Comparison of Chemotherapy With Immunotherapy for Maintenance of Acute Lymphoblastic Leukemia in Children and Adults

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Two hundred and seventeen patients, 1–50 yr old, with acute lymphoblastic leukemia in complete remission were randomized to receive a 1-yr consolidation chemotherapy of either type P, comprising 7 different drugs, or type M, consisting of methotrexate interspersed with prednisone and vincristine. Thereafter, they were randomized a second time to receive a 4-yr maintenance of either chemotherapy or immunotherapy, comprised of allogeneic blasts and bacillus Calmette-Guérin (BCG). Consolidation P caused more toxicity than consolidation M. However, comparison between the consolidation therapies P and M showed no significant difference, neither for disease-free interval nor for duration of survival. Chemotherapy showed more lethal toxicity in adults than in children.

Comparison

Over the last 12 yr, immunotherapy has been used in a number of clinical trials in man with various malignancies. The first clinical trial using Bacillus Calmette-Guérin (BCG) was reported by Mathé et al. on children with acute lymphoblastic leukemia (ALL) in complete remission (CR). This was a randomized study comparing absense of maintenance therapy with active immunotherapy using BCG, irradiated leukemic cells, or both. This trial was based on prior studies on murine leukemia, which demonstrated that immunotherapy was effective, providing the total leukemic population was less than 10^9 cells. On the basis of these observations, the MRC in Great Britain conducted a clinical trial on ALL to evaluate the use of BCG as a form of immunotherapy after 5 mo of intensive cytotoxic treatment, comprised of prednisone, vincristine, 6-mercaptopurine, L-asparaginase, and methotrexate. Patients thereafter received twice weekly methotrexate, BCG, or no treatment. These authors found no benefit from the use of BCG, but it must be remembered that the bacillus (Glaxo BCG) was different from that used by the French workers. A similar study in the USA by Leukemic Study Group A also failed to show benefit from BCG, despite the use of Pasteur Paris BCG. In this study, BCG was ineffective in prolonging drug-induced remissions either early in remission or when the leukemic cell population might have been further reduced after 8 mo of maintenance chemotherapy.

The present study was undertaken in 1971 in order to investigate in ALL patients the role of active immunotherapy recommended by Mathé, i.e., BCG and allogeneic leukemic blasts. It was designed to evaluate the relative effect of immunotherapy and chemotherapy for the maintenance of CR. It was assumed that the possible effect of immunotherapy was dependent on the number of leukemic cells still present when immunotherapy was started. Thus, an eventual failure of immunotherapy could possibly be ascribed to an insufficient consolidation. Therefore, after the induction of CR, a 1-yr intensive consolidation chemotherapy was given to all patients in order to reduce the leukemic burden as much as possible before
any kind of maintenance therapy was initiated. In order to improve our understanding of the role of consolidation chemotherapy, two different consolidation regimens were compared for their efficacy in preparing patients for maintenance therapy.

MATERIALS AND METHODS

The trial was started in May 1971 and the last patient was entered in December 1978. Patients between their first and their 50th anniversary with newly diagnosed ALL induced in complete remission (CR), according to the protocol, were eligible for the trial except in December 1978. Patients between their first and their 50th remission regimens were compared for their efficacy in consolidation chemotherapy, two different consolidation regimens were compared for their efficacy in preparing patients for maintenance therapy.

Remission Induction Treatment

Induction therapy consisted of daily oral prednisone (40 mg/sq m) and weekly intravenous injections of VCR (2 mg/sq m) for at least 4 wk. If after 3 VCR injections, the bone marrow still contained 6%-15% blasts or 16%-25% blasts, the induction was prolonged to, respectively, 5 or 6 wk. If after 3 injections of VCR, the marrow still contained >25% blasts, the induction was prolonged to 6 wk, and 2 weekly injections of daunomycin 60 mg/sq m were added. If CR was not achieved within 8 wk, the patient did not enter the trial. CR was defined as the absence of blasts in the blood, the absence of marrow aplasia, the presence of less than 5% blasts in the bone marrow, and the absence of leukemic infiltration on examination.

No testicular biopsies were performed to confirm CR. No prophylactic treatment of Pneumocystis carinii has been given.

The induction therapy given to the relapsing patient was not standardized, since it was anticipated, and this was indeed the case, that relapse would occur during the administration of a variety of different drugs.

Consolidation Treatment

Although the term "consolidation" has generally been used for a 1-12-wk period of intensive treatment after remission induction, it will be used here for a 1-yr therapy phase in order to separate it clearly from the subsequent phase of 4 yr of less intensive chemotherapy.

Consolidation P (P for polychemotherapy) consisted of 8 successive phases of chemotherapy given within a period of 12 or maximum of 13 mo. The first 4 phases given in 6 mo are repeated during the next 6 mo. Phases 1 and 5 (4 wk) consisted of 1-asparaginase, 150,000 U/sq m given i.v. once a week in 250 ml saline perfusion, and 6-mercaptopurine, 70 mg/sq m/day, per os, in 2 or 3 doses. Central nervous systems (CNS) prophylaxis was administered during phase 1. Phases 2 and 6 (8 wk) consisted of prednisone (PDN) 40 mg/sq m/day, per os, in 3 or 4 doses, and 6-mercaptopurine, 70 mg/sq m/day, per os, in 2 or 3 doses. Phases 3 and 7 (8 wk) consisted of bis-chloroethyl-nitrosurea (BCNU), 50 mg/sq m once a month, i.v. for phase 3 and 100 mg/sq m once a month, i.v. for phase 7, and cyclophosphamide (CPM), 70 mg/sq m/day, per os for 8 wk. Phases 4 and 6 (6 wk) consisted of methotrexate, 15-20 mg/sq m i.m. or per os, twice a week, and VCR, 1 mg/sq m, i.v., once a week. Consolidation M (M because methotrexate was the major agent) consisted of 7 successive phases of chemotherapy given within a period of 12 or a maximum of 13 mo. The 7 phases were identical and consisted of 30 days intermittent MTX followed by 21 days of reinforcement with PDN and VCR. MTX was given at 15 mg/sq m i.v. bolus injection during 3, 4, or 5 consecutive days, depending on tolerance. Three sequences of 3, 4, or 5 days separated by at least 5 days of therapy had to be given over a period of 1 mo. Reinductions were repeated after every 30 days of intermittent MTX: vincristine, 2 mg/sq m i.v. at days 1, 8, and 15, and prednisone, 40 mg/sq m/day, per os, at days 1-15 and then decreased progressively on days 16 and 17. MTX was restarted at day 21 of reinduction.

The doses were reduced in case of toxicity. The l-asparaginase injections were spaced when fibrinogen fell below 50 mg/dl and were reduced to 40,000 U/sq m/wk or discontinued according to severity of transaminase, amylase, diabetic, or CNS abnormalities. For hematologic toxicity, when WBC was <3,000/μl and platelets <100,000/μl, all drugs could be given at 100% of the dose. Below 1,000 WBC/μl and 50,000 platelets/μl, all therapy was stopped. Between these thresholds, adjustments of the doses were recommended: with WBC between 2,000 and 3,000/μl and/or platelets between 50,000 and 100,000/μl, the dose of MTX, 6MP, CPM, and BCNU was reduced by 50%. Between 1,000 and 2,000 WBC/μl; MTX, 6 MP, and CPM were stopped, with asparaginase, VCR, and BCNU (first cycle) being reduced to 50% of the original dose. When, for consolidation M, WBC was 2,000-3,000/μl, only 3 days
of MTX were given, but when WBC was below 2,000/µl, MTX was delayed until WBC reached 2,000/µl.

**Prophylaxis of CNS Relapses**

Prophylactic therapy of CNS leukemia was given to all patients immediately after CR was achieved, during the beginning of consolidation P or M. Before July 1973, 59 patients received 12 monthly intrathecal injections of MTX (5 mg/sq m) and cytosine arabinoside (10 mg/sq m) and craniospinal irradiations, 1,500 rads to the skull and 1,000 rads to the spine. Later on, the promising results reported by Aur et al.\(^3\) prompted us to adopt their regimen, i.e., 2,400 rads cranial irradiation combined with 5 intrathecal injections of MTX (12 mg/sq m) given over a 16-day period; 158 patients were treated this way. The 2 randomizations gave an equal number of patients in the treatment arms before as well as after July 1973.

CNS relapse was defined as more than 10 lymphoid cells/µl or at least 1 leukemic cell in the cerebrospinal fluid.

**Maintenance Treatment**

The patients who were still in continuous CR after 1 yr of consolidation were further randomized, separately for each consolidation arm, to receive either maintenance chemotherapy or immunotherapy for a period of 4 yr.

Maintenance chemotherapy consisted of daily 6MP (90 mg/sq m) and weekly oral or i.m. MTX (15 mg/sq m). These drugs were stopped for 21 days when reinforcement was given: prednisone (40 mg/sq m p.o. days 1–15) and VCR (1.5 mg/sq m i.v. days 1, 8, and 15). These reinforcements were given every 3 mo the first year, every 4 mo the second year, and every 6 mo thereafter.

Patients on immunotherapy received: (A) 2 ml of fresh fluid Bacillus Calmette-Guérin (BCG) (from the Institut Pasteur, Brussels) spread over a 20 x 5 cm scarification on one leg. The preparation contained 8 x 10^6 viable units/ml and was administered twice weekly for 6 mo and once a week thereafter; (B) allogeneic nonirradiated leukemic blasts, 4 x 10^6 blasts injected intradermally once a week for the first 3 mo and then once a month. The blast cells were obtained from one or several leukemic donors before treatment and cyropreserved at –196°C in the presence of 10% dimethylsulfoxide (DMSO). DMSO was not washed out prior to administration to the patient.

Both types of maintenance treatment were stopped after 4 yr, i.e., 5 yr from the beginning of consolidation.

**Data Collection and Statistical Analysis**

All the data were collected, processed, and analyzed at the EORTC Data Center. The criteria of evaluation were disease-free interval (DFI), disease-free survival (DFS), and duration of survival (S). In comparing the consolidation treatments (M versus P), all the curves were calculated from the first randomization, i.e., from the first bone marrow showing CR. When the maintenance treatments were compared (1 versus C), the second randomization was taken as the starting point. The DFI curve gives the probability estimation that a patient has not yet relapsed anywhere (CNS, bone marrow, CNS and bone marrow, testis, etc.) at different time points. The DFS gives the probability estimation that a patient has not yet relapsed or died in CR. The actuarial curves were calculated using the Kaplan-Meier method,\(^6\) and the logrank test\(^7\) was utilized for the curves’ comparison. The Greenwood formula\(^4\) was used in order to obtain a standard error (SE) estimation of the proportion of patients still in first CR or alive at a certain time, calculated from the start of consolidation or maintenance. Differences among treatments concerning the distribution of disease features and side effects were examined using the chi-square test for contingency tables.

**RESULTS**

Two hundred and twenty-five ALL patients were induced in complete remission according to the protocol; 217 were evaluable for consolidation treatment. Eight patients were completely inevaluable because of total absence of follow-up. Three patients were lost for follow-up at start of maintenance treatment and are therefore absent from analysis of maintenance therapies. The mean follow-up for the whole group was 262 wk for treatment P, 269 for M, 227 for I, and 233 for C.

Table 1 shows the group characteristics with regard to age and WBC.

Table 2 shows the total number of patients in each age group and each treatment group. There were 177 in the age group 1–14 (median age 5) and 40 in the age group 15–50 (median age 22). One hundred and twenty-one patients still in CR after 1 yr and receiving maintenance I or C were evaluable.

Table 3 indicates the reasons why the patients went off protocol treatment: it is shown that 21 died in CR, all presumably from complication of the therapy: in 33
TREATMENT OF ALL

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cases the patient or the parents refused the treatment. One 13-yr-old boy, who went off consolidation M for excessive toxicity, subsequently developed eosinophilic granuloma of skin and bones after 1 yr of treatment.

Ten patients went off protocol treatment for protocol violation: 6 for lack of randomization for maintenance, 1 for immunotherapy by BCG only, 1 for lack of CNS prophylaxis, 2 for lack of compliance to consolidation therapy. Since the patients off protocol treatment for protocol violation showed a DFI and S not significantly different from that of the rest of the group, they were included in the general analysis.

When considering hematologic toxicity and liver toxicity, consolidation P was significantly more toxic than consolidation M (<0.001 and 0.04, respectively, in the whole group). However, this was not associated with significantly more infectious episodes in consolidation P compared to consolidation M.

Table 4 shows the reasons for death in complete remission. The overall death rate in CR was 21/217 (9.7%): 17 during the year of consolidation and 4 during the 4 yr of maintenance. It is seen that death occurred in all chemotherapy phases and that no death occurred during immunotherapy. The rate of death in CR is significantly lower ($p = 0.03$) in the childrens' group (13/177, 7.4%) than in the adults' group (8/40, 25%). Globally, consolidation P appeared to be more toxic than consolidation M: 11 patients of 112 died in CR versus 6 of 105 ($p = 0.43$). In adult patients, the difference was more important (5/20 versus 2/20), but still not significant ($p = 0.52$).

Figure 2 shows the DFI of all the patients irrespective of the treatment assigned by randomization, but separately for the 2 age groups (1-14 and 15-50). In the 1-14 age group, 51.1% were free of disease at 4 yr

![Disease-free interval according to the age group. The SE estimations of the CR rates at 4 yr in the 2 age groups are, respectively, 4% and 7.9%.](image-url)
and the median DFS was 144 wk. One relapse occurred at 226 wk. This was an 11-yr-old girl with 11,000 WBC and no enlarged mediastinum at diagnosis. She was on immunotherapy for more than 3 yr when she relapsed in the marrow. For the 15–50 age group, the median DFI was 64 wk and DFS 58 wk. Only 4 adult patients survived free of disease for more than 5 yr. Forty patients of all ages have completed 5 yr of therapy according to the protocol and have been followed for 1 mo to 5 yr since the cessation of therapy without relapse.

Figure 3 shows, for the children's group, the DFI calculated from the beginning of consolidation comparing consolidation P (n = 92) and M (n = 85). No significant difference is seen between the two consolidation therapies. This remains true when the 40 adult patients are included. The same is seen when DFS and S (not shown) are considered.

Figure 4 shows the DFI (calculated from the beginning of maintenance) by maintenance therapy (I or C) for all the children (1–14). Maintenance C was significantly superior to I (p = 0.016); with I, the proportion of patients remaining in continuous complete remission is lower, but also the proportion of patients relapsing shows a rapid falling off, beginning at 1 yr, when immunotherapy was begun. The superiority of C was statistically significant in the whole group (1–50) as well (p = 0.0077). However, when DFS is considered, the superiority of C over I treatment remains, but only at borderline significance: p = 0.062 for the 1–14 age group and 0.046 for the 1–50 age group. This is due to the death of 3 children and 1 adult in CR as a complication of maintenance chemotherapy, while no patient died in CR during I maintenance therapy. Well established signs of poor prognosis, such as an enlarged mediastinum and male sex, were evenly distributed in the various treatment groups. On the other hand, a WBC at diagnosis higher than 25,000/μl was more frequent in the maintenance C group (40%) than in maintenance I group (28%). However, this probably cannot invalidate our conclusion, since after adjustment for WBC at diagnosis (logrank test), C remains significantly superior to I (p = 0.014). Moreover, the WBC at diagnosis (<25,000 or ≥25,000/μl) was not found to have any prognostic value for the DFI taken from start of maintenance for this group of children.

Table 5 shows the various types of first relapses in the different age groups by type of therapy. The number of primary CNS relapses was low during maintenance I (3 cases) and maintenance C (4 cases). The overall incidence of testicular relapse was 7/129 (5.4%) in male patients. It must be emphasized that all the patients who could be followed have reached 3 yr of follow-up.

![Graph of Disease-Free Interval](image)

**Fig. 3.** Disease-free interval for ALL children according to the consolidation treatment. The SE estimation of the CR rates at 4 yr in the 2 treatment groups is 5.6%.
In order to compare the two types of CNS prophylaxis (before and after July 1973), a homogeneous group was examined: the children treated by chemotherapy. This study has shown (not indicated in the table) no difference for DFI and CNS relapse-free interval. However, survival was significantly longer (p = 0.03) and percentage of CNS relapse lower (7% versus 13.6%) for those patients treated after July 1973. No significant difference in the incidence and severity of infections was seen between the two types of CNS prophylaxis. The two groups of CNS prophylaxis were comparable for proportion of P and M consolidation, Hb more or less than 8 g/dl, and WBC more or less than 25,000/μl.

Figure 5 shows all the children receiving maintenance therapy (I or C). The DFI (calculated from beginning of maintenance) was the same whether the consolidation therapy was P or M. The two subgroups, PI and MI, especially close to each other, indicate that the efficacy of immunotherapy was not influenced by the consolidation given for 1 yr before. No significant difference was seen between PC and MC.

Figure 6 shows DFI of children (calculated from beginning of maintenance) by maintenance therapy and by the level of hemoglobin at diagnosis. The group whose hemoglobin level was below 8 g/dl did considerably better with C than with I. On the other hand, the group with more than 8 g/dl showed the same DFI with I and C.

Figure 7 shows that children had the same survival duration (calculated from beginning of maintenance) with maintenance therapies I and C (p = 0.88). The same result was obtained when considering all patients (1-50 age group) (logrank test, p = 0.97).

The rate of second CR obtained in the I group (25/28, 89%) was higher, but not significantly (p = 0.12), than the rate obtained in the C group (9/14, 64%). The survival of the 42 patients relapsing during maintenance therapy calculated from the date of
relapse was examined separately for I and C. The median survival was 114 wk for the 28 who relapsed while on I and 55 wk for the 16 who relapsed while on C ($p = 0.06$). Presently, more survivors exist in the group I (12/28 relapsing) than in the group C (2/14). However, it is too early to draw any conclusion from this observation, the follow-up of these relapsing patients being too short: 14–215 wk (median 80) for I and 105 and 397 wk for C.

**DISCUSSION**

The efficacy of immunotherapy has been demonstrated in several animal malignancies. Its effect in human acute leukemia has recently been reviewed. The only ALL positive trial was the only one to use the association of specific (leukemic blasts) and nonspecific (BCG) immunostimulation. The present study was designed to administer immunotherapy exactly as in Mathé's original trial. A small difference was the use of Pasteur Brussels BCG instead of Pasteur Paris BCG.

The overall therapeutic results obtained for children (1–14) and for adults (15–50) are similar to those obtained by most groups. Indeed, in the 1–14-yr group, the probability of remaining in first CR after 4 yr is approximately 1 in 2. However, these results are inferior to those published by the ALL Therapy Group of Berlin, which has reached 74% in first CR at 3 yr for 325 ALL children. In 40 adult patients, the median DFI in our study was 15 mo. This median DFI was of the same order of magnitude as in other studies. It should be remembered that, in order to make comparisons easier, the age limits of our group were 15–50 yr and that DFI was calculated until relapse of any type: marrow, CNS, mediastinum, etc.

Hematologic toxicity and liver toxicity of consolidation P were significantly more severe than that of consolidation M. Nevertheless, no significant difference was seen between the two consolidation treatments concerning DFI, DFS, S, lethal toxicity, infectious episodes, number of primary CNS, or other extramedullary relapses and influence on the therapeutic effect of subsequent maintenance by immunotherapy or by chemotherapy. When considering the impact of consolidation on the effect of subsequent maintenance, it must be pointed out that the consolidations P and M represent two quite different therapies for those patients maintained by immunotherapy, but not so for those maintained by chemotherapy. Indeed, the difference between P and M given for 1 yr was probably considerably moderated by the subsequent 4 yr of maintenance C.

When comparing I and C maintenance treatments, it is clear that C is better than I to maintain remission. Not only were there more relapses in I during the first 2 yr, but in addition, relapse took place much earlier in those patients treated by I than in the relapsing patients treated by C. This indicates that C not only
Fig. 6. Disease-free interval for ALL children according to the maintenance treatment and the level of hemoglobin at diagnosis (< or ≥8 g/dl). The difference between I and C in the group with <8 g hB/dl is highly significant (p = 0.009). The SE estimations of the CR rates at 3 yr in the 4 groups are, respectively, 10.1%, 9.8%, 5.2%, and 11.4%.

Fig. 7. Duration of survival for ALL children according to the maintenance treatment. The SE estimations of the CR rates at 3 yr in the 2 maintenance groups are, respectively, 6.6% and 6.2%.
increases the proportion of patients in continuous CR, but also delays the onset of relapse for those patients relapsing. Nevertheless, the only relapse after 4 yr in CR occurred in a patient receiving maintenance I. When evaluated in terms of DFS, maintenance chemotherapy partially lost its advantage. This was due to the toxicity of C maintenance, which caused the death of 4 patients in CR, whereas no such deaths were seen in maintenance I. It must be pointed out, however, that of the 21 deaths in CR, presumably from toxicity of treatment, 8 of them (4 from varicella and 4 from Pneumocystis carinii) could be prevented today by adequate therapy.

An important finding is that no difference can be seen between I and C for duration of survival. The equal chances of survival up to now with C or I maintenance are due to the fact that relapsing patients in group I have a higher rate of second CR and a longer duration of survival than those in group C. Thus, chemotherapy given to relapsing patients (not standardized in the present study) appeared more efficient in patients who had been on maintenance I than on those who had received maintenance C. Whether this will result in more long-term survivors or cure in relapsing I than in relapsing C is too early to ascertain. In any case, the negative impact on survival of the greater relapse rate in the immunotherapy group could become evident sometime in the future. As shown for CNS relapse, it is possible that the effect of relapse on survival may become significant only after 10 yr of follow-up of all the patients. It should be emphasized that for isolated extramedullary relapses, there was apparently no difference between I and C. Whether this indicates that for patients who received CNS prophylaxis, maintenance therapy plays no role in preventing CNS relapses, should be examined in a larger group of patients.

A control arm without maintenance therapy was deliberately avoided in this study for ethical reasons. Nevertheless, superiority of C over I at least indicates that maintenance given after 1 yr of consolidation can still modify the course of the disease. Moreover, based on previous studies, it can be reasonably assumed that maintenance C is better than no maintenance. However, whether maintenance is better, worse, or equivalent to absence of maintenance cannot be derived from the present study. It should be remembered that two randomized studies have shown that immunotherapy (using BCG only) gave results similar to those obtained in a control arm receiving no maintenance therapy.

The study was initiated in 1971 and, therefore, most patients did not have tumor cell surface markers done. This makes it impossible to compare T-type ALL and common ALL for their response to I and C. However, this question could be examined indirectly. Indeed, T-ALL has been shown to be characterized by a mean hemoglobin level at diagnosis above 8 g/dl, whereas in common ALL it was below 8 g/dl. The results shown in Fig. 6 indicate that maintenance immunotherapy, as opposed to chemotherapy, is insufficient for those patients with a level of hemoglobin less than 8 g/dl at diagnosis (possibly those with common ALL). They indicate, on the other hand, that for the patients with hemoglobin greater than 8 (possibly those with T-ALL), maintenance chemotherapy was just as insufficient as maintenance immunotherapy, in other words, that much better treatment is needed for these patients. Whatever its correspondence with the cell type of ALL, the level of hemoglobin at diagnosis could represent a simple and potent indicator of the need of maintenance chemotherapy after 1 yr of treatment of ALL. This observation requires confirmation, since prognostic factors are often dependent on the type of therapy used.

The overall lethal toxicity for patients in CR reached almost 10% (21/217), a death rate found by other authors in children and in adults with ALL. This observation deserves several comments. It should be pointed out that the overall death rate in CR decreased with the years: 8 deaths in 1971–1972, 6 in 1973–1974, 3 in 1975–1976, 3 in 1977–1978 and 1 in 1979–1980. This suggests that, with time, the medical teams became notably more acquainted with complications of chemotherapy and/or that the new active agents against infectious complications that have emerged between 1970 and 1980 played a role. This seems to be the case for varicella, which caused 4 deaths in CR in the first years of the study (1 in 1972, 2 in 1973, and 1 in 1976), but none later on when more specific agents became available: anti-zoster gammaglobulins, adenine arabinoside, acyclovir, etc. The decrease of the death rate with the years could also be due to the introduction of the trimethoprim-sulfamethoxazol association active on Pneumocystis carinii. The implication of these comments is that if this study were to be repeated now, the survival would be improved in the chemotherapy arm. It must be emphasized that the death rate in CR was significantly higher in adults (20%) than in children (7.3%) and that a high death rate (5/20) was encountered in the group of adult patients receiving consolidation P. Of these 5 patients, 3 were receiving L-asparaginase: I died with acute abdominal symptoms probably related to acute pancreatitis, another died of CNS hemorrhage, and the third of acute liver failure. The high frequency of
life-threatening or lethal toxicity related to the use of L-asparaginase in ALL has been reported by another cooperative group.  

REFERENCES

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