BCG in the Treatment of Acute Lymphocytic Leukemia

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Children with acute lymphocytic leukemia, who were in remission after induction with prednisone and vincristine and consolidation with intravenous methotrexate, were randomized into three groups receiving (1) no further therapy, (2) BCG, and (3) chemotherapy with biweekly methotrexate and monthly prednisone and vincristine. Children continuing in remission after 8 mo on chemotherapy in group 3 were rerandomized into three similar groups, i.e., no therapy, BCG, and chemotherapy. In the primary randomization, the median duration of remission was identical in the groups receiving no therapy or BCG, (4 and 4.3 mo respectively), and both were significantly less than the median duration of remission on chemotherapy which had not been reached prior to secondary randomization at 8 mo. Results of secondary randomization were similar to those of primary randomization. As used 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 FIRST CLINICAL trial using BCG in acute lymphoblastic leukemia was reported by Mathé et al. in 1969.[1] This trial was based on prior studies in murine leukemia which demonstrated a role for immunotherapy when given either before or after the inoculation of leukemic cells.[2] Immunotherapy in mice was not effective after the inoculation of leukemic cells unless the total leukemic cell population was less than 10^5 cells. In the clinical trial, patients were put into remission with chemotherapy and then given active immunotherapy with BCG, irradiated leukemic cells, or both. Those receiving immunotherapy remained in remission significantly longer than a group which continued on no therapy. There was no significant difference in remission duration among the three categories of immunotherapy. The groups were not homogeneous, however, with respect to either chemotherapy, age, or diagnosis.

Mathé's report stimulated the controlled clinical trial subsequently undertaken by Children's Cancer Study Group (CCSG) to evaluate further the use of BCG in children with acute lymphocytic leukemia (ALL). The objectives of the study were twofold: (1) to evaluate the use of nonspecific immunotherapy with BCG in prolonging an unmaintained complete remission, and (2) to compare the effect of BCG after 2 and 10 mo of complete remission. The latter objective was undertaken to determine whether BCG might be more effective

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Investigators, institutions, and grant support are given in Appendix 1.

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when used in patients who presumably would have a smaller leukemic cell population. To achieve this purpose, one arm of the study involved the use of methotrexate maintenance with monthly pulses of vincristine and prednisone. The results of the BCG phases form the main part of this report.

MATERIALS AND METHODS

Children under 16 yr of age with previously untreated ALL were eligible for the study. Pretreatment studies included bone marrow examination, chest film, PPD or Tine test, liver function tests, and a complete blood count with platelet count. During remission, bone marrow examination, SGOT, and alkaline phosphatase were done at 2-mo intervals. Physical examination and complete blood counts were done at monthly intervals. Informed consent was obtained from parents prior to entering a child in the study.

The schema for the study plan is given in Fig. 1. Remissions were induced with 6 wk of oral prednisone, 60 mg/sq m/day, and vincristine sulfate, 2 mg/sq m/wk intravenously. Those patients achieving either an M1 marrow (5% or less blasts) or an M2 marrow (between 6% and 25% blasts) were given consolidation therapy with four 5-day courses (15 mg/sq m/day) of intravenous methotrexate every 2 wk. All patients who had M1 marrows and had not developed evidence of central nervous system (CNS) leukemia by the end of consolidation were randomized into one of three primary maintenance regimens. A minimum absolute granulocyte count of 1500/cu mm and lymphocyte count of 500/cu mm were required to begin primary maintenance. The three primary maintenance regimens were: regimen 1, no therapy; regimen 2, BCG; and regimen 3, drug therapy with oral methotrexate, 30 mg/sq m twice a week, and monthly courses of 5 days of prednisone and a single dose of vincristine. The doses of prednisone and vincristine were the same as those used for induction. Children in regimens 1 and 2 continued without chemotherapy until either marrow or CNS relapse. Those with marrow relapse (25% or more blasts) were then reinduced and reconsolidated as before and, if in remission, were put on regimen 3 maintenance chemotherapy. If CNS leukemia developed during regimens 1 or 2, the patient was treated with intrathecal methotrexate, and systemic chemotherapy (as in regimen 3) was begun. Patients who were in regimen 3 and who continued without CNS or marrow relapse for 8 mo were rerandomized at that point into three regimens identical to those in primary maintenance. Regimen 4 received no therapy, regimen 5 received BCG, and regimen 6, chemotherapy. Children who developed CNS or marrow relapse on these regimens were treated in similar fashion to patients in relapse on regimens 1, 2, and 3. Children were considered off the study when they developed marrow relapse on drug therapy. Children were not given "prophylactic" therapy to the CNS in this study.

In order to insure that an adequate number of patients would be available for secondary randomization, the study was designed so that three-fifths of the patients randomized to primary maintenance entered regimen 3, and one-fifth entered each of regimens 1 and 2.

The BCG used was obtained from the Research Foundation in Chicago, Ill. This strain of

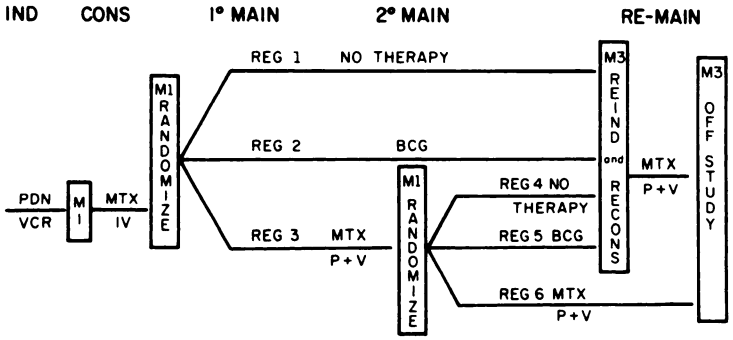

Fig. 1. Schematic plan for the use of immunotherapy with BCG following chemotherapy for induction and consolidation. The regimens for primary and secondary maintenance are designated.

Table 1. Summary of Induction Phase of 502 Patients Entered in the Study

Status at end of induction	
M1	432 (86.0%)
M2	21
M3	13
Expired during induction	18
Lost to follow-up	8
Toxicity before 42 days	1
Protocol error	9
Total	502
Reasons for not entering consolidation phase	
M3	13
Expired	18
Lost to follow-up before 42 days	8
Lost to follow-up at 42 days	4 (4 M1)
Toxicity	2 (1 M1)
Protocol error, progressive disease	12 (3 M1)
Total	57
Patients entering consolidation	445

bacillus Calmette-Guerin was originally obtained from the Pasteur Institute in Paris in 1954. It was cultured in pellicle culture and prepared for use as a freeze-dried preparation. Sterile water, 0.7 ml, was added to a single vial to make a reconstituted wet weight of 75 mg/ml. Three drops of the resuspended vaccine were put on each of two skin sites which were rotated between the upper arms and thighs. A vaccinating disc with 36 prongs was held on a magnet-type holder and applied to the area of skin containing the vaccine. The prongs were imbedded into the skin by pressure applied on the holder. This procedure was then repeated at the second skin site. Patients in regimens 2 and 5 were vaccinated twice a week for the first 4 wk and then once a week until marrow or CNS relapse.

RESULTS

Patients Entered

Table 1 summarizes the number of patients entered in the study and their fate during the induction phase. Patients were entered in the study over a 20-mo

Table 2. Summary of 445 Patients Entered on Consolidation Phase

Status at end of consolidation	
M1	371
M2	52
M3	14
Expired	3
Lost to follow-up	3
Protocol error	2
Total	445
Reasons for not entering primary randomization	
M2	52
M3	14
Expired	3
Lost to follow-up	4
CNS leukemia	22
Total	95
Patients randomized to primary maintenance	350

Table 3. Summary of Patients Randomized and Evaluable (in Parentheses) in Primary and Secondary Maintenance

Randomized to primary maintenance	350
Regimen 1, no therapy	31 (28)
Regimen 2, BCG	34 (28)
Regimen 3, chemotherapy	285 (247)
CNS leukemia	43
M3	35
M2 at 8 mo	16
Protocol error	11
Lost to follow-up	27
Randomized to regimens 4, 5, 6	153
Total	285
Randomized to secondary maintenance	153
Regimen 4, no therapy	52 (49)
Regimen 5, BCG	44 (41)
Regimen 6, chemotherapy	57 (48)

period, from February 1970 to October 1971. A total of 502 patients was entered, with 86.0% achieving an M1 marrow after induction with prednisone and vincristine. Thirteen children (2.5%) failed induction, and 18 (3.5%) expired during the first 6 wk of therapy. Table 2 summarizes the outcome of patients during the consolidation phase and accounts for those patients who were not randomized to primary maintenance.

Table 3 summarizes the number of children entered on all therapy regimens and the details of patient loss in regimen 3 prior to rerandomization. Three hundred and fifty patients were available for randomization to primary maintenance. Thirty-one received no therapy; 34, BCG; and 285, chemotherapy. There were 153 children available for rerandomization to secondary maintenance. Fifty-two were randomized to no therapy, 44 to BCG, and 57 to continuing chemotherapy. The number of patients evaluable in each regimen is given in parentheses.

Primary Maintenance

The outcome of primary randomization is shown in Fig. 2. The number of evaluable patients in each regimen was 28 in regimens 1 and 2 and 247 in regimen 3. In regimen 1 there were 25 marrow and three CNS relapses. Relapses in regimen 2 included 22 marrow, three CNS, and two simultaneous marrow and CNS. One patient remains in remission on BCG in regimen 2. The three regimens were compared at 7 mo following randomization, since patients on regimen 3 were destined to be further randomized to secondary maintenance at 8 mo. At 7 mo, 25% of patients were still in remission on no therapy, and 20% continued in remission on BCG. By contrast, 79% of children receiving maintenance chemotherapy were still in complete remission. The median duration of remission of regimen 3 patients had not been reached prior to secondary randomization. There was no difference between the outcome of regimen 1 versus regimen 2 patients. The difference between the number of patients still in remission in these two regimens and regimen 3, however, was statistically significant according to the logrank chi-square test ($p < 0.01$).[3] Since there

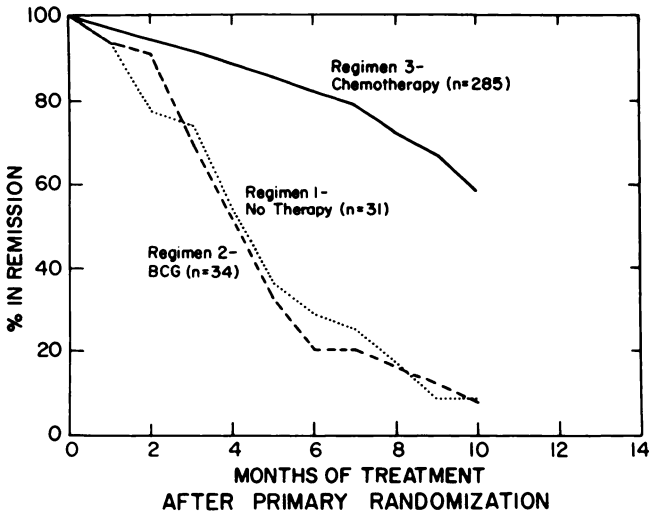

Fig. 2. The duration of remissions in regimens 1, 2, and 3 in primary maintenance is shown as the percentage of patients in remission on each regimen for each month of treatment after randomization. All cases are included in the curves; nonevaluable cases are followed only for periods properly at risk, and evaluable cases are followed until outcome.

appeared to be little difference in remission duration between regimens 1 and 2 early in the study and both were considerably shorter than in regimen 3, concern was raised over the potential risk to which regimen 1 and 2 patients were being subjected. Because of this concern, randomization was limited as soon as differences appeared statistically significant. This change accounted for the smaller number of patients in regimens 1 and 2 compared to regimens 4 and 5.

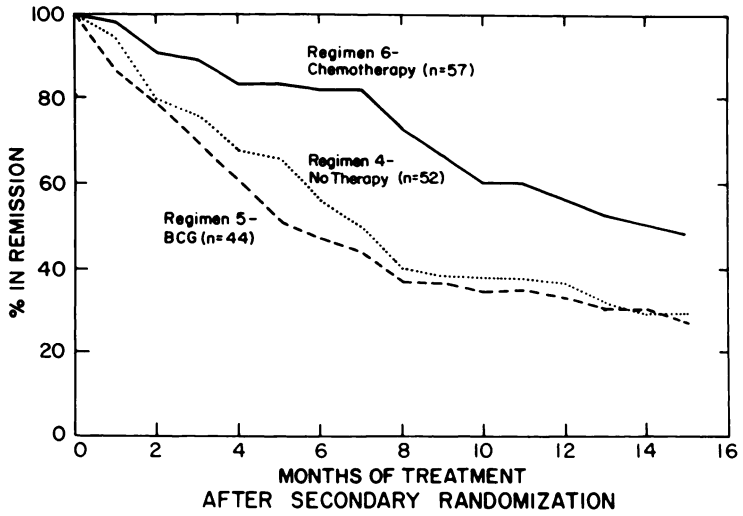

Fig. 3. The duration of remissions in regimens 4, 5, and 6 in secondary maintenance is shown as the percentage of patients in remission on each regimen for successive months after randomization. All cases are included in the curves; nonevaluable cases are followed only for periods properly at risk, and evaluable cases are followed until outcome.

Secondary Maintenance

Patients in secondary maintenance have been followed a minimum of 14 mo. A comparison of regimen 4 (no therapy), regimen 5 (BCG), and regimen 6 (chemotherapy) is shown in Fig. 3. As with primary randomization, the relapse rate (CNS or M3) is almost identical for the groups receiving BCG or no therapy. By contrast, patients receiving chemotherapy relapsed at a significantly slower rate according to the logrank chi-square test ($p < 0.01$). At 12 mo, 36% and 32% of patients were still in remission on regimens 4 and 5, respectively, whereas 56% were in remission on regimen 6. Eleven children continue in remission on no therapy, and ten have been on BCG for intervals of 15–32 mo. Sixteen children have continued on chemotherapy in regimen 6 for similar intervals. Five children on drug therapy have been removed from the study in marrow remission because of drug toxicity. Three of these were for liver toxicity due to methotrexate, and two children developed osteoporosis and fractures felt to be related to methotrexate, prednisone, or both. Three other children in remission on chemotherapy expired with infections. These included one with varicella, one with pneumocystis pneumonia, and one with an unidentified pneumonia.

BCG Reactions

BCG vaccinations were generally well tolerated. In the primary randomization (regimen 2), 78.5% of the children receiving BCG developed a skin reaction at the vaccination site within the first three vaccinations compared to 56% in the secondary randomization (regimen 5). Another 15% of children in both regimens 2 and 5 developed a skin response between the fourth and sixth vaccination. Two children in regimen 2 and five children in regimen 5 did not have a positive reaction at the vaccination site before relapse occurred. Although half the children developed one or more regional nodes larger than 1.0 cm, none was suppurative, and none required incision or drainage.

Two problems were encountered with BCG vaccination. One was the exacerbation of previously vaccinated sites with new vaccinations. Extending the interval between vaccinations allowed healing and less reactivation to occur. The second problem was the occurrence of a papular, erythematous, and pruritic rash with or without fever, headache, vomiting, and malaise after vaccinations. These symptoms could also be lessened by increasing the intervals between vaccinations. Two children were removed from the study because of the reactivation of previously vaccinated sites or the papular rash. Two additional children on BCG (with M1 marrows) were removed from study at the parents' request because of an unwillingness to continue off chemotherapy.

DISCUSSION

Following Mathé's report in 1969 on the efficacy of BCG and irradiated leukemic cells as immunotherapy in ALL, a trial supported by the Medical Research Council in England was begun to compare BCG, intermittent methotrexate, and no therapy as maintenance programs following 5 mo of chemotherapy.[4] This study differed from Mathé's in several important respects.

BCG of a different source (Glaxo Laboratories, Ltd.) was given by percutaneous inoculation rather than scarification, patients were uniformly treated prior to randomization, and intrathecal methotrexate was given as "prophylaxis" to the CNS. Following induction of remission in the present study, the period of intensive chemotherapy utilized methotrexate as the sole chemotherapeutic agent for 8 wk, while the previously reported studies used a number of agents over more extended periods. Although from different sources, the wet weight of BCG used was calculated to be 75 mg/ml in the present study in an attempt to make it similar to the Pasteur Institute material. Different volumes of the liquid material were placed on the skin in each of the studies. In spite of differences, the median duration of remission in primary maintenance with no therapy or BCG was similar in the British and in the present study. Median remission durations on no therapy were 122 and 119 days in the British and present study, respectively. Remissions with BCG were 111 days in the present study and 189 days in the British study. Since the median duration of remission for the chemotherapy regimens in these studies was so much longer than without chemotherapy, any design proposed to test the efficacy of BCG in prolonging remission after optimal chemotherapy would have difficulty unless BCG was particularly active.

The purpose of rerandomizing patients who had been in remission 10 mo on chemotherapy was to test the effect of BCG in a group which may have had a further reduction in leukemic cells. Although remissions were longer in both the no-therapy and BCG groups than in primary maintenance, remissions with chemotherapy were significantly better. The longer remissions with BCG or no therapy in secondary maintenance were probably related to the fact that high-risk patients had relapsed prior to rerandomization, allowing for a degree of selection in secondary maintenance.

Table 4 summarizes the median initial white blood cell count in each regimen related to the time of relapse. Although patients in this study were not randomized on the basis of initial white blood count (WBC), the median initial WBC was similar in regimens 1, 2, and 3. Children relapsing prior to 90 days in each of the regimens in primary randomization had a significantly higher WBC than those relapsing after 90 days.[5] Similar findings occurred in secondary randomization with the exception of regimen 6. The earlier relapse of patients in regimen 3 with higher initial counts allowed for a selection of better-risk patients for secondary randomization.

Table 4. White Blood Cell Count at Diagnosis Related to Time of Relapse

Regimen	Median WBC $\times 10^3$ for Total Group	Relapse Within 90 Days		in Remission Beyond 90 Days		Statistical Significance Mann-Whitney Test[5]
		No. of Patients	Median WBC $\times 10^3$	No. of Patients	Median WBC $\times 10^3$	
1	8.2	8	27.5	22	6.05	$p < 0.01$
2	8.4	9	18.2	19	7.1	$p < 0.05$
3	9.0	24	19.0	256	8.0	$p < 0.001$
4	6.8	12	27.8	39	6.2	$p < 0.001$
5	6.1	13	14.5	30	4.3	$p < 0.001$
6	9.0	6	15.3	50	10.7	NS

At the present time there are no parameters by which one can measure the immunologic effect of BCG on the leukemic process. Although animal studies show a positive correlation between successful immunization and tumor response to immunotherapy, support for such a relationship in human studies has been limited to malignant melanoma.[6] Skin tests were not done as a planned part of the present study except for pretreatment Tine or PPD skin tests, all of which were negative. Most of the children were skin tested after relapse on BCG and while on a variety of chemotherapeutic agents. Twenty of the children who received BCG as primary maintenance were tested, and of these nine (45%) had a positive reaction. In secondary maintenance 75% of the children tested (32 of 41) had positive skin tests. Because of the variable times at which skin testing was done, no valid correlation can be made between response to immunotherapy and the ability to develop an immune response to BCG.

In a retrospective review subclassifying the cell types of acute lymphoblastic leukemia, Mathé et al. were able to show that only two of their four morphologic categories, i.e., microlymphoblastic and prolymphocytic, were associated with the cumulative survival duration plateau observed in patients treated with chemotherapy and immunotherapy.[7] Thus, morphologic subclassification might present still another variable in the evaluation of response to immunotherapy in ALL.

Since the reports of Mathé and the Medical Research Council trial in Great Britain, several studies using immunotherapy in acute myelogenous leukemia (AML) have been reported. The study reported by Crowther et al.[8] and Powles[9] of acute myelogenous leukemia in adults has generated particular interest. Patients were put in remission with rubidomycin and cytosine arabinoside. Various induction schedules and further consolidation treatment were given the majority of patients. Those in remission after these two phases of treatment were randomized into three subgroups for maintenance. One group received chemotherapy alone; one, chemotherapy plus immunotherapy; and the third, immunotherapy alone. Chemotherapy consisted of monthly courses of cytosine arabinoside, 6-thioguanine, and rubidomycin. Immunotherapy consisted of Glaxo BCG and irradiated leukemic cells given in separate sites weekly. Both remission length and survival were doubled in the groups receiving immunotherapy compared to the group receiving chemotherapy alone. The median duration of remission in the immunotherapy group was 16.5 mo, and the median survival had not been reached at 2 yr. Powles commented on the fact that half of the patients who relapsed achieved second remissions with chemotherapy, contributing to the prolonged survival in the immunotherapy group. The small group of patients who received only immunotherapy (9 of 32) appeared to fare as well as those receiving chemotherapy in addition. Freeman et al.[10] reported on a group of 32 adult patients with acute myeloid leukemia treated in similar fashion to those of Powles. Only 8 of 32 patients achieved complete remission and seven of eight were given immunotherapy with BCG and irradiated leukemic cells. The mean duration of remission in this uncontrolled study was 28 wk. Although chemotherapy was not given as a planned part of maintenance therapy, frequent marrow examinations during remission revealed early relapses in several of the patients who were then given

courses of reinduction chemotherapy. These authors also commented on the high rate of reinduction in this small group of patients but were unable to say whether it related to the immunotherapy or to the fact that the patients had not been on chemotherapy and might have avoided drug resistance. The controlled study in myeloblastic leukemia in adults reported by Vogler and Chan used Tice-strain BCG given twice weekly for 4 wk combined with methotrexate twice weekly for remission maintenance.[11] This group was compared to one which received only methotrexate. The median duration of remission of the immunotherapy group was 20.4 wk, compared to 9.7 wk for the methotrexate group. Gutterman et al. have reported recently on chemoimmunotherapy in adult acute leukemia.[12] Immunotherapy consisted of the use of fresh liquid Pasteur-strain BCG given by scarification at the beginning of wk 2, 3, and 4 of each month of maintenance therapy. Chemotherapy using cytosine arabinoside, prednisone, and vincristine was given for the first 5 days of each month. Thirty-three patients (21 AML) received chemotherapy alone, whereas 20 (14 AML) received chemoimmunotherapy. The remainder of patients in each group had ALL or AUL. Prolongation of remission duration was seen in the patients with AML only. The median duration of remission in the AML patients on chemotherapy was 60 wk, while that of AML patients on chemoimmunotherapy will be greater than 72 wk.

Sokal et al. have reported on patients with chronic myelocytic leukemia who received BCG and cultured cells in mixture as immunotherapy.[13] When compared to a group of selected controls, the authors felt that survival in the immunized group had been favorably influenced by immunotherapy. This study is the only one which has used cells and BCG together. Whether or not remission duration in ALL could be improved with this maneuver is unknown.

Although many variables are present among these studies, the results raise several interesting questions. One is the apparent response to immunotherapy in AML compared to ALL. Gutterman et al. suggest that one reason for this may be the fact that leukemic myeloblastic cells are more antigenic than leukemic lymphoblasts. These authors provide another interesting finding in the use of in vitro lymphocyte blastogenic reactivity in patients receiving chemoimmunotherapy. The lymphocytes of patients who remained in remission longest had either a negative or weak response to their own remission marrow cells. Patients whose lymphocytes remained active to their own remission marrow cells have all relapsed, suggesting the continuing presence of leukemic cells within the marrow.

Remission reinduction following relapse on immunotherapy in the present study (ALL) did not occur with greater ease, as was suggested in the AML studies above. Remission reinduction rates were similar in patients who relapsed on the control and BCG regimens and who were reinduced according to protocol. Those patients relapsing in primary maintenance on regimen 1 (control) showed an M1 reinduction rate of 84%, whereas those on regimen 2 (BCG) had an M1 reinduction rate of 86.9%. In secondary maintenance, patients relapsing on regimen 4 (control) had an M1 reinduction rate of 96.7%, and those on regimen 5 (BCG), 100%. The better reinduction rate in patients relapsing in secondary maintenance may relate to the fact that either theirs is a

select and more responsive group, or that the longer period off chemotherapy compared to regimens 1 and 2 aided them in avoiding drug resistance.

The current study and those cited above present many questions which are as yet unanswered. As used in this study, BCG alone was ineffective in prolonging drug-induced remission after either 2 or 10 mo of maintenance chemotherapy in ALL.

Appendix 1

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Appendix 1 *(continued)*

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