The Therapy of Acute Leukemia in the Adult
A Progress Report

Peter H. Wiernik, M. D.

Section of Medical Oncology
National Cancer Institute,
Baltimore Cancer Research Center
at the
University of Maryland Hospital
Baltimore, Maryland, USA

Introduction

Complete remissions in adult patients with acute leukemia were unusual, if not rare, fifteen years ago. The discovery of highly effective antileukemic drugs such as cytosine arabinoside and daunorubicin and the development of more effective combinations of active chemotherapeutic agents largely through empiric clinical trial and error have dramatically changed that situation so that today 70 % or more of previously untreated patients achieve complete remission status. This improvement has been facilitated by major developments in supportive care. The use of allopurinol for the prevention of urate nephropathy has eliminated that serious complication of antileukemic therapy. Newer antibiotics active against *Pseudomonas aeruginosa* have allowed for the successful treatment of many life threatening infections which occur in the granulocytopenic leukemia patient. Laminar air flow rooms which provide essentially sterile air, and oral nonabsorbable antibiotics which sterilize the gastrointestinal tract, protect the leukemia patient in large measure from microbial hazards in his external and internal environments. Blood cell component therapy allows for replacement of platelets and granulocytes in cytopenic patients. It is the purpose of this paper to detail some of these achievements.

Reprint Requests to:
Peter H. Wiernik, M. D.
Baltimore Cancer Research Center
22 South Greene Street
Baltimore, Maryland 21201
USA

Induction Chemotherapy for Acute Nonlymphocytic Leukemia (ANLL)

The first drug combination that proved effective as therapy for acute nonlymphocytic leukemia was the POMP regimen, which consisted of high intravenous doses of prednisone, vincristine, methotrexate and mercaptopurine (1). This therapy was successful in producing complete remissions in approximately 25 % of adult patients and was the first clinical proof that combinations of effective drugs could be more active than single agents. Shortly after this demonstration, cytosine arabinoside (Ara C) became available for clinical trial and it soon proved to be a drug as active as the POMP combination (Table 1). The discovery of the clinical antileukemic activity of daunorubicin (DNM) shortly thereafter represents a turning point in the history of the therapy of acute nonlymphocytic leukemia. DNM alone will produce complete remissions in over 40 % of patients with ANLL (Table 1) and, more importantly, it (or a related anthracycline antibiotic, adriamycin) has become the cornerstone around which the most effective combination therapies to date have been built (Table 2). These new combinations have produced complete remissions in up to 70 % of previously untreated adults with ANLL.

Table I: Representative Results of Induction Therapy for ANLL using Cytosine Arabinoside or Daunorubicin alone in Previously Untreated Patients

Author	Ref	Regimen	CR rate
Wiernik	1	DNM 60mg/M² day 1–3	50 %
Wiernik	5	DNM 60mg/M² day 1–3	49 %
Wiernik (ALGB)	4	DNM 60mg/M² day 1–3	43 %
Ellison (ALGB)	12	Ara C 30mg/M² daily in 12 hr infusion to hypoplasia	24 %
Goodell	19	Ara C 40–70mg/M² in 4 hr infusion daily x 4	25 %
Armentrout	20	Ara C 4mg/kg in 8 hr infusion daily x 4–14 days	42 %
SWOG	14	Ara C 1.0gm/M² infused over 12 hrs	39 %

In an effort to achieve the greatest response rate with the least amount of induction therapy and, therefore, the least risk of serious (or even fatal) toxicity from induction therapy, a nonrandomized study has recently been initiated at the Baltimore Cancer Research Center in which patients are allocated to receive DNM 60 mg/M²/dayx3, or Ara C 200 mg/M²/dayx7 continuous IV infusion, or DNM 45 mg/M²/day x 3, days 1–3 and Ara C 100 mg/M²/day, days 1–7 continuous IV infusion, on the basis of certain biochemical tests performed on each patient's leukemic marrow cells. Patients whose cells have a high DNM reductase activity level (2)* but a low kinase:deaminase activity ratio (3)** receive DNM alone. Patients whose cells have a high kinase:deaminase activity ratio but a low DNM reductase activity level receive Ara C alone, and patients in whom both enzyme

Table II: Current Induction Therapy Results in Previously Untreated Patients with ANLL using Drug Combinations which include Cytosine Arabinoside and an Anthracycline Derivative

Author	Ref	Regimen	CR rate
Glucksberg	18	DNM 1.5mg/kg on day 1 VCR 1mg/M² on day 1 Pred. 1mg/kg day 1–5 Ara C 2mg/kg q 12 hr day 1–5 TG 2mg/kg q 12 hr day 1–5	59 %
Glucksberg	18	DNM 1.5mg/kg day 1–3 VCR 1mg/M² day 1 & 7 Pred. Ara C, TG as above	70 %
Brincker	17	DNM 80 mg q 5 days Ara C 150 mg daily Both given until hypoplasia	53 %
Masami	13	DNM 25mg/M² Ara C 80mg/M² 6-MPR 300mg/M² day 1–4 Pred. 60mg/M²	61 %
McCredie	15	ADM day 1 VCR day 1 Pred. days 5–9 Ara C days 1–9	70 %
Wiernik (ALGB)	4	DNM 100mg/M² day 1 TG 100mg/M² q 12 hr day 1–5 Ara C 100mg/M² 12 hr day 1–5	50 %
Wiernik	5	DNM 75mg/M² day 1 Ara C 75mg/M² q 12 hr day 1–5 TG 75mg/M² q12 hr day 1–5 Pyrimethamine 1mg/kg day 1–5	46 %
Yates	16	DNM 45mg/M² day 1–3 Ara C 100mg/M² day 1–7 (cont. IV infusion)	67 %
Rai (ALGB)	56	DNM 45mg/M² day 1–3 Ara C 100mg/M² day 1–7 (cont. IV infusion)	66 %*

* Some patients with M-1 marrows did not technically fulfill all requirements for CR because of drug induced peripheral cytopenia.

measurements are high, low or not performed for technical reasons receive both drugs. It is too early to evaluate this study since only 25 patients have completed therapy. It is evident already, however, that only about 25 % of patients will receive either Ara C or DNM alone when the above criteria for selection are applied. Thus far, with 35 patients who received both drugs evaluable, the complete remission rate is 70 % for that group of patients in the current BCRC study.

Maintenance Therapy for ANLL

Complete remission duration in adults with ANLL is disturbingly short and does not seem to vary greatly with induction or maintenance chemotherapy schemes. As an example, in a recent study of 3 induction regimens performed by Acute Leukemia Group B (protocol 7221) median complete remission duration was 5.5–6.6 months despite the use of monthly moderately intensive maintenance chemotherapy (4). It seems clear, however, that while such maintenance therapy commonly sustains complete remission for only approximately six months, the results are superior to those obtained when similar induction therapy is followed by no maintenance chemotherapy. In an early BCRC study (1) DNM 60 mg/M^2 daily x3 was used as an induction therapy and no maintenance treatment was given. The median duration of complete remission was 2.3 months. In a later BCRC study (5) and in the ALGB study referred to above (4) the same dose and schedule of DNM was used as an induction therapy option and moderately

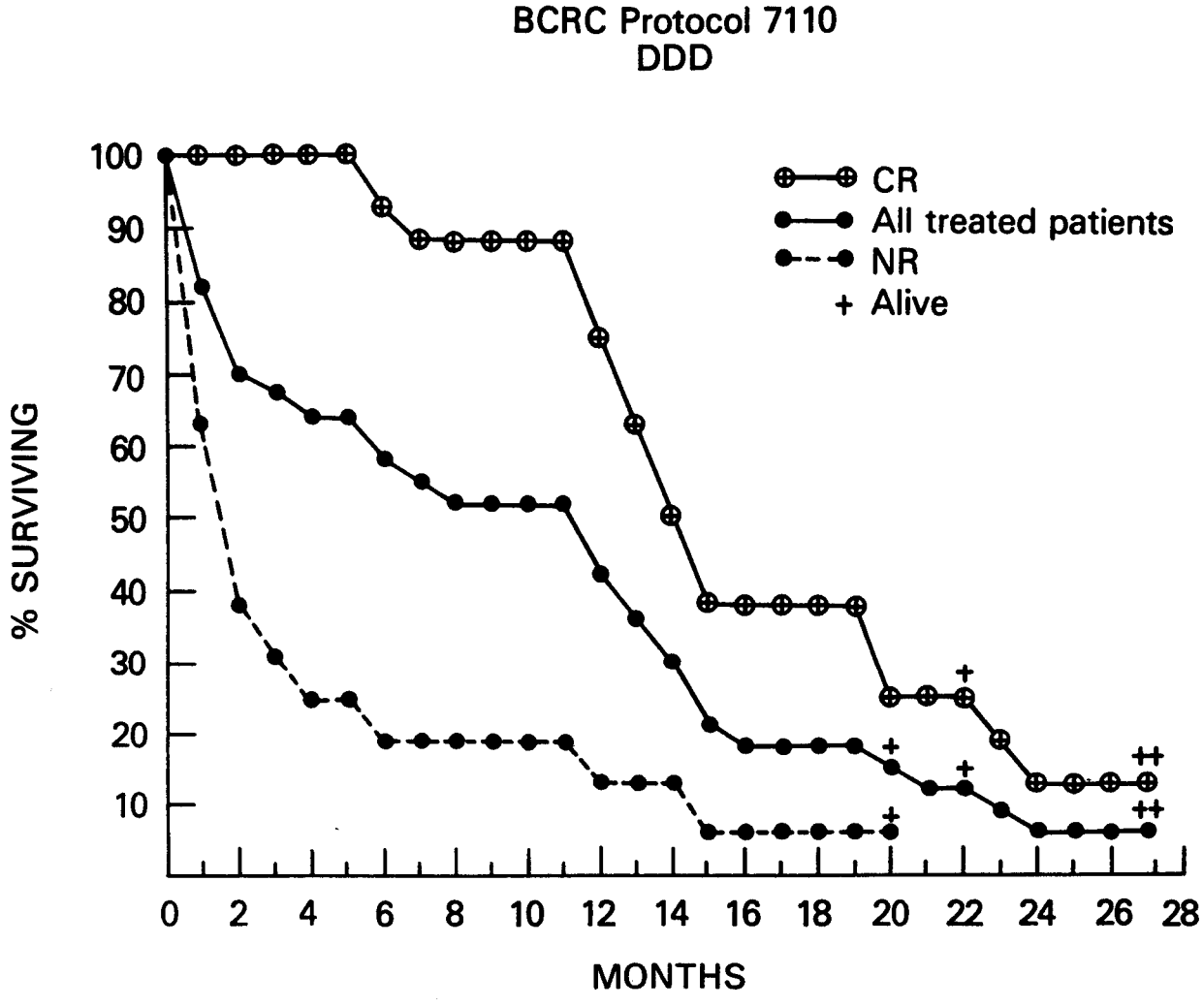

Fig. 1: Survival curves drawn by the life table method for patients with ANLL treated with daunorubicin alone for induction therapy in a recent BCRC study. The curves illustrate the significant survival advantage seen in all studies for patients who achieve complete remission.

intensive maintenance therapy was administered monthly. The median durations of remission in those studies were 6.8 and 6.2 months respectively.

Early data from Bodey, et al (6) suggest that when intensive re-induction courses of chemotherapy are given after a substantial complete remission has occurred, remission duration may be further prolonged. Such therapy is not without hazard, however, and results in significant morbidity and potential mortality.

The most significant contribution of immunology to clinical cancer therapy has been the development of immunotherapy maintenance regimes for ANLL. Studies in which BCG (7), the methanol extractable residue (MER) of BCG (8), or neuraminidase-treated allogenic leukemic cells (9) have been used for maintenance therapy of ANLL in conjunction with anti-leukemic drugs have all resulted in significant enhancement of remission duration of 2–3 fold over control patients maintained with chemotherapy alone. Such therapy is not innocuous and can result in severe local pain and disfigurement. However, although the mechanism of action of such agents is by no means clear, it *is* clear that they do favorably affect remission duration in ANLL. The clinical action of these substances derived from living unicellular material is reminiscent of "spontaneous" remission in acute leukemia observed rarely after bacterial infection (10).

Maintenance therapy with cyclophosphamide and 1, 3-bis (2-chloroethyl)-1-nitrosourea has recently been observed to produce a median duration of complete remission in ANLL comparable to that observed after immunotherapy (11). This observation has not yet been confirmed, however.

New Drugs for Induction Therapy of ANLL

Three new drugs currently under investigation for their antileukemic activity are of interest: 5-azacytidine, VP16-213, and neocarcinostatin.

5-azacytidine, a pyrimidine nucleotide analogue, produced a 28 % complete remission rate in one study (21) in which patients refractory to DNR, thioguanine, and Ara C were treated. The drug's mechanism of action is unclear and some data suggest (22) that it may act in a manner unlike any other antileukemic drug. Gastrointestinal, marrow, and mucous membrane toxicity are common with the drug. In addition a neuromuscular toxicity syndrome consisting of myalgia and weakness occasionally occurs. It has been suggested that this syndrome is due to hypophosphatemia secondary to hyperphosphaturia which results from a nephrotoxic action of 5-azacytidine (23).

VP16-213 (4-demethyl-epipodophyllotoxin-B-D-ethylidene glucoside) is a semi-synthetic derivative of podophyllotoxin. The drug prevents cells from accomplishing mitosis and has been shown to have antileukemic activity in certain animal systems. In one small study (24) a complete remission was obtained in one-third of patients with ANLL. A 50 % complete remission rate was obtained in a smaller group of patients who had a monocytic component to their leukemia. Marrow and gastrointestinal side effects are apparently less severe than with many other induction therapy drugs.

A remarkable 55 % complete remission rate with neocarcinostatin in patients with ANLL was reported from Japan (25). This drug, an acidic single chain polypeptide, is elaborated by *Streptomyces sp.* and has been shown to be active

against a number of animal tumor systems. Further evaluation of this drug is clearly warranted.

Adult Acute Lymphocytic Leukemia (ALL)

Adult ALL is responsive to the same chemotherapeutic agents used successfully in childhood ALL but lower complete remission rates and shorter durations of remission have been the rule (26, 27). Thus, while almost 90 % of children with ALL achieve complete remission with vincristine and prednisone most therapeutic trials in adults have produced complete remission in less than 50 % of patients, and while the median duration of remission approaches 5 years in some childhood studies most adult studies have yielded median remission durations of 1 year or less.

Vincristine in combination with prednisone has been employed in virtually all programs for initial induction therapy in both childhood and adult ALL. Chemotherapeutic agents which have shown beneficial effects when combined with vincristine and prednisone for remission induction therapy include methotrexate and 6-mercaptopurine (POMP) (28), L-asparaginase (29), daunorubicin (27), and adriamycin (30).

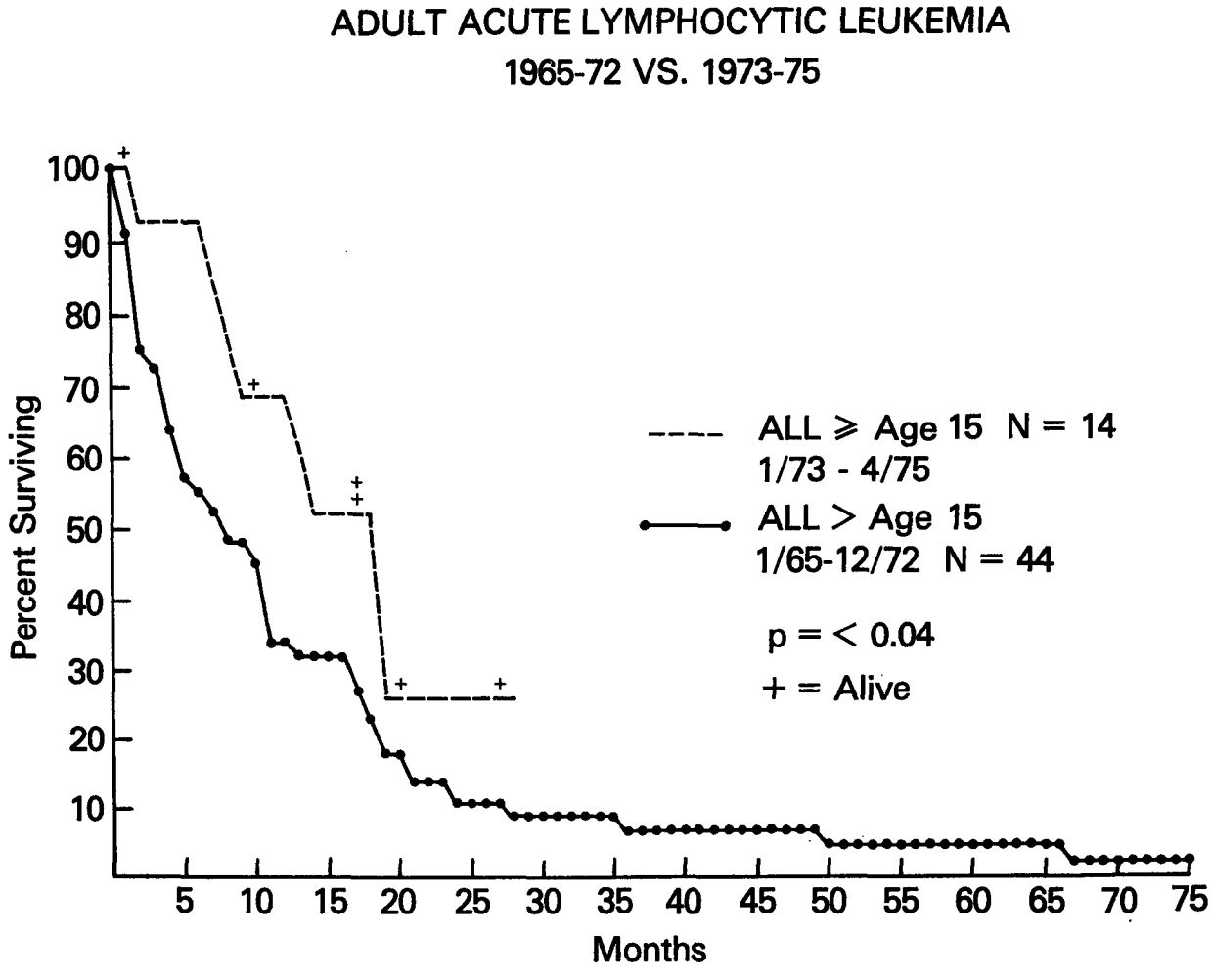

Fig. 2: Survival curves for all treated adults with ALL seen at the BCRC since 1965. The curves compare those patients treated most recently with those treated earlier and show a statistically significant advantage for the most recent patients (two-tailed analysis, method of Gehan (55)).

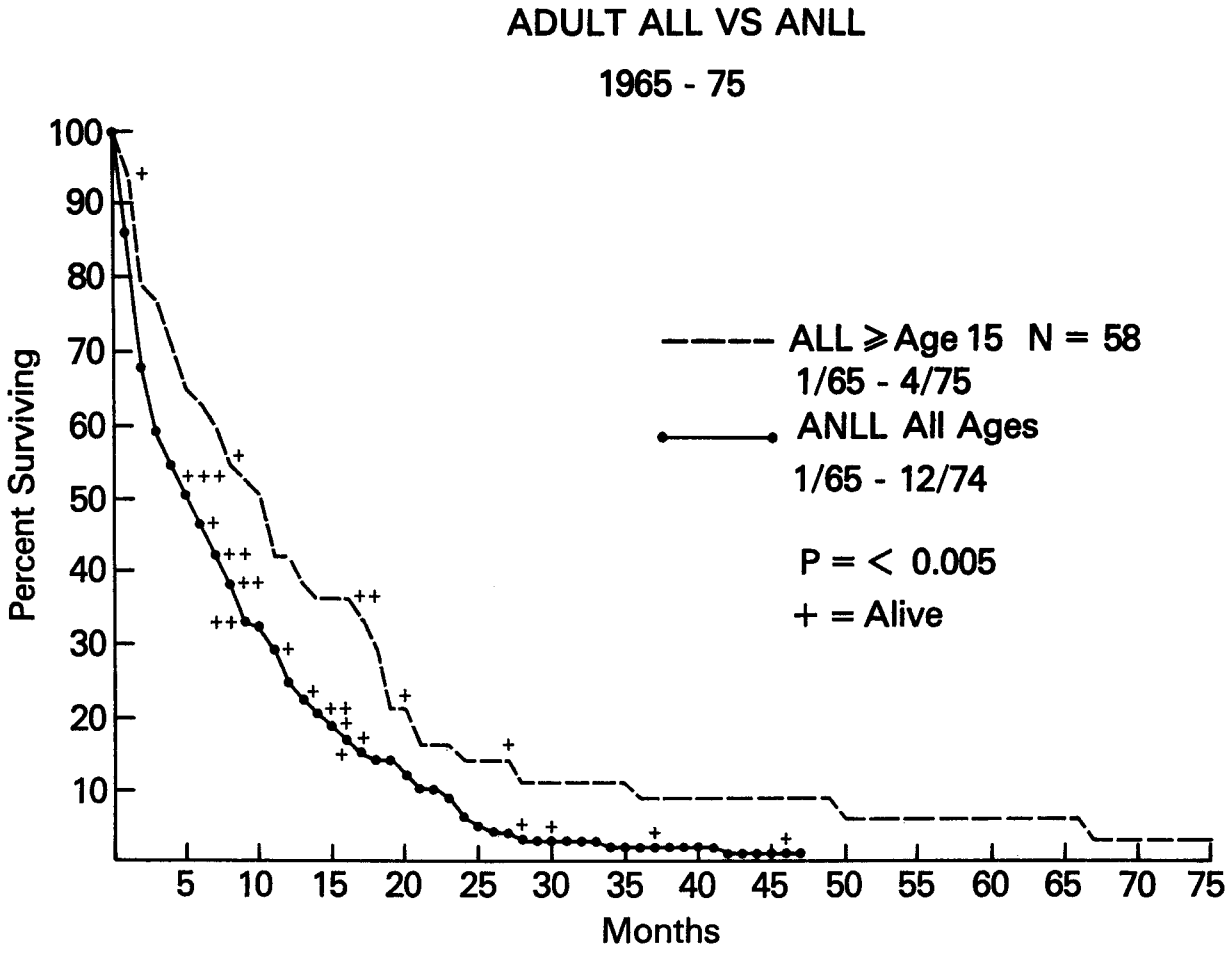

Fig. 3: Survival curves comparing all adult ALL patients with all ANLL patients (N = 276) treated at the BCRC since 1965. There is a highly significant advantage for the ALL patients (55).

In a recent study of induction therapy of adult ALL at the Baltimore Cancer Research Center 6-thioguanine, vincristine, dexamethasone and pyrimethamine were given in combination (31). Dexamethasone, a corticosteroid which increases the mobilization of granulocytes (32) was used for its potentially beneficial effect on infection in the induction period. Thioguanine, which has been shown to be as active as other purine antagonists in childhood ALL (33), was chosen instead of 6-mercaptopurine because its metabolism is not influenced by the concurrent administration of allopurinol. Pyrimethamine is a weak antifol that crosses the blood-brain barrier when given orally. The drug was reported to have activity against meningeal leukemia (34) and was studied in this regimen for its potential as a prophylactic meningeal leukemia agent. It has been clearly demonstrated in childhood ALL that prophylactic meningeal leukemia therapy significantly prolongs complete remission duration (26). In this study 53 % of adult patients achieved complete remission. However, severe infections occurred in more than half the patients and approximately one third developed meningeal leukemia. Thus, dexamethasone and pyrimethamine were not successful in this study. The median survival of all treated patients was more than 13 months, and complete responders had a median survival of 16+ months. These figures represent some improvement over earlier studies at this institution. Two recent investigations, one conducted

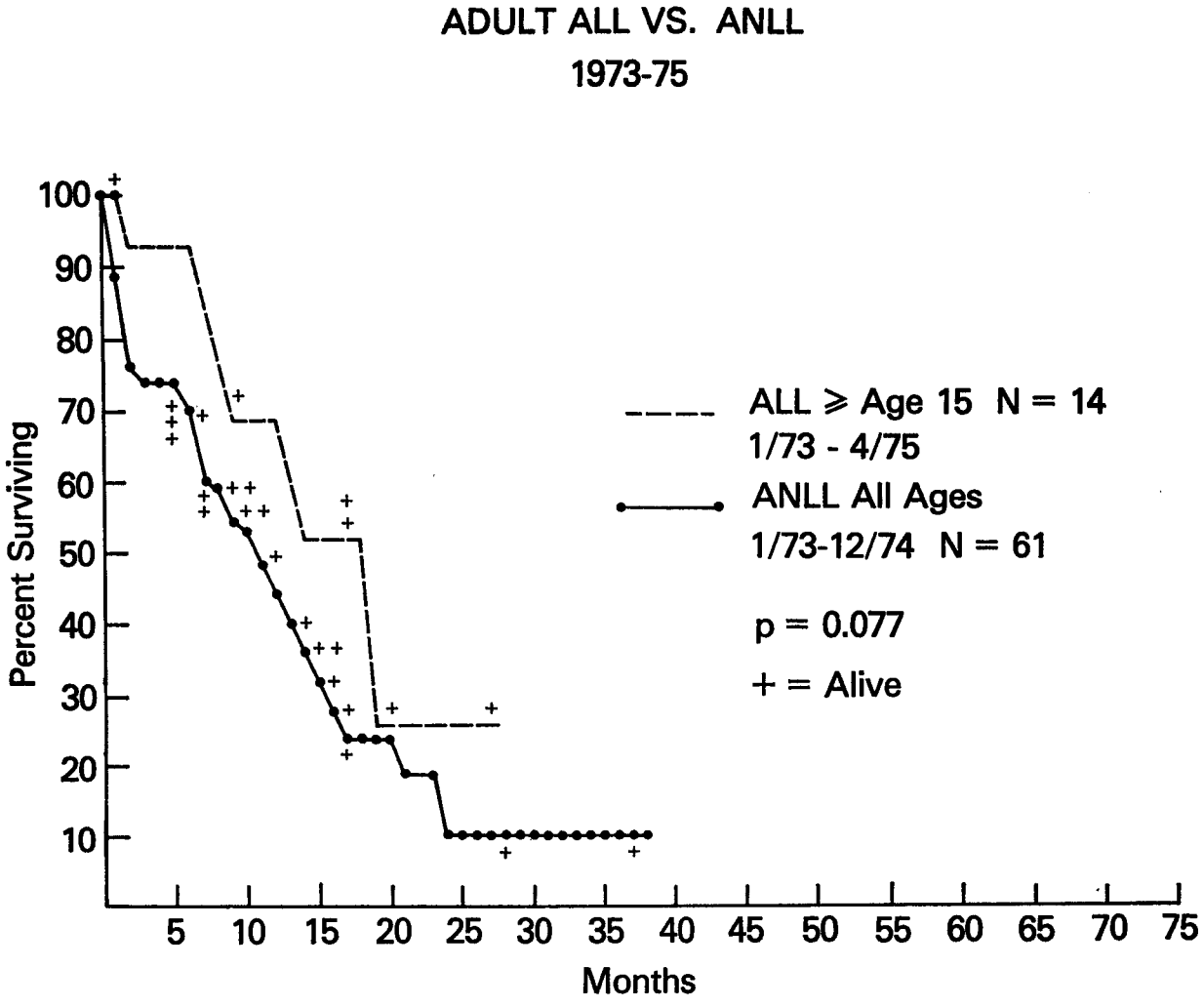

Fig. 4: Survival curves comparing the most recently completed study of therapy for ANLL with that for ALL at the BCRC. Significant improvement in the management of both diseases has lessened the heretofore significant survival difference between ALL and ANLL.

by Henderson for ALGB (29) and one reported by Capizzi, et al (35) are of special interest. In Henderson's study treatment with L-asparaginase for 10 days after several vincristine and prednisone courses has resulted in complete remission in 80 % of adults so treated. Based on kinetic data determined both in animal leukemia models and human lymphoblasts in vitro (36), Capizzi et al have studied asparaginase and methotrexate sequentially as induction therapy in previously treated adult ALL patients. Early results have indicated an 80 % complete response rate in such patients (35). It appears that asparaginase not only increases the sensitivity of leukemic cells to methotrexate by producing a rapid regrowth phase 9–10 days after asparaginase administration (36) but also that asparaginase diminishes methotrexate toxicity when given 24 hours after methotrexate. Marrow and mucous membrane toxicity were minimal in Capizzi's study but allergic reactions to asparaginase became a significant problem after several months of intermittent aspariginase treatment (35). Other data suggest that if an allergic reaction occurs with *E-coli* asparaginase patients can be safely treated subsequently with asparaginase prepared from *Erwinia sp.* (37). Capizzi, et al (35) have continued sequential methotrexate and asparaginase indefinitely during remission as mainte-

nance therapy and have obtained a median duration of remission of approximately 1 year in previously treated patients. The Capizzi regimen obviously deserves a trial in previously untreated patients. A study recently initiated at the Baltimore Cancer Research Center for such patients incorporates the Capizzi regimen. In that study patients receive a 10 day induction course as follows: on day 1 methotrexate 100 mg/M^2 given rapidly IV., Vincristine 2 mg, is given on day 2 and asparaginase 500 IU/kg is given as a 30 minute infusion beginning 24 hours after the methotrexate injection. Dexamethasone 6 mg/M^2 p. o. is given daily for 10 days. Induction courses are repeated if necessary and methotrexate doses are augmented to tolerance in subsequent courses. Six courses of methotrexate followed by asparaginase in the above doses are given as consolidation therapy beginning with the onset of complete remission, with 10 days between courses. Following that therapy 12 monthly courses of vincristine, dexamethasone, high dose methotrexate (100 mg/kg) and citrovorum factor are planned. Therapeutic results are not yet available from this study. However, early experience with the induction regimen indicates that marrow and mucous membrane toxicity may occasionally be much more severe than that originally observed by Capizzi, et al.

The Blastic Phase of Chronic Myelocytic Leukemia (CML)

Most patients with CML die shortly after a blastic transformation of the disease occurs. After this transformation the disease takes on many of the characteristics of ANLL except for one important difference: while, as noted above, real progress has been made in the treatment of ANLL, the blast phase of CML is essentially refractory to all known antileukemic drugs. Recently, in a study of the Acute Leukemia Group B some benefit from the combination of vincristine, prednisone, hydroxyurea, and 6-mercaptopurine has been noted, with approximately one-third of patients showing a favorable response with few complete remissions (38). However, the median survival of all patients treated in that study (from the onset of treatment for the blastic phase) is still only approximately 4 months. This median survival is comparable to that of many other studies.

Several new drugs deserve critical evaluation in the blastic phase of CML because of their demonstrated antileukemic activity in that disease. Butocin, an ethyl ester derivative of buthiopurine synthesized by Semonsky in Prague (39) was reported by Cerny (40) to have a high degree of activity in the CML blast phase, with over 40 %of a small group of patients obtaining a complete or partial remission in a mean treatment time of approximately one month. The duration of maximal response varied from 10 to 37 weeks, and the total drug dose necessary to achieve maximal response varied from 219 to 2028 mg/kg. A large trial of this drug in the blastic phase of CML should have high priority in therapeutic research in CML.

Piperazinedione and VP16-213 are agents recently made available for clinical trial that have demonstrated some degree of activity in the blastic phase of CML, although the number of patients treated is small (41, 42). Further study of these drugs may be productive.

Supportive Care

Infectious Disease Considerations: Patients with acute leukemia are particularly predisposed to serious infection because of granulocytopenia caused by the disease and its therapy. Poor leukocyte function, and easy access of bacteria through oral or intestinal mucosal ulcerations often resulting from chemotherapy are contributing factors as are other iatrogenic provocations such as indwelling venous catheters. It seems clear from recent studies at the Baltimore Cancer Research Center that the major causes of serious infection in acute leukemia patients are hospital-acquired organisms (43). As an example of this problem, I cite the recent evidence associating aspergillus infections in leukemia patients with fire-proofing materials used in the construction of a new hospital (44). It is, therefore, critical to offer the patient maximal protection against the acquisition of potentially lethal pathogens while granulocytopenic. Ample evidence has now been gathered from a number of centers which strongly suggests that patients placed in a sterile air environment acquire fewer pathogens than control patients and have fewer significant infections. Such an environment is best provided by laminar air flow room reverse isolation units equipped with high-efficiency particulate air filters (45). The incidence of pneumonia in leukemia patients so treated has been reduced by 50 %. Since pneumonia is the most frequent infection observed in granulocytopenic leukemia patients who are hospitalized without the benefit of such specialized units, the importance of the unit is clear. The addition of orally administered non-absorbable antibiotics to this regimen may add a further measure of protection to the patient by sterilizing his gastrointestinal tract. Indeed high dose, frequently administered oral gentamicin, vancomycin, and nystatin has recently been shown to significantly reduce the frequency of gram-negative bacteremia even when used alone, without the laminar air flow isolation units (46).

Two significant disadvantages of laminar air flow rooms are their great expense and the permanent installation that they require. We have been evaluating simpler, less expensive, portable equipment that utilizes the same type of filter as the laminar air flow rooms (Med Assist Filters, Med-Assist Devices, Chestnut Hill, Mass.). Thus far 9 patients have been evaluated while undergoing treatment in regular hospital rooms equipped with the Med-Assist filter units. Surveillance cultures were regularly obtained from predetermined room and patient sites. Careful housekeeping routines and reverse isolation procedures were employed. The air filtration units were effective in markedly reducing the number of airborne organisms. The room never became contaminated by organisms brought into it initially by the patient, and only 2 of the 9 patients acquired any new organism while under treatment. Although this initial study was primarily designed to test environmental control by the Med-Assist filter units, it is also apparent that significant infections were reduced in this small group of patients and no pneumonias were observed (47). It therefore appears that the Med-Assist air filtration system can reduce airborne infection in granulocytopenic patients, and more studies are indicated to define the precise role of these units relative to standard laminar air flow rooms in the supportive care of granulocytopenic leukemia patients.

Although the measures discussed above have clearly served to reduce the incidence of serious infection in acute leukemia patients, infection is still the most frequent

cause of death in patients with that disease. Many serious infections in granulocytopenic patients can be successfully resolved with early use of appropriate antibiotics. Since most infections in granulocytopenic patients are not accompanied by classic localizing signs such as abscess formation (48) it is imperative that the physician act quickly at the first observance of a fever of unexplained origin. To procrastinate often means death to the patient (49). The proper, proven reaction to such a fever is the institution of empiric, broad spectrum antibiotic therapy after blood, urine, sputum and rectal cultures have been obtained. The empiric therapy should include at least one antibiotic with significant activity against *Pseudomonas aeruginosa,* such as gentamicin or carbenicillin (50). In 24–48 hours, appropriate changes in antibiotic therapy can usually be made on the basis of culture results and clinical reassessment. Such practice is of proven life-saving value in the management of the febrile granulocytopenic leukemia patient.

Blood Component Therapy: There is no doubt that granulocyte transfusions have been on occasion life saving to the infected granulocytopenic leukemia patient (51), especially when large numbers of cells are transfused (52). Transfused granulocytes have been demonstrated to circulate and to localize in infected soft tissue, although they rarely result in a rise in the peripheral granulocyte count. Several devices have been developed for the procurement of granulocytes from normal donors and all utilize a differential centrifugation principle (53) or the ability of granulocytes to adhere to nylon fibers – a process that can be reversed by the lowering of the pH of the system (51). Granulocyte transfusion has gained widespread clinical acceptance in the last year or two.

It is generally accepted now that platelet concentrate transfusions administered prophylactically to markedly thrombocytopenic leukemia patients *prevent* bleeding, and that donor platelets HL-A matched to the recipient significantly delay the onset of platelet transfusion "resistance." This practice of prophylactic platelet transfusion has all but eliminated serious bleeding in leukemia patients so treated (54).

It should be clear from the foregoing summary that significant progress has been made in the management of adult patients with acute leukemia. It should also be clear that progress has been much less dramatic than that which has occurred in the management of children with ALL. However, new drug therapies currently under investigation, and new experimental modalities of therapy ("immuno" therapy) coupled with refinements in supportive care currently under evaluation may soon serve to more favorably alter prognosis for the adult patient with acute leukemia.

References

1. Wiernik, P. H., Serpick, A. A.: A randomized clinical trial of daunorubicin and a combination of prednisone, vincristine, 6-mercaptopurine, and methotrexate in adult acute non-lymphocytic leukemia. Cancer Res 32: 2033, 1972.
2. Greene, W., Huffman, D., Wiernik, P. H., et al: High dose daunorubicin therapy for acute nonlymphocytic leukemia: correlation of response and toxicity with pharmacokinetics and intracellular daunorubicin reductase activity. Cancer 30: 1419, 1973.

3. Steuart, C. D., Burke, P. J.: Cytidine deaminase and the development of resistance to arabinosyl cytosine. Nature New Biol 233: 109, 1971.
4. Wiernik, P. H., Glidewell, O. J., Holland, J. F.: Comparison of daunorubicin with cytosine arabinoside and thioguanine, and with a combination of all three drugs for induction therapy of previously untreated AML. Proc Amer Assn Cancer Res 16: 82, 1975.
5. Wiernik, P. H., Schimpff, S. C., Schiffer, C. A., et al: A randomized clinical comparison of daunorubicin alone with a combination of daunorubicin cytosine arabinoside, thioguanine and pyrimethamine for the treatment of acute nonlymphocytic leukemia. Cancer Treatment Rep 60: 41, 1976.
6. Bodey, G. P., Freireich, E. J., McCredie, K. B., et al: Late intensification chemotherapy for patients with acute leukemia in remission. Proc Amer Assn Cancer Res 14: 110, 1973.
7. Gutterman, J. V., Rodriguez, V., Mavligit, G., et al: Chemoimmunotherapy of adult acute leukemia. Prolongation of remission in myeloblastic leukemia with B.C.G. Lancet 2: 1405, 1974.
8. Cuttner, J., Holland, J. F., Bekesi, J. G., et al: Chemoimmunotherapy of acute myelocytic leukemia. Proc Amer Soc Clin Oncol 16: 264, 1975.
9. Bekesi, J. G., Holland, J. F., Yates, J. W., et al: Chemotherapy of acute myelocytic leukemia with neuraminidase treated allogenic leukemic cells. Proc Amer Assn Cancer Res 16: 121, 1975.
10. Wiernik, P. H.: "Spontaneous" regression of hematologic malignancy. Nat Cancer Inst Monogr, in press, 1976.
11. Manaster, J., Cowan, D. H., Curtis, J. E., et al: Remission maintenance of acute non-lymphoblastic leukemia with BCNU (NSC-409962) and cyclophosphamide (NSC-26271). Cancer Chemother Rep 59: 537, 1975.
12. Ellison, R. R., Holland, J. F., Weil, M., et al: Arabinosyl cytosine: a useful agent in the treatment of acute leukemia in adults. Blood 32: 507, 1968.
13. Masami, H., Akimitsu, M., Fujio, S., et al: Quadruple combination chemotherapy of acute leukemia using daunomycin, cytosine arabinoside, 6-mercaptopurine riboside and prednisone. Jap J Clin Hematol 13: 951, 1972.
14. Southwest Oncology Group: Cytarabine for acute leukemia in adults. Arch Int Med 133: 251, 1974.
15. McCredie, K. B., Bodey, G. P., Burgess, M. A., et al: The management of acute leuke. in adults. Proc 14th Ann Clin Conf, M. D. Anderson Hosp, in press, 1975.
16. Yates, J. W., Wallace, Jr. H. F., Ellison, R. R., et al: Cytosine arabinoside (NSC-63878) and daunorubicin (NSC-83142) therapy in acute nonlymphocytic leukemia. Cancer Chemother Rep 57: 485, 1973.
17. Brincker, H.: Treatment of acute myeloid leukemia with cytosine arabinoside and daunorubicin in combination. Scand J Haematol 9: 657, 1972.
18. Glucksberg, H., Buckner, C. D., Fefer, A., et al: Combination chemotherapy for acute non-lymphoblastic leukemia in adults. Cancer Chemother Rep 59: 1131, 1975.
19. Goodell, B., Leventhal, B., Henderson, E.: Cytosine arabinoside in acute granulocytic leukemia. Clin Pharmacol Ther 12: 599, 1971.
20. Armentrout, S. A., Burns, C. P.: Cytosine arabinoside as a single agent in the therapy of adult acute leukemia. Amer J Med Sci 268: 163, 1974.

21. Levi, J. A., Wiernik, P. H.: A comparative clinical trial of 5-azacytidine and guanazole in previously treated adults with acute nonlymphocytic leukemia. Cancer, in press, 1975.
22. Presant, C. A., Vietti, T., Valeriote, F.: Delayed dytotoxicity of 5-azacytidine (Aza C). Proc Amer Assn Cancer Res 16: 62, 1975.
23. Ho, M.: personal communication, 1975.
24. European Organization for Research on the Treatment of Cancer, Clinical Screening Group: Epipodophyllotoxin VP-16213 in treatment of acute leukemia, hematosarcomas, and solid tumors. Brit Med J 3: 199, 1973.
25. Kitajima, K., Kamimura, O., Hiraki, K.: Neocarcinostatin: A new chemotherapeutic approach to acute leukemia. Acta Haem Jap 37: 316, 1974.
26. Henderson, E. S.: Acute lymphoblastic leukemia, in Holland, J. F., Frei, E., eds: *Cancer Medicine*, Lea & Febiger, Phila 1973, pp. 1173–1199.
27. Jacquillat, C., Weil, M., Gemon, M., et al: Combination therapy in 130 patients with acute lymphoblastic leukemia (protocol 66 LA 66 – Paris) Cancer Res 33: 3278, 1973.
28. Henderson, E. S.: Combination chemotherapy of acute lymphocytic leukemia in childhood. Cancer Res 27:2570, 1967.
29. Henderson, E. S., Glidewell, O.: Combination therapy of adult patients with acute lymphocytic leukemia. Proc Amer Assn Cancer Res 15:407, 1974 and personal communication, 1975.
30. Shaw, M. T.: Successful induction therapy in adults with acute lymphocytic leukemia. Proc Amer Assn Cancer Res 16: 1031, 1975.
31. Smyth, A. C., Wiernik, P. H.: Combination chemotherapy of adult acute lymphocytic leukemia. Clin Pharmacol Ther 19: 240, 1976.
32. Peters, W., Holland, J. F., Senn, H. J., et al: Corticosteroid administration and localized leukocyte mobilization in man. N Engl J Med 286: 1972.
33. Ellison, R. R., Karnofsky, D., Burchenal, J. H.: Clinical evaluation of chloroquine and thioguanine. Proc Amer Assoc Cancer Res 2: 36, 1955.
34. Geils, G., Scott, C., Baugh, C., et al: Treatment of meningeal leukemia with pyrimethamine. Blood 38: 131, 1971.
35. Capizzi, R., Castro, O., et al: Treatment of acute lymphocytic leukemia (ALL) with intermittent high dose methotrexate and asparaginase. Proc Amer Assoc Cancer Res 15:793, 1974 and personal communication, 1975.
36. Capizzi, R.: Biochemical interaction between asparaginase and methotrexate in leukemia cells. Proc Amer Assoc Cancer Res 15: 308, 1974.
37. King, O. Y., Sutow, W. W.: Therapy with Erwinia L-asparaginase in children with acute leukemia after anaphylaxis to *E. coli* L-asparaginase. Cancer 33: 611, 1974.
38. Coleman, M.: personal communication, 1975.
39. Slavik, M.: personal communication, 1975.
40. Cerny, V.: Preliminary clinical trial with a purine analogue butocine. Neoplasma 18: 489, 1971.
41. Strauss, G. M., Slavik, M.: Piperazinedione (NSC-135758) Clinical Brochure. Investigational Drug Branch, Cancer Therapy Evaluation, Division of Cancer Treatment, National Cancer Institute (USA).
42. Wiernik, P. H.: unpublished observation.

43. Schimpff, S. C.: Diagnosis of infection in patients with cancer. Europ. J. Cancer 11: 529, 1975.
44. Aisner, J., Schimpff, S. C., Bennett, J. E. et al: Aspergillus infections in cancer patients: an association with fire-proofing materials in a new hospital. J Amer Med Assn 235: 411, 1976.
45. Schimpff, S. C., Greene, W. H., Young, V. M., et al: Infection prevention in acute nonlymphocytic leukemia. Laminar air flow room reverse isolation with oral, nonabsorbable antibiotic prophylaxis. Ann Int Med 82: 351, 1975.
46. Hahn, D., Schimpff, S. C., Fortner, C., et al: Changing spectrum of infection in acute leukemia patients receiving oral nonabsorbable antibiotic prophylaxis. Proc 15th Interscience Conf Antimicrob Agents and Chemother, Session 6, Wash., D.C., 1975.
47. Schimpff, S. C., Young, V. M.: Unpublished data.
48. Sickles, E. A., Greene, W. H., Wiernik, P. H.: Clinical presentation of infection in granulocytopenic patients. Arch Int Med 135: 715, 1975.
49. Wiernik, P. H.: Management of the acute leukemia patient. Conn Med 39: 681, 1975.
50. Greene, W. H., Schimpff, S. C., Young, V. M., et al: Empiric carbenecillin, gentamicin, and cephalothin therapy for presumed infection in patients with granulocytopenia and cancer. Ann Int Med 78: 825, 1973.
51. Schiffer, C. A., Buchholz, D. H., Aisner, J., et al: Clinical experience with transfusion of granulocytes obtained by continuous flow filtration leukopheresis. Amer J Med 58: 373, 1975.
52. Higby, D. J., Yates, J. W., Henderson, E. S., et al: Filtration leukopheresis for granulocyte transfusion therapy. New Engl J Med 292: 761, 1975.
53. Eyre, H. J., Goldstein, I. M., Perry, S., et al: Leukocyte transfusions: function of transfused granulocytes from donors with chronic myelogenous leukemia. Blood 36: 432, 1970.
54. Wiernik, P. H.: Advances in the management of acute nonlymphocytic leukemia. Arch Int Med, in press, 1976.
55. Gehan, E. A.: A generalized Wilcoxon test for comparing arbitrarily singly censored samples. Biometrika 52: 203, 1965.
56. Rai, K. R., Holland, J. F., Glidewell, O.: Improvement in remission induction therapy of acute myelocytic leukemia. Proc Amer Soc Clin Oncol 16: 265, 1975.

* Performed by Dr. Nicholas R. Bachur.
** Performed by Dr. Bruce Chabner.