IMMUNOTHERAPY OF HUMAN CANCER

EDITED BY

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AND

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Preface

The past decade has been a period of great enthusiasm for the application of immunologic manipulations to the treatment of human cancers. Various techniques, most centering on nonspecific stimulation of the immune system, have been used in an attempt to modulate the host response to established cancers. The apparently positive results of early studies led to a profusion of clinical trials exploring the application of immunotherapy to virtually every major subtype of human cancer. As experience in this area increased, the design of clinical trials became more sophisticated and, in recent years, definitive studies of certain immunotherapeutic regimens have been completed.

In this book, we have attempted to collate current experience with the clinical application of immunotherapeutic techniques for the treatment of human cancer. The clinical trials presented include, primarily, well-designed studies that permit the investigators to reach definite conclusions, positive or negative.

The fact that most well-designed trials have not demonstrated significant therapeutic benefits should not be surprising and should in no way decrease enthusiasm for a continued orderly exploration of the value of other forms of immunotherapy. We hope that the comprehensive overview of the current status of the application of immunologic techniques to the treatment of human cancer presented in this book will be helpful to students of this field and to investigators concerned with the further development of cancer immunotherapy.

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SECTION

I

ACUTE MYELOGENOUS LEUKEMIA

BCG Immunotherapy of Acute Myelogenous Leukemia

George A. Omura, W. R. Vogler, and John Lefante

The effect of Tice strain bacillus Calmette-Guerin (BCG) on remission duration and survival of adults with acute myelogenous leukemia was studied in a prospective randomized cooperative trial. After randomized remission induction with arabinosyl cytosine (ara-C) plus vincristine plus methotrexate plus leucovorin, thioguanine plus ara-C plus daunorubicin, or daunorubicin plus ara-C, complete remissions were consolidated with an additional 9–10 weeks of combination chemotherapy. Ninety-seven patients were randomized to no further treatment or to maintenance with BCNU plus ara-C or BCG vaccination; there was no difference in median remission duration (6, 7, and 8 months, respectively) or survival (16, 16, and 22 months). Our data failed to show a statistically significant benefit with BCG vaccination.

Introduction

Several previous studies including one of our own [1] have reported benefits from bacillus Calmette-Guerin (BCG) vaccination in the treatment of acute myelogenous leukemia (AML). Our own study showed that remission was prolonged when 1 month of BCG therapy preceded methotrexate maintenance compared with the remission achieved by methotrexate alone. In the present study, we wished to separate the chemotherapy and BCG effects on remission duration and survival. In addition, the results of three different remission induction regimens [2, 3] were evaluated.

(Writing Committee for the Southeastern Cancer Study Group)
From the University of Alabama in Birmingham, Birmingham, Alabama, and Emory University, Atlanta, Georgia.

Patients and Methods

Newly diagnosed patients age 15 and over with AML and its variants, but excluding the blastic phase of chronic myelogenous leukemia, were eligible for study after written informed consent. The diagnosis was made from smears of blood and bone marrow by individual investigators. A complete remission was diagnosed according to previously published criteria [4]; remission duration was measured from the point when all criteria for complete remission were met until the marrow became abnormal.

Treatment Schedules

Patients were randomly assigned to an induction regimen. Initially, the regimen was either AVML or TAD (see below). Patients with less than a complete remission were to be crossed over to the other induction regimen. In June 1975, the AVML arm was closed and DA substituted. Patients who failed to achieve complete remission during the TAD-DA comparison went off study.

AVML: Cytosine arabinoside (ara-C), 100 mg/m² intravenous (IV) push days 1, 2, and 3, plus vincristine, 1 mg/m² 48 hr after the ara-C was completed, plus methotrexate, 50 mg/m² per os (PO) q6hr × 4 starting with the vincristine dose, plus leucovorin, 5 mg PO q6hr × 9–15 starting 18 hr after the methotrexate was completed, were given as a course; this regimen was repeated every 10 days until complete remission or for five courses.

TAD: Thioguanine, 100 mg/m² PO q12hr × 10, plus ara-C, 100 mg/m² IV push q12hr × 10, plus daunorubicin, 10 mg/m² IV push q24hr × 5, were given; this combination was repeated every 10 days until complete remission or for five courses.

DA: Daunorubicin, 10 mg/m² IV push days 1, 2, and 3, plus ara-C, 100 mg/m² q24hr × 7 by continuous IV infusion; this combination was repeated every 10 days until complete remission or for three courses.

Consolidation. Remitters on AVML received another five courses of AVML given every 14 days. Remitters on TAD or DA received thioguanine, ara-C, and daunorubicin once per day for 5 days every 21 days for three courses.

Maintenance. Before the maintenance phase was entered, a follow-up marrow exam was done to confirm continuing remission. Then a second randomization was carried out:

No further treatment: No more chemotherapy was given as long as remission continued.

BCNU plus ara-C: BCNU, 50 mg/m² IV was given monthly plus ara-C, 100 mg/m² subcutaneously (SC), was given weekly for 12 months.

BCG: Tice strain BCG (Research Foundation, Chicago, Illinois) was given by the tine technique twice weekly in all four proximal extremities for 4 weeks. Approximately 3×10^8 viable organisms were given each time. Two weeks later, a first strength partial protein derivative (PPD) skin test was done. In those patients whose skin test had converted or become more strongly positive than it was pretreatment, vaccinations were continued every 4 weeks for 1 year. All others had a repeat marrow exam to rule out relapse; if still in remission, they repeated the intensive vaccination cycle.

After the maintenance phase monthly blood counts and periodic marrow exams were done and all patients were followed for the duration of remission and survival.

Statistical Methods

Response rates were compared using a chi-square test on proportions. The generalized Wilcoxon test was used for comparing duration of remission and survival curves. A p value of 0.05 or less was considered significant.

Results

From May 1974 through November 1977, 586 patients entered the study. The median ages for TAD, DA, and AVML patients were 54, 54, and 48 years, respectively. There was a higher proportion of males on TAD than on DA or AVML ($p = 0.03$). Other pretreatment characteristics of the various treatment groups were comparable. Of 208 evaluable patients on TAD, 105 (50%) achieved complete remission; of 188 patients on DA, 97 (52%) achieved complete remission; 15 of 59 patients (25%) on AVML had remissions. AVML was significantly inferior to TAD ($p = 0.025$). A detailed analysis of induction and consolidation will be reported elsewhere [5]. There was a progressive attrition through the phases of the protocol because of ineligibility, incomplete data, protocol

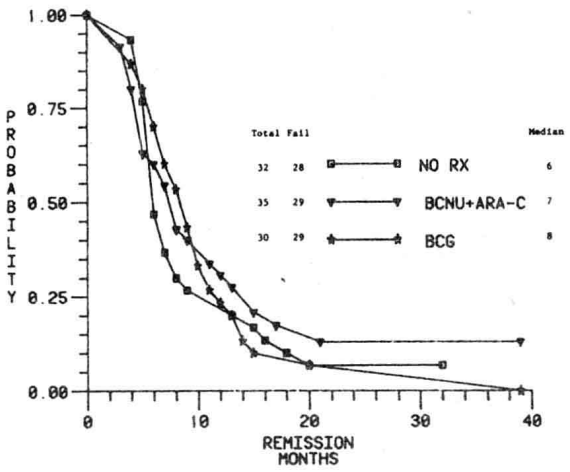


Figure 1. Life table plot of remission duration. There are no significant differences with different treatment protocols.

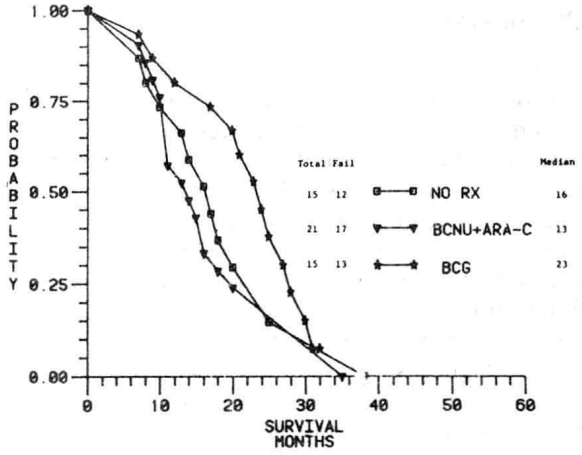
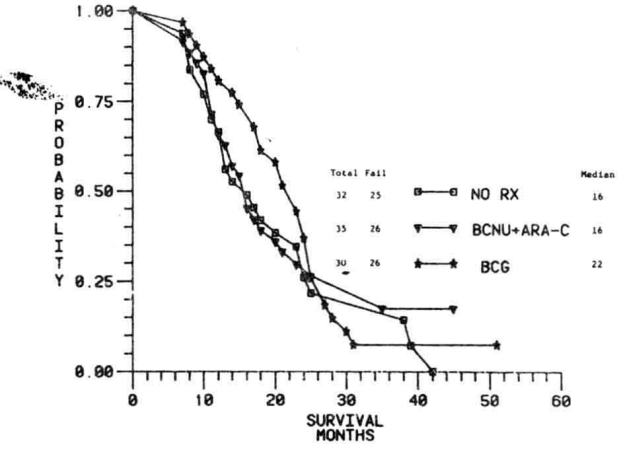


Figure 3. Survival from entry on study of patients induced with thioguanine plus ara-C plus daunorubicin. Survival after BCG therapy is longer than after BCNU plus ara-C ($p = 0.06$) but not longer than with no further treatment ($p = 0.13$).

violations, and early relapse, leaving 97 patients evaluable for the maintenance phase (51 on TAD, 36 on DA, and 10 on AVML), of whom 86 have relapsed and 11 remain in first remission.

Considering all patients evaluable for the maintenance phase, there was no significant difference in median remission duration (6, 7, and 8 months) or survival (16, 16, and 22 months) for those who received no further treatment, chemotherapy, and BCG, respectively (Figures 1 and 2). Since the quality of remissions induced by different regimens might differ, the remission duration and survival were examined separately for patients on DA and those on TAD. There were no significant differences noted; patients induced with TAD and maintained with BCG survived somewhat longer than those maintained with chemotherapy ($p = 0.06$; Figure 3) but no longer than those who received no further treatment. The median survival of TAD-BCG patients (23 months) was not significantly different from that of DA-BCG patients (17 months).

Figure 2. Survival from entry on study of those patients evaluable for the maintenance phase. There are no significant differences with different maintenance programs.



Toxicity

There were no unexpected toxicities. Nine patients (30%) receiving BCG had marked local reactions; one other developed disseminated BCG infection which was successfully treated with isoniazid.

Salvage Therapy

A variety of reinduction regimens were used since salvage therapy was not an integral part of the protocol. The most successful reinduction was an anthracycline plus ara-C with a complete remission rate of 60% (12/20) for those for whom postrelapse information is available. The BCG patients (2 of 6 had complete remissions) were not easier to reinduce with such treatment than the others (10 of 14 had complete remissions). There was no significant difference in duration of second remissions after relapse from BCG (13 weeks) no maintenance (18 weeks) or chemotherapy maintenance (19 weeks).