

IMMUNOTHERAPY OF HUMAN CANCER

**EDITED BY
WILLIAM D. TERRY
AND
STEVEN A. ROSENBERG**

Elsevier North Holland, Inc.
52 Vanderbilt Avenue, New York, New York 10017

Sole distributors outside the USA and Canada:
Elsevier Science Publishers B.V.
P.O. Box 211, 1000 AE Amsterdam, The Netherlands

© 1982 by Elsevier North Holland, Inc.

Library of Congress Cataloging in Publication Data

Main entry under title:

Immunotherapy of human cancer.

Bibliography: p.

Includes index.

1. Immunotherapy.	2. Cancer—Treatment.	3. Cancer—
Immunological aspects.	I. Terry, William D.	II. Rosen-
berg, Steven A.		

RC271.I45I47 616.99'4061 82-4970

ISBN 0-444-00614-1 AACR2

Manufactured in the United States of America

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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Contents

Preface xi

List of Senior Contributors xiii

SECTION I

ACUTE MYELOGENOUS LEUKEMIA

BCG Immunotherapy of Acute
Myelogenous Leukemia 3

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

A Phase III Trial Comparing BCG Alone,
Cytosine Arabinoside plus Daunorubicin,
and a Combination of BCG, Cytosine
Arabinoside, and Daunorubicin for
Maintenance Therapy in Acute
Myelogenous Leukemia 7

William R. Vogler, Elliott F. Winton,
David S. Gordon, Rhonda Jarrell, John Lefante,
and Elaine Hearn

A Successful Randomized Trial of
Immunotherapy Alone Versus No-
Maintenance Treatment in Acute
Myelogenous Leukemia 11

R. Harris, S. Z. Zuhrie, C. B. Freeman,
A. P. Read, J. E. MacIver, C. G. Geary, and
I. W. Delamore, and J. A. Tooth

BCG plus Leukemic Cell Therapy in
Patients with Acute Nonlymphoblastic
Leukemia: Effect in Groups with High and
Low Remission Rates 17

P. Reizenstein, B. Andersson, M. Björkholm,
G. Brenning, L. Engstedt, G. Gahrton, R. Hast,
G. Holm, P. Hörnsten, A. Killander, B. Lantz,

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Active Immunotherapy for the Treatment of
Acute Myelogenous Leukemia: The Use of
Intravenous BCG and a Comparison
Between BCG and Irradiated Leukemic
Blast Cells 23

J. A. Whittaker, R. Bailey-Wood, and
S. Hutchins

A Controlled Trial of
Chemoimmunotherapy of Acute
Myelogenous Leukemia with the Methanol
Extraction Residue of Tubercle Bacilli
(MER) 33

Janet Cuttner, Oliver Glidewell, and
James F. Holland

Immunotherapy of Acute Myelogenous
Leukemia Using *Corynebacterium Parvum*
and Allogeneic Cells 39

Robert Peter Gale, Kenneth A. Foon,
Coralee Yale, and Jacob Zigelboim

SECTION II

ACUTE LYMPHOCYTIC LEUKEMIA, NON- HODGKIN'S LYMPHOMA, AND MULTIPLE MYELOMA

Levamisole Therapy During Maintenance
of Remission in Patients with Acute
Lymphoblastic Leukemia 47

Santiago Pavlovsky, Guy Garay,
Federico Sackmann Muriel, Eva Svarch,
Jorge Braier, Berta Vergara, Cristina Scaglione,
Mariana Eppinger-Helft, Renato Failace,
Eduardo Dibar, and Jorge M. Divito

Chemoimmunotherapy of Malignant
Lymphoma 55

Stephen E. Jones

Chemoimmunotherapy for Multiple
Myeloma: Effect of Levamisole During
Maintenance 61

Sydney E. Salmon, Raymond Alexanian, and
Dennis Dixon

SECTION III LUNG CANCER

Intratumoral BCG Immunotherapy Prior to
Surgery for Carcinoma of the
Lung: Preliminary Results 69

Richard A. Matthay, Donald A. Mahler,

Malcolm S. Mitchell, Darryl H. Carter,
Jacob Loke, Gerald J. Beck, Arthur E. Baue,
and Herbert Y. Reynolds

Intralesional BCG in Pulmonary
Tumors 81

E. Carmack Holmes, Kenneth P. Ramming,
Sidney H. Golub, Richard Edelstein,
Masayuki Niitsuma, Marshall Bein, and
Walter Coulson

Four-Year Follow-up on the Albany
Experience with Intrapleural BCG in Lung
Cancer 87

Martin F. McKneally, Carole Maver,
Harvey W. Kausel, Joseph B. McIllduff,
Thomas M. Older, Eric O. Foster,
Ralph D. Alley, and Lloyd Lininger

Surgical Adjuvant Immunotherapy in Non-
Oat Cell Carcinoma 93

The National Lung Cancer Study Group

Intrapleural BCG in Lung Cancer
Treatment 101

R. W. Baldwin, P. B. Iles, M. J. S. Langman,
J. Lowe, and D. F. Shore

Adjuvant Immunotherapy with Intrapleural
BCG and Levamisole in Patients with
Resected, Non-Small Cell Lung
Cancer 105

Peter W. Wright, Lucius D. Hill,
Arthur V. Peterson, Richard P. Anderson,
Samuel P. Hammar, Lloyd P. Johnson,
Edward H. Morgan, and Roland D. Pinkham

Intrapleural *Corynebacterium parvum* as
Adjuvant Therapy in Operable
Bronchogenic Non-Small Cell
Carcinoma: Preliminary Report 111

The Ludwig Lung Cancer Study Group

Adjuvant Immunotherapy of Lung Cancer
with BCG Cell Wall Skeleton 117

Yuichi Yamamura

Four-Year Results from Double-Blind Study
of Adjuvant Levamisole Treatment in
Resectable Lung Cancer 123

W. K. Amery, J. Cosemans, H. C. Gooszen,
E. Lopes Cardozo, E. Louwagie, J. Stam,
J. Swierenga, R. G. Vanderschueren, and
R. W. Veldhuizen

Yorkshire Trial of Adjuvant Therapy with
Levamisole in Surgically Treated Lung
Cancer 135

H. M. Anthony

Thymosin Fraction V Prolongs Survival of Intensively Treated Small-Cell Lung Cancer Patients 141

Martin H. Cohen, Paul B. Chretien,
Anita Johnston-Early, Daniel C. Ihde,
Paul A. Bunn, Jr., Byron E. Fossieck, Jr.,
Robert M. Uch, Mary J. Matthews,
Stanley E. Shackney, and John D. Minna

Immunotherapy of Carcinoma of the Lung with Intradermal BCG and Allogeneic Tumor Cells 147

J. W. Reid, E. Perlin, R. K. Oldham,
J. L. Weese, W. Heim, M. Mills, C. Miller,
J. Blom, D. Green, S. Ballinger, G. B. Cannon,
I. Law, R. Connor, and R. B. Herberman

Specific Active Immunotherapy of Stage I Lung Cancer Patients 153

T. H. M. Stewart, A. C. Hollinshead,
J. E. Harris, and S. Raman

Specific Active Immunotherapy of Squamous Cell Lung Carcinoma 159

H. Takita, A. C. Hollinshead,
J. N. Bhayana, F. Edgerton, D. Conway,
R. M. Moskowitz, R. H. Adler, M. Ramundo,
T. Han, U. Rao, R. G. Vincent, A. Federico,
L. Takita, and R. Smith

SECTION IV BREAST CANCER

Adjuvant Immunotherapy with Polyadenylic-Polyuridylic Acid in Operable Breast Cancer 167

Jean Lacour, Fanny Lacour,
Alfred Spira, Michael Michelson,
Jean-Yves Petit, Genevieve Delage,
Daniele Sarrazin, Genevieve Contesso,
Jeanine Viguier, and Evelyne Merlin Nahon

Adjuvant Chemotherapy with 5-Fluorouracil, Doxorubicin (Adriamycin) and Cyclophosphamide, With or Without BCG Immunotherapy in Stage II or III Breast Cancer 175

Aman U. Buzdar, George R. Blumenschein,
Gabriel N. Hortobagyi, Sewa S. Legha,
Hwee-Yong Yap, Luis T. Campos, and
Evan M. Hersh

A Stratified Randomized Trial of 5-Fluorouracil, Doxorubicin (Adriamycin), and Cyclophosphamide Alone or with BCG in Stage IV Breast Cancer 183

P. B. McCulloch, M. Poon, P. B. Dent, and
P. Dawson

Combination of Levamisole Immunotherapy with Conventional Treatments in Breast Cancer 187

Pentti Klefström, Paul Holsti,
Pentti Gröhn and Erkki Heinonen

Inefficacy of Postradiotherapeutic BCG Immunotherapy in T₃-T₄ Breast Cancer Patients: A Randomized Trial 195

B. Serrou, H. Sancho-Garnier,
P. Cappelaere, R. Plagne, R. Metz,
M. Schneider, P. Chollet, M. Namer,
H. Pujol, J. Gary-Bobo, G. Meyer,
and G. Mathé

The Influence of Levamisole on the Survival of Patients with Disseminated Mammary Carcinoma Treated with Chemotherapy 199

E. J. W. Stephens, Helen F. Wood, and
Barbara Mason

SECTION V COLORECTAL CANCER

SWOG Study of Adjuvant Chemotherapy With and Without Oral BCG in the Postoperative Treatment of Cancer of the Colon: An Update 205

Frank J. Panettiere and T. Timothy Chen

Treatment of Radically Operated Colorectal Cancer Patients with Combined Adjuvant Therapy: Radiotherapy, Chemotherapy, and Methanol Extraction Residue of BCG 217

E. Robinson, A. Bartal, Y. Cohen, J. Mohiliver,
and T. Mekori

Adjuvant Immunotherapy with *Corynebacterium parvum* in Colorectal Cancer 221

R. G. Souter, P. G. Gill, and P. J. Morris

Levamisole Therapy in Patients with Colorectal Cancer 225

H. Verhaegen, J. De Cree, W. De Cock,
M. L. Verhaegen-Declercq,
and F. Verbruggen

Interim Analysis of a Trial of Levamisole and 5-Fluorouracil in Metastatic Colorectal Carcinoma 231

Ernest C. Borden, Thomas E. Davis,
John J. Crowley, William H. Wolberg,
Barbara McKnight, and Michael A. Chirigos

**SECTION VI
MELANOMA****Intralesional BCG Therapy of Patients with Primary Stage I Melanoma 239**

Steven A. Rosenberg, Herbert Rapp,
William Terry, Berton Zbar, Jose Costa,
Claudia Seipp, and Richard Simon

Adjuvant Immunotherapy of Malignant Melanoma: Results of a Randomized Trial in Patients with Lymph Node Metastases 245

Donald L. Morton, E. Carmack Holmes,
Frederick R. Eilber, and Kenneth P. Ramming

Treatment of Stage I and II Malignant Melanoma with Adjuvant Immunotherapy or Chemotherapy: Preliminary Analysis of a Prospective Randomized Trial 251

William D. Terry, Richard J. Hodes,
Steven A. Rosenberg, Richard I. Fisher,
Robert Makuch, Harriet G. Gordon, and
Susan G. Fisher

Progress Report of a Controlled Study of Prolonged Chemotherapy, Immunotherapy, and Chemotherapy plus Immunotherapy as an Adjuvant to Surgery in Malignant Melanoma 259

WHO Collaborating Centres for Evaluation of
Methods of Diagnosis and Treatment of
Melanoma

Adjuvant Chemoimmunotherapy in Stage I and II Melanoma 265

William C. Wood, A. Benedict Cosimi,
Robert W. Carey, and S. D. Kaufman

A Controlled ECOG Study of Adjuvant Therapy with BCG or BCG plus DTIC in Patients with Stage I and II Malignant Melanoma 271

Thomas J. Cunningham, David Schoenfeld,
Larry Nathanson, Janet M. Wolter,
W. Bradley Patterson, and Ernest C. Borden

Adjuvant Chemoimmunotherapy with DTIC and BCG in Patients with Poor Prognosis Primary Malignant Melanoma and Completely Resected Recurrent Melanoma 279

Ian C. Quirt, Patricia A. Kersey,
Michael A. Baker, Audley J. Bodurtha,
Michael H. King, Stevens T. Norvell,
David Osoba, Peter B. Dent,
Peter B. McCulloch, Ulo Ambus,
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James H. Goldie, Henry Krieger,
George J. Kutas, and Arnold D. Tepperman

Malignant Melanoma: Intravenous *Corynebacterium parvum* with DTIC and Cyclophosphamide 285

Cary A. Presant, Alfred A. Bartolucci,
Richard V. Smalley, and W. Ralph Vogler

Levamisole in the Treatment of Melanoma 289

Lynn E. Spitler, Richard Sagebiel,
Robert Allen, David Minor, Cleo Dymott, and
Thomas Drake

Preliminary Report of a Controlled Study of DTIC Alone, with BCG, or with *Corynebacterium parvum* in the Treatment of Advanced Malignant Melanoma 293

WHO Collaborating Centres for Evaluating of
Methods of Diagnosis and Treatment of
Melanoma

**SECTION VII
GENITOURINARY CANCER****Adjuvant BCG Immunotherapy in the Prophylaxis and Treatment of Noninvasive Bladder Cancer 301**

A. Morales and A. Ersil

Treatment of Superficial Bladder Cancer with Intravesical BCG 309

Carl M. Pinsky, Fernando J. Camacho,
Derek Kerr, David W. Braun, Jr.,
Willet F. Whitmore, Jr., and Herbert F. Oettgen

Intravesical and Percutaneous BCG Immunotherapy of Recurrent Superficial Bladder Cancer 315

D. L. Lamm, D. E. Thor, S. C. Harris,
V. D. Stogdill, and H. M. Radwin

BCG Immunotherapy in Advanced Prostate Cancer 323

P. Guinan, E. Totonchi, R. Crispin, K. Mouli,
and M. Shaw

**SECTION VIII
GYNECOLOGIC CANCER****Preliminary Report on the Treatment of Women with Cervical Cancer, Stages IIB, IIIB, and IVA (Confined to the Pelvis and/or Periaortic Nodes), with Radiotherapy Alone versus Radiotherapy plus Immunotherapy with Intravenous *Corynebacterium parvum*, Phase III 331**

Philip J. DiSaia, Stanley Gall, David Levy,
C. Paul Morrow, Steven L. Curry, and
Brian Bundy

**Chemoimmunotherapy in Primary Stage III
Ovarian Epithelial Cancer 337**

Stanley A. Gall, William T. Creasman,
John A. Blessing, John K. Whisnant, and
Phillip J. DiSaia

**A Randomized Trial of Doxorubicin and
Cyclophosphamide plus BCG Versus
Doxorubicin and Cyclophosphamide
Therapy of Advanced Ovarian Cancer 343**

David S. Alberts, Nancy L. Mason,
Robert O'Toole, John Neff, Robert Hilgers,
David Carlin, and Thomas E. Moon

**SECTION IX
OTHER CANCERS**

**Randomized Trial of Levamisole in Patients
with Squamous Cell Carcinoma of the Head
and Neck: Preliminary Results 353**

Carl M. Pinsky, Harold J. Wanebo,
Elias Y. Hilal, Elliot W. Strong,
Howard T. Thaler, and Herbert F. Oettgen

**Clinical Trial of *Corynebacterium parvum*
and Radiotherapy in the Treatment of Head
and Neck Carcinoma 361**

Vincent S-T. Cheng, Herman D. Suit,
C. C. Wang, John Raker, Sheldon Kaufman,
Kenneth Rothman, and Alexander Walker

**Specific and Nonspecific Immunotherapy
as an Adjunct to Chemotherapy and
Surgery in Skeletal and Soft Tissue
Sarcomas 367**

Frederick R. Eilber and Donald L. Morton

**Randomized Trial of Immunotherapy in the
Treatment of Advanced Neuroblastoma 377**

Thomas F. Necheles, Melvin Tefft, and
Vivian Weinberg

**SECTION X
PRELIMINARY TRIALS**

**Interferon Therapy of Patients with
Myeloma 387**

H. Mellstedt, A. Aahre, M. Björkholm,
B. Johansson, H. Strander, G. Brenning,
L. Engstedt, G. Gahrton, G. Holm, L. Lehrner,
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A-M. Stalfeldt, B. Simonsson, B. Ternstedt,
and B. Wadman

**Evaluation of Human Leukocyte Interferon
in Patients with Non-Hodgkin's Lymphoma
and Hodgkin's Disease 393**

James G. Gallagher, Arthur C. Louie,
Karol Sikora, Ronald Levy,
Thomas C. Merigan, and Saul A. Rosenberg

**Phase II Trial of Human Leukocyte
Interferon in Non-Small Cell Lung
Cancer: Preliminary Result 397**

Susan E. Krown, Mark B. Stoopler,
Richard J. Gralla, Susanna Cunningham-
Rundles, William E. Stewart II,
Marilyn S. Pollack, and Herbert F. Oettgen

**Interferon Therapy in Juvenile Laryngeal
Papillomatosis 407**

S. Haglund, P. G. Lundquist, S. Ingimarsson,
K. Cantell, and H. Strander

**Interferon Induction, Toxicity, and Clinical
Efficacy of Poly ICLC in Hematologic
Malignancies and Other Tumors 411**

A. S. Levine, B. Durie, B. Lampkin,
B. G. Levantahl, and H. B. Levy

**Intratumoral Therapy with BCG Cell Wall
Preparation in Patients with Head and
Neck Cancer 419**

J. Bier, H. Pickartz, S. Schlesinger,
S. Kleinschuster, B. Zbar, H. Rapp,
T. Borsos, M. Röllinghoff, H. Wagner

**Clinical, Hematologic, and Immunologic
Effects of Intravenous Methanol Extraction
Residue of BCG in Patients with Solid and
Hematologic Neoplasms 427**

Jorge R. Quesada, Evan M. Hersh,
Samuel G. Murphy, Gary Spitzer,
Michael Keating, Dharmvir Verma,
Jean A. Maroun, Herman I. Libshitz,
Stephen Richman, and Jordan U. Gutterman

**Phase I Study with *Nocardia rubra* Cell
Wall Skeleton 437**

Yuichi Yamamura

**Phase I Study of Immunotherapy with
Streptococcus pyogenes Preparation
(OK-432) 443**

M. Micksche, E. M. Kokoschka, R. Jakesz,
Th. Luger, K. Moser, H. Rainer, P. Sagaster,
A. Spitz, and A. Uchida

Phase I Evaluation of Bestatin in Patients
Bearing Advanced Solid Tumors 453

B. Serrou, D. Cupissol, H. Flad, A. Goutner,
J. M. Lang, H. Spitzglas, R. Plagne,
M. Beltzer, P. Chollet, M. Marneur, and
G. Mathé

Phase I Study of Immunotherapy with
Imexon 459

M. Micksch, P. Sagaster, E. M. Kokoschka,
O. Kokron, and U. Bicker

Phase I Study of Azimexon in
Immunodepressed Cancer Patients 471

A. Goutner, L. Schwarzenberg, and G. Mathé

Phase I Trial of Xenogenic Immune RNA
Therapy in Advanced Renal Cell
Carcinoma 477

Jerome P. Richie, Bosco S. Wang,
Glenn D. Steele, Jr., Richard E. Wilson,
and John A. Mannick

Radiolabeled Antibody to Tumor-
Associated Proteins 485

Stanley E. Order, Jerry L. Klein,
David Ettinger, Philip Alderson,
Stanley Siegelman, and Peter Lechner

Index 495

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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.

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 \times 4 starting with the vincristine dose, plus leucovorin, 5 mg PO q6hr \times 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 \times 10, plus ara-C, 100 mg/m² IV push q12hr \times 10, plus daunorubicin, 10 mg/m² IV push q24hr \times 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 IV push q12hr \times 7 by continuous infusion over 72 hr; 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

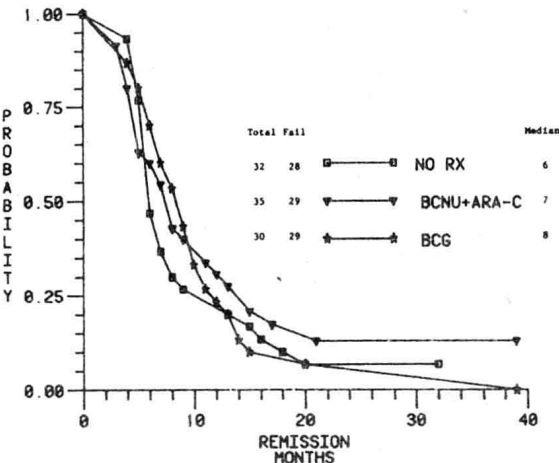


Figure 1. Life table plot of remission duration. There are no significant differences with different treatment protocols.

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

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

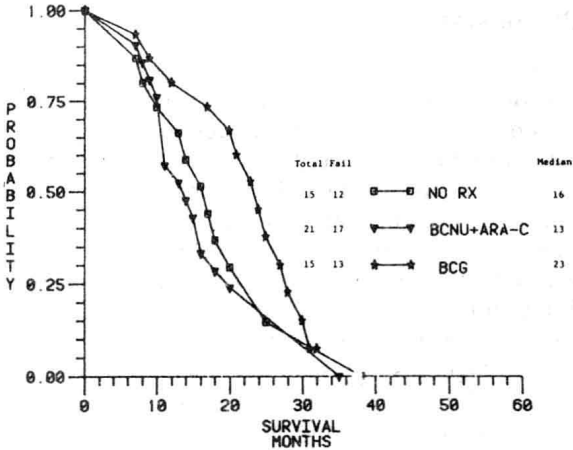
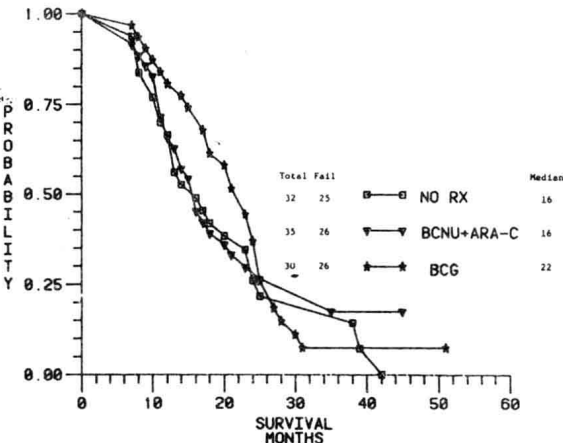


Figure 3. Survival from entry on study of patients induced with thioguanine plus ara-C plus daunorubicin. Survival after BCG therapy is longer than after BCNU plus ara-C ($p = 0.06$) but not longer than with no further treatment ($p = 0.13$).

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).

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).