hopes of developing a less toxic administration of this agent. In

protocol 95-01, all high-risk patients received doxorubicin in bolus form but were randomized to receive or not receive the cardioprotective agent dexrazoxane prior to each dose of doxorubicin. Results of these studies have not been compiled or published, but it appears that the 24-hour infusion is not safer than the bolus, and no short-term difference in toxicity was observed. Protocol 95-01, studying dexrazoxane, is still in progress.

Asparaginase

Having used asparaginase for many years as a component of the induction chemotherapy regimen, we promoted it to a role in the phase of chemotherapy intensification following remission induction. Asparaginase was administered for 20 weeks in intensification in most trials, but was given for 30 weeks in protocol 91-01. Doses and forms of asparaginase have been compared in an investigational window at the beginning of induction (7), and patients were randomized to receive either *E. coli* asparaginase (Elspar®) or pegaspargase in intensification.

In studies of the pharmacokinetics of the asparaginases comparing their efficacy and toxicity, we have observed a relatively high rate of asparaginase-related toxicities (8-10). Protocol 91-01 resulted in 15% allergic reactions, 7% pancreatitis, and 4.5% coagulopathy; 1% of patients experienced a CNS thrombosis. Of the patients receiving pegaspargase, 25% experienced a toxic reaction compared with 36% of patients assigned to *E. coli* asparaginase. However, there was no difference in the incidence of dose-limiting toxicities, such as *severe* allergic reaction, severe pancreatitis, or CNS thrombotic events. The event-free survival (EFS) of patients who were able to receive at least 26 weeks of asparaginase therapy was significantly better than those who received less (90% vs. 68%; $p<0.01$) (unpublished observations).

Prophylactic Irradiation

The issue of CNS prophylaxis has been a difficult one for us. There is a great deal of controversy concerning the benefits and risks of radiation to the CNS in the attempt to eliminate leukemia in the brain and spinal cord. Over 3 decades ago, the routine administration of craniospinal radiation to children with ALL but no evidence of CNS involvement became the original breakthrough in childhood leukemia management. The CNS relapse rate dropped considerably (11). However, administration of radiation to so much bone marrow rendered these patients less able to tolerate an adequate dosage of chemotherapy. Subsequent efforts included reducing both the dosage of radiation and the target field (i.e., employing cranial irradiation rather than craniospinal).

The question remains, however, as to whether prophylactic cranial irradiation is worse than drug treatments to prevent CNS leukemia relapse. For example, Ochs et al randomized patients to receive radiation or other treatment besides radiation, and performed neuropsychological testing to compare the groups. They were unable to find a difference (12). Other studies have suggested that patients who are older than 5 or 6 years of age (the age at which myelination of the brain is relatively complete) may not suffer from such irradiation in the same way that younger children might (13-15).

In protocol 87-01, we attempted to eliminate cranial irradiation entirely from our standard-risk group of children. Traditionally, patients with ALL have been divided into two or three groups, based upon the likelihood that they will experience a relapse of ALL. The operative concept was that those patients with a higher risk of relapse, interpreted as indicating a more aggressive disease, should be treated correspondingly more aggressively. Various clinical criteria comprised the description of these groups: patients 2-9 years of age with an initial white blood cell count <20,000, no evidence of CNS disease at diagnosis, no mediastinal mass on X-ray, no Philadelphia chromosome, no T-cell disease (or mature B-cell disease), and who entered remission by the end of 1 month of induction treatment. Patients meeting these criteria were placed in the standard-risk group; all others were placed in the high-risk group (16). On some protocols, children <1 year of age or with a white blood cell count >100,000 were placed in a group with a "very high risk" of relapse. [Relatively recently, the National Cancer Institute sought to bring a uniformity of approach to the treatment of childhood ALL by standardizing these definitions of risk groups (17). We are now using the government-standard definitions. In brief, the standard-risk definition of acceptable age is now 1-10 (i.e., 10.0) and white blood cell count $\leq$50,000. There is no "very high risk" group.]

Gender Differences in Radiotherapy Requirements

The results of protocol 87-01 were surprising: standard-risk girls could do without cranial radiation without demonstrating a very high rate of CNS relapse. However, standard-risk boys did demonstrate an unacceptably high rate of CNS relapses without cranial radiation(18). In many cases, these relapses occurred several years from diagnosis. When this risk of relapse was appreciated, this aspect of the study was aborted. All standard-risk boys were then recalled for cranial radiation, and those who had already completed their planned 2 years of chemotherapy were given an additional year. This approach, at least, was effective in curtailing the excessive rate of CNS relapse in the group of nonirradiated boys. Previously, such a sex difference had only been seen in a Finnish study of ALL, which reported a significant difference in overall EFS, due to a difference in outcomes for high-risk patients, but not based upon a difference in *CNS*-EFS (19). [EFS indicates survival without relapse; failure to achieve remission, relapse of disease, or death while in remission will cause the curve to drop.]

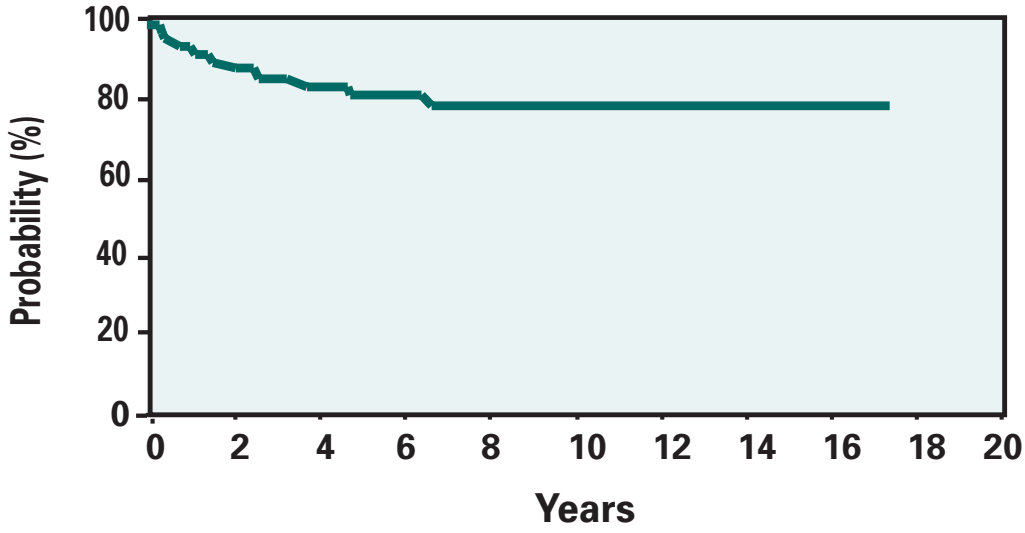


Figure 2: Approximate Kaplan-Meier estimate of event-free survival of 85 consecutive children diagnosed with acute lymphoblastic leukemia (ALL) or acute undifferentiated leukemia (AUL) at Ochsner since 1983.

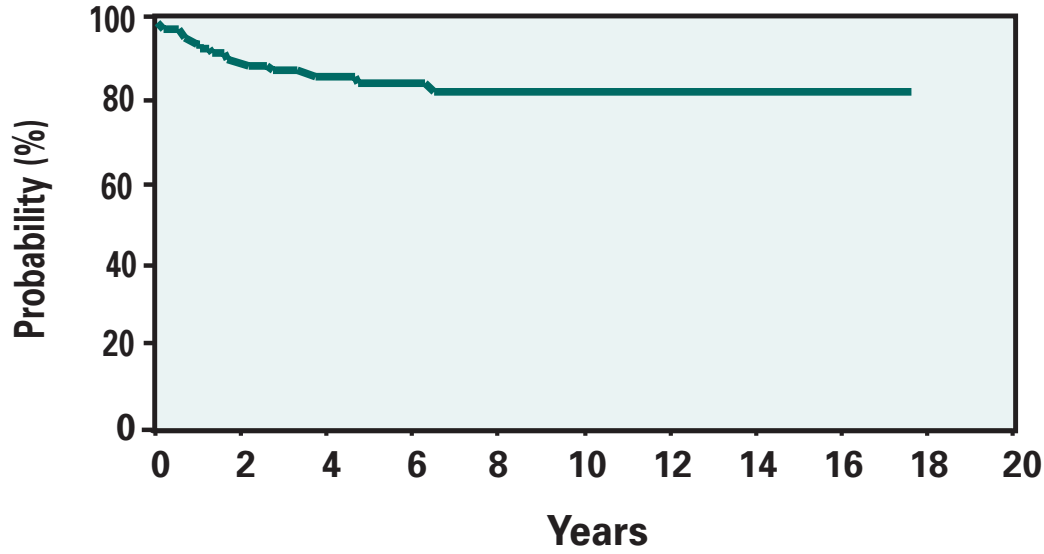


Figure 3: Approximate Kaplan-Meier estimate of event-free survival of 81 consecutive children diagnosed with acute lymphoblastic leukemia (ALL) at Ochsner (exclusive of patients with acute undifferentiated leukemia [AUL]).

Dosage Variation

We have also reduced the dosage of cranial radiation from 28 Gy to 24 Gy and now 18 Gy, and have studied a "hyper-fractionation" program consisting of twice-a-day irradiation at half-a-dose per fraction (i.e., same total daily dose) versus conventional fractionation (20). Some of the children who fall into the standard-risk group are now receiving intensive intrathecal therapy but no radiation. This group receives chemotherapy with three drugs (methotrexate, cytarabine, and hydrocortisone) given intrathecally every 9 weeks for a total of six doses, after which they go on to our standard regimen of intrathecal chemotherapy every 18 weeks.

Another group of standard-risk patients is receiving radiation therapy as well. This group—along with all high-risk patients—is randomized to receive once-daily or twice-daily cranial irradiation (and two intrathecal medications: methotrexate and cytarabine). Although the results are preliminary (and as yet unpublished), the intensive intrathecal regimen seems to be as effective as the radiation regimens in the standard-risk group, but the hyperfractionated cranial irradiation is perhaps less effective than standard radiation—and no less toxic.

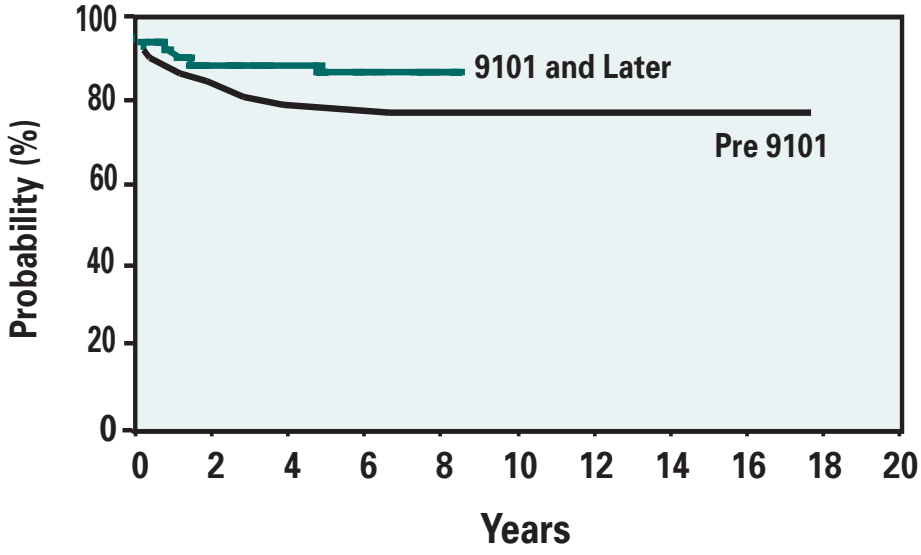


Figure 4: Approximate Kaplan-Meier estimate of event-free survival of 85 consecutive children diagnosed with acute lymphoblastic leukemia (ALL) or acute undifferentiated leukemia (AUL) at Ochsner, by date of diagnosis and protocol. 43 children were treated "pre-9101" and 42 on protocol 9101 and later.

For standard-risk males on protocol 91-01, there was no difference in EFS, leukemia-free survival (LFS), or CNS-EFS based upon CNS radiation randomization (p=0.84, 0.79, and 0.36, respectively). However, for high-risk patients, the 5-year EFS and LFS were lower for those randomized to receive hyperfractionated cranial radiation (p=0.05 and 0.02, respectively), although there was no difference in CNS-EFS based upon randomized radiation schedule (p=0.24) (21). These unexpected results have yet to be satisfactorily explained. However, it appears that hyperfractionated cranial radiation in the context of this protocol was not as effective as standard-fractionation radiation.

Conclusion

Our single-institution results over the past 17 years have been consistently good throughout this period, in which we have seen increasing sophistication in supportive care, evolving approaches to treatment, and improvements in outcomes. Figure 2 shows the results obtained at Ochsner for all 85 children with newly-diagnosed ALL or acute undifferentiated leukemia (AUL). This latter condition was once indistinguishable from ALL and treated in a similar fashion, but there is now a trend toward treating such cases along the lines of acute *non-lymphoblastic* leukemia instead. Elimination of the four AUL patients from the curve of Figure 2 yields the curve of Figure 3. Figure 4 shows progress in treatment, comparing results of the 43 patients diagnosed up to 1991 with the better results in the 42 patients diagnosed since 1991.

The details of our approach to treatment of ALL at Ochsner have varied over the years, but our commitment has remained true: to deliver the best possible patient care in the context of reasonable clinical trials in which progress can be made—and it has!

Acknowledgements

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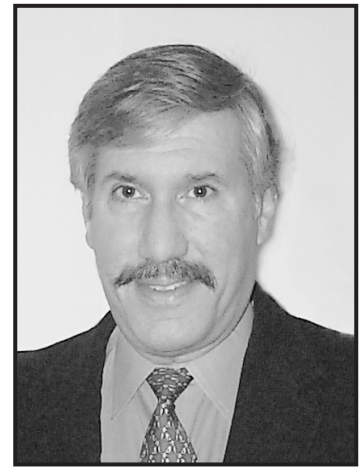
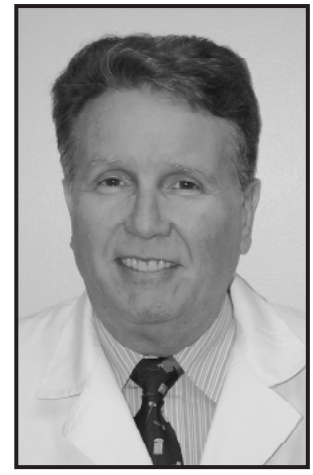


Dr. Schorin has been the head of the Section on Pediatric Hematology/Oncology at the Ochsner Clinic since moving from Boston in 1983. His main research interest is in the management of children with ALL.



Dr. Ducos was formerly the head of Pediatric Hematology/ Oncology at LSU and Children's Hospital in New Orleans. He came to Ochsner in 1988.