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# L-Asparaginase, Vincristine, and Prednisone for Induction of First Remission in Acute Lymphocytic Leukemia[1]

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## SUMMARY

L-Asparaginase was added to vincristine and prednisone for induction of first remission in 815 children with acute lymphocytic or acute undifferentiated leukemia. This combination resulted in an overall remission rate of 93%. The addition of L-asparaginase to the standard induction regimen using prednisone and vincristine did not significantly increase the morbidity or mortality rate during the induction period. The most common side effect was transient L-asparaginase-induced hyperglycemia. The safe administration of L-asparaginase i.m. and the dose efficacy of 6000 I.U./sq m were confirmed. For these reasons, L-asparaginase should be combined with vincristine and prednisone for the initial induction of children with acute lymphocytic or acute undifferentiated leukemia.

## INTRODUCTION

The use of VCR[3] and PDN as standard chemotherapy for induction of 1st remission in patients with acute lymphocytic or acute undifferentiated leukemia has resulted in a remission induction rate of 83 to 95% (1, 5, 8, 13, 14); however, the higher figures were obtained in studies involving less than 75 patients. The CCSG has recently reported a study (CCG 903) in which a remission rate of 86% was attained with PDN and VCR in 499 patients who were previously untreated. The addition of a 3rd chemotherapeutic agent to the induction phase without adding significant morbidity is important, not only because it may induce remission in a greater number of patients, but because it could also result in a decreased burden of leukemic cells at the time of the 1st remission and prior to intensification therapy.

As part of a total therapy evaluation, CCSG designed a study (CCG 101/143) to determine the relative efficacy of various prophylactic CNS therapies. The combination of L-asparaginase, VCR, and PDN was used to induce 1st remission. This paper presents the results of the use of this induction combination in 815 children with previously untreated acute lymphocytic or acute undifferentiated leukemia and compares it to the previous study where only PDN and VCR were used.

## MATERIALS AND METHODS

All previously untreated children under 16 years of age with acute lymphocytic or acute undifferentiated leukemia were eligible for the study. Patients with CNS leukemia at the time of diagnosis were also eligible for the study. The CCSG criteria for evaluation of the status of acute leukemia (3) were applied to these studies. According to these criteria, a complete remission is achieved only if the bone marrow, blood, and physical findings are within the specified ranges for normal children and if no findings ascribable to leukemia are present. To qualify for a marrow remission ($M_1$), the sample must have less than 5% blasts and have qualitative and quantitative normal hematopoiesis.

The treatment schedule consisted of PDN at a dosage of 40 mg/sq m/day for 28 days p.o., VCR at 1.5 mg/sq m weekly i.v. for 4 doses (Days 0, 7, 14, and 21), and L-asparaginase (Merck, Sharp and Dohme, Inc., Rahway, N. J.) at 6000 IU/sq m i.m. 3 times a week for a total of 9 doses, beginning on Day 3. PDN and VCR were continued to Day 42 if $M_1$ was not obtained by Day 28. The upper limit for the weekly VCR dose was 2 mg. During the induction phase, patients were seen once a week, and complete blood and platelet counts were obtained. Investigations performed on Days 0 and 28 included: bone marrow aspiration, serum glutamicoxaloacetic transaminase alkaline phosphatase, blood urea nitrogen, uric acid, cerebrospinal fluid examination (to include cell count, stained preparation of the sediment, opening and closing pressure, and cerebrospinal fluid protein), and chest film, posteroanterior and lateral.

The following drug modifications were specified on the protocol: PDN, VCR, and L-asparaginase therapy was not modified for leukopenia unless the marrow was hypoplastic. If severe allergic manifestations due to L-asparaginase occurred, this drug was discontinued. The occurrence of both pancreatitis or hyperosmolar hyperglycemia was an indication for stopping L-asparaginase. Severe pain and gastrointestinal toxicity were indications for reducing the

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[3] The abbreviations used are: VCR, vincristine; PDN, prednisone, CCSG, Children's Cancer Study Group; CNS, central nervous system.

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Table 1
*Influence of initial WBC on induction*

| Parameters | CCG 101 and CCG 143 patient distribution | | |
|---|---|---|---|
| | Total | WBC <20,000 | WBC ≥20,000 |
| Evaluable | 815 | 556 | 259 |
| Off study | 41 | 31 | 10 |
| Failure to obtain $M_1$ | 16 (2)[a] | 9 (1.6) | 7 (2.8) |
| Remission ($M_2$) | 758 (93) | 524 (93.8) | 236 (91.1) |

[a] Numbers in parentheses, percentage distribution.

next dose of VCR by one-half, and paresis indicated the need for discontinuation of the drug.

The influence of different factors in the remission rate was analyzed, and the results obtained, including toxicity and complications, were compared to a previous CCSG study (CCG 903) using VCR and PDN without L-asparaginase. Study CCG 903 was activated in April 1970 and was closed in October 1971 to be immediately followed by study CCG 101/143.

## RESULTS

Of 823 children entered on study, 8 were considered ineligible, 4 because of previous treatment and 4 because of incorrect diagnosis. There were 815 patients available for analysis (Table 1). There were 41 patients removed from the study during induction for various reasons: 26 (3.2%) deaths, 5 (0.6%) because of toxicity, and 10 (1.2%) lost to follow-up. All of these were included in the overall evaluation (Table 2). Only 16 patients (2%) failed to achieve remission by Day 42, and 758 of the 815 evaluable patients achieved a complete remission ($M_1$), 635 on Day 28 and 123 by Day 42, for an overall remission induction rate of 93%. Analysis of the administration of the drugs as called for in the protocol demonstrated that 94.5% PDN, 95.8% VCR, and 95.6% L-asparaginase of the total calculated doses were administered.

The response to induction therapy according to the patient's initial WBC count was marginally superior in patients with counts less than 20,000 cells/cu mm (Table 1). Of 556 patients whose initial WBC counts were less than 20,000 cells/cu mm, 522 achieved a remission (93.8%). In the group of 259 patients with initial WBC counts greater than 20,000 cells/cu mm, 236 obtained a remission (91.1%). Eighty-eight % (77 of 88) of the patients with initial WBC counts of over 100,000 cells/cu mm achieved remission.

Other factors (age and CNS disease at diagnosis), which have been reported to affect remission induction, were also evaluated. Ninety-three % (637 of 681) of children under 10 years of age achieved a remission, while 91% (121 of 134) of children over 20 years of age achieved a remission. Nine patients had CNS leukemia at the time of diagnosis, and of these, 8 obtained a remission.

**Nonfatal Toxicity.** Five patients (0.6%) were taken off study because of toxicity. Two of these were removed because of severe peripheral neuropathy after 2 and 4 doses of VCR. L-Asparaginase-induced toxicity required removal of 2 other patients from the study, 1 because of diabetic ketoacidosis. Neutropenia associated with sepsis was the reason for discontinuation of therapy for a 5th patient.

Table 2
*Comparison of 2 different regimens for the induction of 1st remission in all*

| Parameters | Patient distribution | |
|---|---|---|
| | CCG 101 and CCG 143 | CCG 903 |
| Evaluable | 815 | 499 |
| Failure to obtain $M_1$ | 16 (2)[a, b] | 34 (6.7) |
| Remission ($M_1$) | 758 (93)[a] | 429 (86) |
| Deaths | 26 (3.2) | 18 (3.6) |
| Toxicity | 5 (0.6) | 2 (0.4) |
| Lost to follow-up | 10 (1.2) | 16 (3.2) |

[a] Significant at 0.05 level.
[b] Numbers in parentheses, percentage distribution.

Toxic effects related to L-asparaginase not requiring cessation of therapy were observed in 35 patients (4.3%). Hyperglycemia, the most common toxic effect associated with L-asparaginase, occurred in 20 patients (Table 3), and, in accordance with the protocol, the medication was discontinued. Fifteen of the patients who developed hyperglycemia were 10 years of age or older, and both sexes were equally affected. Eleven patients had initial WBC of over 20,000/cu mm, and 16 received individual doses of L-asparaginase of 6,000 IU or over. Seven patients developed hyperglycemia after 1 dose of L-asparaginase, 3 patients each developed it after 2, 3, 4, and 5 doses, respectively, and 1 patient developed it after 6 doses of medication. All patients were simultaneously receiving PDN at the time they developed hyperglycemia. In 5 patients the PDN dose was decreased by half, and in another patient the dose was decreased by 60%. Fifteen of the 20 patients received insulin for a period ranging from 1 to 56 days, but none became insulin dependent.

Five of 6 patients who reported minor allergic reactions were males. A maculopapular skin rash was the most common manifestation in this group, with 4 instances being reported. Of these 4 patients, 3 were simultaneously receiving antibiotic therapy. One episode of hypotension and 1 episode of brief respiratory distress were reported and thought to be directly related to L-asparaginase. Five of the 6 patients with allergic reactions had received 5 or more doses of L-asparaginase. Hypofibrinogenemia, not associated with bleeding manifestations, was reported in 4 patients. However, since fibrinogen quantitation was not a requirement of the protocol, the incidence of this complication could not be determined.

Acute pancreatitis was reported in 4 patients. Two of these episodes were severe and included the presence of

Table 3
*Incidence of hyperglycemia associated with L-asparaginase treatment*

| Patient No. | Age (years) | Sex | Sq m | Initial WBC count | L-asparaginase dose (IU) | Doses received | Insulin received | Length of insulin treatment (days) | PDN dose (mg) | PDN Decreased (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 15 | M | 1.73 | 183,600 | 10,000 | 1 | + | 5 | 70 | |
| 2 | 10 | M | 0.9 | 46,900 | 5,400 | 4 | + | 4 | 35 | |
| 3 | 9 | M | 1.5 | 82,700 | 12,200 | 1 | + | 6 | 60 | |
| 4 | 15 | F | 1.44 | 162,000 | 9,300 | 2 | + | 35 | 60 | 50 |
| 5 | 13 | M | 1.6 | 3,300 | 9,600 | 2 | + | 14 | | 50 |
| 6 | 15 | F | 1.6 | 8,900 | 9,000 | 4 | + | 8 | 60 | 50 |
| 7 | 7 | M | 0.9 | 15,100 | 5,000 | 5 | + | 28 | 40 | |
| 8 | 5½ | F | 0.75 | 9,300 | 4,200 | 2 | + | 56 | 30 | |
| 9 | 11 | F | | 12,100 | 7,200 | 5 | + | 7 | 48 | 60 |
| 10 | 3 | F | 1.0 | 5,500 | 6,000 | 1 | + | 28 | 40 | |
| 11 | 12 | M | 1.5 | 85,000 | 9,000 | 3 | + | 7 | 60 | |
| 12 | 11 | F | 1.7 | 20,000 | 10,000 | 4 | 0 | | 60 | |
| 13 | 10 | F | 1.6 | 1,300 | 8,500 | 1 | + | 16 | 60 | |
| 14 | 15 | M | 1.7 | 131,000 | 9,600 | 1 | 0 | | 60 | |
| 15 | 4 | F | 0.7 | 39,800 | 4,200 | 5 | 0 | | 75 | |
| 16 | 11 | M | 1.1 | 316,800 | 6,600 | 6 | + | 9 | 40 | |
| 17 | 11 | F | 1.1 | 1,000 | 6,600 | 3 | 0 | | 45 | |
| 18 | 14 | M | 1.4 | 114,600 | 8,200 | 3 | + | 1 | 55 | |
| 19 | 12 | F | 1.37 | 318,000 | 8,400 | 1 | 0 | | 55 | 50 |
| 20 | 10 | M | 1.1 | 2,500 | 6,600 | 1 | + | 21 | 45 | |
| | | | | | | | | | | 50 |

shock in 1 patient. One episode of transient renal insufficiency and 1 of hepatotoxicity were also reported.

**Deaths.** Twenty-six (3.2%) of 815 evaluable patients died during the induction phase (Table 4). Infection was the most frequent cause of death during induction, accounting for 21 deaths. Sixteen of these occurred within the 1st 2 weeks of therapy. The causative organisms of sepsis were: *Staphylococcus aureus*, coagulase positive, 6; *Pseudomonas* spp., 4; *Escherichia coli*, 2; *Diplococcus pneumoniae*, 1; α-streptococcus, 1; systemic candidiasis, 1; and viral encephalitis, 1. There were 2 cases of fatal sepsis resulting from an unidentifiable gram-negative organism. In 3 patients death was attributed to sepsis, but no organisms were identified.

Three patients expired from hemorrhage associated with thrombocytopenia. Death was not related to L-asparaginase, since 2 of the patients expired within 72 hr of diagnosis and prior to initiation of the medication. Another patient died of massive hemorrhagic pancreatitis, with fatty metamorphosis of the liver 3 days after receiving the 9th dose of L-asparaginase. The remaining death occurred in a patient 14 hr after admission to the hospital because of superior mediastinal syndrome associated with a large anterior mediastinal mass.

**Duration of Remission.** The median duration of remission for patients treated according to study CCG 101/143 has not been reached, since 70% of the patients are still maintaining their initial remission.

Table 4
*Deaths during induction phase*

| Cause of death | Patient distribution: WBC <20,000 | WBC >20,000 | Total |
|---|---|---|---|
| Infection | 14 | 7 | 21 |
| Hemorrhage | 2 | 1 | 3 |
| Toxicity | 1 | 0 | 1 |
| Other | 1 | 0 | 1 |
| Total | 18 | 8 | 26 |

## DISCUSSION

The efficacy of L-asparaginase for induction of remission in advanced acute lymphocytic leukemia when used alone (9), or in combination (12), has been previously reported. The present study indicates that the addition of L-asparaginase treatment to VCR and PDN resulted in a significant increase in the number of patients attaining a complete remission when compared to the results of a previous study where only PDN and VCR were used (7). The results obtained in this study (CCG 101 and CCG 143) were compared with those of CCSG study CCG 903 where remissions were induced with 6 weeks of PDN at 60 mg/sq m/day p.o. and VCR at 2 mg/sq m/week i.v. Although studies CCG 101/143 and CCG 903 were not done concurrently, they were successive studies performed by the same investigators utilizing the same criteria, and comparable patient characteristics existed for the 2 studies (Table 5).

Comparisons of the results obtained with these 2 studies by patient age at diagnosis and initial WBC are shown in Table 5. The remission rate ($M_1$) of 93% obtained in CCG 101 and CCG 143 was superior to the 86% observed in CCG 903. This difference was statistically significant at the 0.05 level. Treatment failures accounted for 2% of the total patients entered on CCG 101 and CCG 143, while CCG 903 had 6.7% treatment failures. This difference was also significant at the 0.05 level. The percentage of patients dying during induction therapy was similar in both studies; however, 1 patient died of L-asparaginase toxicity in the present study, and no drug-related deaths were reported in study CCG 903. Ninety-three % of patients with initial WBC between 20,000

Table 5
*Induction results by age and WBC*

$M_1$ was considered as successful induction.

| WBC/cu mm | Age <2 | 2–5 | 5–10 | >10 | Total |
|---|---|---|---|---|---|
| | | *CCG 101 and CCG 143* | | | |
| <10,000 | 21/23 = 0.91 | 197/205 = 0.96 | 123/131 = 0.94 | 68/74 = 0.92 | 409/433 = 0.94 |
| 10–20,000 | 7/10 = 0.70 | 56/60 = 0.93 | 41/42 = 0.98 | 9/11 = 0.82 | 113/123 = 0.92 |
| 20–100,000 | 16/18 = 0.89 | 77/80 = 0.96 | 41/45 = 0.91 | 25/28 = 0.89 | 159/171 = 0.93 |
| >100,000 | 16/18 = 0.89 | 25/30 = 0.83 | 17/19 = 0.90 | 19/21 = 0.91 | 77/88 = 0.88 |
| Total | 60/69 = 0.87 | 355/375 = 0.95 | 222/237 = 0.94 | 121/134 = 0.90 | 758/815 = 0.93 |
| | | *CCG 903* | | | |
| <10,000 | 16/20 = 0.80 | 92/104 = 0.89 | 82/95 = 0.86 | 33/35 = 0.94 | 223/254 = 0.88 |
| 10–20,000 | 7/8 = 0.88 | 28/34 = 0.82 | 15/16 = 0.94 | 9/10 = 0.90 | 59/68 = 0.87 |
| 20–100,000 | 13/13 = 1.00 | 44/52 = 0.85 | 33/41 = 0.81 | 14/15 = 0.93 | 104/121 = 0.86 |
| >100,000 | 9/12 = 0.75 | 11/14 = 0.79 | 10/15 = 0.67 | 13/15 = 0.87 | 43/56 = 0.77 |
| Total | 45/53 = 0.85 | 175/204 = 0.86 | 140/167 = 0.84 | 69/75 = 0.92 | 429/499 = 0.86 |

and 100,000 cells/cu mm achieved complete remission in CCG 101 and CCG 143, while the remission rate for the same category of patients in study CCG 903 was 86% (Table 5). The difference was even greater in patients whose initial leukocyte counts were over 100,000 cells/cu mm. This result constitutes a further advance in the efforts to improve therapy for this group of patients thought to have a particularly poor prognosis.

The addition of L-asparaginase to VCR and PDN did not result in any appreciable increase in the frequency of toxic effects. Hyperglycemia, the most common complication associated with the therapy, was observed in 20 patients. This was most likely induced by the administration of L-asparaginase, since this complication only occurred once on study CCG 903 where patients were induced with PDN and VCR. The more frequent incidence of this complication in patients with high initial WBC counts (11 of 20) is of interest, considering that only 31% of the patients entering the study had initial WBC counts of over 20,000 cells/cu mm. Since hyperglycemia was mainly observed in children older than 10 years of age who had received doses of over 6000 IU, it is possible to identify those patients at risk for this complication. The fact that 9 of 49 patients over 10 years of age whose initial WBC counts were greater than 20,000 cells/cu mm developed hyperglycemia documents the predisposition of these patients for this complication. Two possible mechanisms can be invoked to explain the hyperglycemia: pancreatic infiltration with leukemia, or depletion of asparagine, which is a constituent of the insulin molecule (4). It is conceivable that the increased leukemic population with the exaggerated demand for L-asparaginase decreases the supply of the amino acid to the B-cells of the pancreas necessary for insulin synthesis.

The extent to which the simultaneous administration of corticosteroids contributed to the development of hyperglycemia is unknown; however, postasparaginase diabetes has been observed in patients not receiving adrenal steroids (15). It is also of significance that most patients developed the diabetic state after receiving the initial few doses. Hyperglycemia was transient and was followed by a rapid and complete recovery, with none of the patients involved becoming insulin dependent. The incidence of acute pancreatitis was negligible, with only 4 patients developing the complication, and with 1 fatality.

The use of a more purified L-asparaginase in the present study probably resulted in a decreased incidence of hypersensitivity reactions associated with the enzyme in comparison with previous reports (6, 17). Hypersensitivity reactions were minimal in severity and frequency and did not require discontinuation of the medication. The explanation for this decrease could be the use of a product containing less contaminating endotoxin and the simultaneous use of the immunosuppressive agent PDN (10). Other toxic effects, especially to the pancreas and liver, were observed and may be attributable to the inhibitory effect of L-asparaginase on protein synthesis (6). However, since this effect appears to be dose related (2), it was minimized by using doses of 6000 IU/sq m. The efficacy of this dose, as well as the decreased incidence of toxic effects by administering the medication i.m. rather than i.v., has been reported previously by the CCSG (9). The results of this study confirmed the importance of the route of administration and the dose of medication in minimizing side effects.

The data presented justify the recommendation that L-asparaginase be used as a 3rd agent for the induction treatment of newly diagnosed acute lymphocytic or acute undifferentiated leukemia and represents a major advance in the continuous progress being made in the treatment of this disease. Other factors which may contribute to further progress, such as CNS prophylaxis, type and length of maintenance therapy, and front-end prognostic factors, are presently under evaluation.

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**APPENDIX**

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