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A Cancer Journal for Clinicians

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CA Cancer J Clin 2002;52;363-371

DOI: 10.3322/canjclin.52.6.363

This information is current as of March 9, 2010

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The Difficult Problem of Acute Myeloid Leukemia in the Older Adult

Richard M. Stone, MD

ABSTRACT Acute myeloid leukemia (AML) in older adults is a biologically and clinically distinct entity. Based on analysis of cytogenetic and molecular data, it is known that leukemic cells in older patients are intrinsically resistant to standard chemotherapy. Due to comorbid disease and impaired bone marrow stem cell reserve, older adults tolerate myelosuppressive chemotherapy poorly, with a treatment-related mortality rate of 25 percent. About 35 percent of adults under age 40 are cured, but the complete remission rate (likelihood of temporary disease eradication) is 45 percent in those over age 60, considerably lower than the 75% rate among younger patients, and the possibility of long-term disease free survival is 20 percent in those achieving remission or less than 10 percent overall. Standard allogeneic bone marrow transplantation is too dangerous to be considered as a means to eradicate minimal residual disease after remission is obtained and myelointensive chemotherapy is not a beneficial post-remission strategy in this age cohort. These disappointing results call for more effective and less toxic therapeutic options. Advances in our understanding of the pathophysiology of AML and promising early clinical data suggest that the era of truly targeted therapy in this difficult disease may soon be a reality. (*CA Cancer J Clin* 2002;52:363-371.)

Dr. Stone is Clinical Director, Adult Acute Leukemia Program, Dana-Farber Cancer Institute and Associate Professor of Medicine, Harvard Medical School, Boston, MA.

This article is available online at <http://CAonline.AmCancerSoc.org>

INTRODUCTION

Although the incidence of leukemia demonstrates a small peak in children ages 0 to 4 due predominantly to acute lymphoblastic leukemia (ALL) (7.4 cases per year/100,000 people), the incidence rises among adults (to 11.4 cases per year/100,000 people in the sixth decade of life and to over 85 cases per year/100,000 people above age 80).¹ Although leukemia is the most common malignancy of children aged 15 years and younger, most cases of leukemia are diagnosed in older adults. The median age of acute myeloid leukemia is 68.¹ Unfortunately, the outcome of these older patients with acute myeloid leukemia is remarkably inferior to the results found in younger patients with the same diagnosis, and vastly inferior to the 87% cure rate among children with ALL.² Comorbid disease with decreased therapeutic tolerance in the host and particularly the adverse biology of the underlying disease undoubtedly accounts for the differences in outcomes.

Epidemiological and Biological Considerations

The incidence of acute leukemia is considerably less than that of epithelial neoplasms, such as breast, prostate, colon, and lung cancer. There are approximately 10,600 new cases of acute myeloid leukemia and 3,800 cases of acute lymphoblastic leukemia annually in the United States.³

However, because of the older median age of AML patients and demographic shifts in the US population, the overall occurrence of this disease is likely to increase. Other than congenital chromosome breakage syndromes, such as Bloom's Syndrome⁴ and Fanconi's anemia,⁵ and a few rare families with a predisposition to leukemia,⁶ leukemia is

Author disclosure: Richard Stone, MD, serves as a consultant to Wyeth Pharmaceuticals, Janssen Pharmaceutica, L.P., and Novartis Pharmaceuticals Corporation. He also serves on the speaker's bureau for Wyeth Pharmaceuticals and Novartis Pharmaceuticals Corporation.

not a disease where inheritance is important. Exposure to chemotherapy,⁷ radiation exposure⁸ due to industrial, military, or therapeutic uses, or exposure to industrial solvents⁹ have all been shown to increase the risk for AML.

There are two syndromes of treatment-related AML. First, the classic “alkylating-agent type” in which exposure to drugs such as melphalan¹⁰ and cyclophosphamide¹¹ increase the risk for secondary AML with a latency period of about five to eight years. Alkylating-agent-induced AML is believed to be a disease of early stem cells in the hematopoietic compartment, and is often associated with abnormalities of chromosome 5 and/or chromosome 7. The more recently recognized type of secondary leukemia develops after exposure to agents that inhibit the DNA repair enzyme topoisomerase II, such as etoposide, teniposide, and anthracyclines like doxorubicin. It has a shorter latency period and is associated with abnormalities of the long arm of chromosome 11 at the location of the MLL gene.¹²

Particularly in the case of the alkylating agent-induced leukemias, the response to therapy is poor.⁷ The level of intrinsic disease resistance displayed by those who are exposed to prior chemotherapy is similar to that noted in older patients with AML without such exposures.⁷ Moreover, given the increasing use of chemotherapy and the fact that patients may be living longer after exposure to such agents, there may be an enrichment of exposure-related AML in those who are older adults.

Over and above the issue of exposure to agents that damage DNA, older adults generally present with an intrinsically different type of de novo leukemia. Perhaps the most cogent evidence in this regard is the increased prevalence of various chromosomal abnormalities in older adults compared with younger patients with acute leukemia.¹³ The importance of karyotype in defining the pathophysiology, natural history, and response to therapy in acute leukemia is a key concept.^{14,15}

Moreover, there has been a shift toward usage of the new karyotypically- and biologically-

based World Health Organization (WHO) classification system¹⁶ compared with the “old” morphologically based French-American-British (FAB) system.¹⁷ The WHO system delineates diseases according to their chromosomal abnormalities. For example, AMLs with certain balanced translocations, including t(8;21), inversion 16, and t(15;17) respond well to chemotherapy; those with “alkylating-agent-type abnormalities” including loss of the entire chromosome 5 or 7 (or the long arm of these chromosomes) respond poorly to therapy.^{14,15} ALL patients whose blasts display the Philadelphia chromosome t(9;22) can not be cured with standard chemotherapy alone and require a dose-intensive approach.¹⁸ There is a significantly higher incidence of adverse chromosome abnormalities in AML^{13,14} and ALL¹⁸ with older patient age. This difference in chromosomal pattern probably accounts for a good measure of the difference in resistance to treatment.

There are other differences in biology that cannot be explained by chromosomal abnormalities alone. The expression of genes that mediate drug resistance is more common in leukemic cells from older adults compared with leukemic cells from younger adults.^{19,20} The best-studied example is the MDR-1 gene product, a glycoprotein (gp170) capable of causing the efflux of a wide variety of naturally occurring chemotherapeutic agents, such as vinca alkaloids and anthracyclines.²¹ Expression of gp170 (and an associated inferior prognosis) is more common in older adults with AML.²⁰ Just as karyotypic differences can explain different outcomes in younger patients with AML, biological factors may be used to separate older adults with AML who may respond more like young patients compared with the more typical poorly-responsive older adults. For example, in the study by Leith, et al. based on data from samples obtained from patients enrolled in the Southwest Oncology Group (SWOG) trials, it was shown that a small, subset of older adults with AML with a favorable prognosis could be identified on the basis of

lack of MDR-1 expression and lack of adverse chromosomal abnormalities in the leukemic blasts.²⁰

Treatment Considerations: Induction Therapy

The goal of remission induction therapy in leukemia is to reduce the leukemic burden to a level undetectable by standard morphologic techniques. Given the presumption that patients with AML at presentation harbor approximately 10^{12} leukemic cells,¹² three logs of cyto-reduction are required to decrease the number of marrow blasts to below five percent at a time after the peripheral blood counts have recovered.²²

The standard agents used to achieve such a result include an anthracycline given daily by brief infusion for three days in combination with cytarabine, usually given by continuous intravenous infusion for seven days ("3+7"). While the same strategy is employed in patients with AML of all ages, the results are markedly inferior (45% versus 75% complete response rate) in older adults compared with younger adults.^{23,24} One reason for the inferior remission and survival rates is a high (25 percent) treatment-related mortality rate.^{23,24} Phase I and III studies in older adults performed by the Cancer and Leukemia Group B (CALGB)^{25,26} have shown that it is possible to escalate the daunorubicin dosage to 60 mg/m²/day for three days (the usual dose is 45 mg/m²/day) and also administer etoposide (100 mg/m²/d for three days) without an obvious change in the remission or mortality rates; whether or not this approach will result in a better long-term outcome is not known.

Much attention has been paid to the question of which is the optimal anthracycline or anthracycline-like drug to be given in conjunction with cytarabine in patients with AML of all ages. Three trials performed in the 1990s,²⁷⁻²⁹ (one restricted to older adults with AML)²⁹ purported to show a benefit of idarubicin compared with daunorubicin. Whether the apparent benefit associated with

idarubicin in terms of a higher complete remission rate was due to a higher equivalent dose of idarubicin rather than to true drug difference is unclear. Moreover, a recent study restricted to elderly adults that compared mitoxantrone, idarubicin, and daunorubicin showed no difference among these three drugs when given in conjunction with cytarabine.³⁰ Another study in older adults comparing mitoxantrone to daunorubicin showed no benefit for the mitoxantrone.³¹ The standard induction regimen therefore remains "3+7."

Post-remission Therapy

Once an older adult with acute myeloid leukemia has achieved remission, the optimal additional therapy is not clear. First, it is important to ensure that the patient has recovered as completely as possible from the myelosuppressive, gastrointestinal, infectious, psychological, and constitutional side effects of induction chemotherapy. Many require a rest period to allow resolution of impaired renal function, often secondary to nephrotoxic antimicrobial agents, and/or hepatic abnormalities due to chemotherapy. Most importantly, a few weeks' rest at home is advisable to recover performance status from the decline sustained due to the debilitation that accompanies even the most well-tolerated induction therapy in this age group.

Once a reasonably-fit older adult has recovered from therapy sufficiently to consider post-remission treatment, he or she has the same theoretical set of options as a younger patient in the same situation. Options for post-remission treatment include: re-induction, myelo-intense post-remission chemotherapy with an agent such as high-dose ara-C, high-dose chemotherapy with autologous peripheral blood stem cell support, or allogeneic transplantation. Three-year disease free survival rates of 45 percent in younger adults with AML have been achieved using intensive post-remission therapy, best exemplified by high-dose ara-C, as given in CALGB protocol

8525.²³ In this clinical trial, patients who were randomized to receive high-dose ara-C (3 gm/m² over three hours every 12 hours on days one, three, and five) enjoyed a superior disease-free overall survival compared with patients randomized to lower doses of ara-C.

However, it is critically important to note that these benefits were only seen in patients younger than age 60. In the older-age cohort, the disease-free survival was a disappointing 14 percent, which was identical in each of the post-remission arms, high-dose ara-C, moderate-dose ara-C, or relatively-low dose ara-C (100mg/m² per day given by continuous intravenous infusion for five days for four courses). CALGB 8923 failed to show a benefit of a novel regimen of modified high-dose ara-C plus mitoxantrone compared with a standard lower dose ara-C scheme.³² Therefore, there is little justification for routinely administering potentially life-threatening therapy to an older adult given that the benefits are not clear cut. In the rare older adult whose leukemic cells display a favorable chromosomal abnormality, it might be reasonable to consider high-dose ara-C-based post-remission therapy, but only for selected patients.

Because of insufficient supporting data, high-dose myeloablative chemotherapy with autologous peripheral blood stem cell support is also difficult to justify in the older adult. Randomized prospective trials designed to answer the question of “autologous transplant” compared with chemotherapy were all restricted to patients under age 60.³³⁻³⁵ Though it may be likely that selected older adults could tolerate this approach, extrapolating from the data in the high-dose versus low-dose chemotherapy studies discussed above,^{23,32} it seems unlikely that the relatively small-dose increase made possible by peripheral blood stem cells would make a big difference in outcomes. Because of the inherent chemoresistance displayed by most older adults with AML, there has been much interest in applying allogeneic bone marrow transplant with its associated benefits of graft-versus-leukemia

effect to older adults with AML. However, the high rate of graft-versus-host disease in this cohort as well as the hepatic and pulmonary toxicities of high-dose chemo and/or chemo/radiation therapy has precluded the application of this technology among older adults.

Non-myeloablative allogeneic transplantation could provide a qualitatively different approach to the post-remission management of older adults with AML. The principal of non-myeloablative bone marrow transplantation is that the primary antineoplastic effect emanates not from the preparative chemotherapy, but rather from the graft-versus-leukemia effect. Two major issues in this strategy are: controlling graft-versus-host disease and understanding the strategy's efficacy against varying degrees of disease. In the past two years, there have been many reports of the feasibility of non-myeloablative transplantation. However, these studies have been Phase II single-institution reports (generally in adults under age 60) that have employed a variety of myeloablative and anti-graft-versus-host disease strategies, and provide limited data on long-term efficacy.³⁶ Nonetheless, it seems likely that the non-myeloablative approach will be applied to older adults with AML. Once an agreed-upon and well-tolerated regimen has been determined, a Phase III trial against standard chemotherapy will enable the treating community to understand the value of such a toxic and costly endeavor.

Should Older Adults With Acute Leukemia Receive Induction Chemotherapy?

Because of the high morbidity and mortality rates associated with standard induction therapy for AML and because of low-complete remission and survival rates, some have questioned the value of curative-intent therapy; although older adults who achieve remission status are often able to return to their previous quality of life and functional capacity. Even in older adults with AML treated in cooperative

group studies, there is only a 10-month median survival with a 10 percent likelihood of long-term disease free survival.³²

Given these discouraging statistics, coupled with the high (25 percent on average) treatment-related mortality rates and the certitude of significant toxicities, the question, “*Is treatment worth it?*” is viable. There have been no studies comparing supportive care alone to standard treatment for purposes of determining both quality of life and traditional outcome measures. However, two studies performed in Europe approximately 20 years ago do shed some light on this dilemma. One study randomized patients to either low-dose chemotherapy or standard induction chemotherapy.³⁷ Patients who received the standard myelosuppressive chemotherapy did experience a prolonged survival (from 9 to 13 months) but did so at a cost of 31 percent treatment-related mortality compared with 10 percent in the lower-dose arm.

Another study compared standard induction treatment given at the time of diagnosis versus a policy of “watch and wait” where patients whose disease was relatively stable would be observed with treatment being given only in the event of intractable problems such as refractory thrombocytopenia.³⁸ Those who received immediate chemotherapy did enjoy a slightly-longer median survival rate (21 versus 11 weeks) but, as in the case with the low-dose versus standard study, no quality-of-life companion was included.

While a straightforward study of chemotherapy versus indefinite observation will probably never be performed, there is still room for research into questions surrounding the appropriateness of treating older adults with AML using currently available chemotherapeutic strategies. A preliminary attempt at such an investigation was performed by Sekeres, et al. who attempted to discern the factors that influence a patient’s decision whether to be treated or not as well as the consequences of that decision. The results suggested a vast overestimation of beneficial

outcomes associated with therapy on the part of patients compared with the feelings and expectations expressed by their own physicians.³⁹

At present, several generalizations can be made about the current status of therapy for adults with acute leukemia: 1) the standard approach is probably to administer non-dose attenuated induction chemotherapy, although the very elderly (those over 80) are probably rarely treated; 2) the results reported in the literature, largely based on cooperative group trials (using selected patients well enough to enter such studies) probably grossly overestimate the true response rates, the duration of remission, and overall survival rates; and 3) older adults are excellent candidates for enrollment into clinical trials due to the lack of any effective standard therapy.

SUPPORTIVE CARE ISSUES

Hematopoietic Growth Factors

Because the induction mortality rate is so high among older adults with AML, numerous efforts directed at improving this dismal figure have been undertaken. Many of the induction deaths occur due to infection during the period of chemotherapy-induced marrow hypoplasia. Therefore, it was natural that hematopoietic growth factors, which could potentially reduce the duration of neutropenia, would be employed in such patients. The chief barrier to clinical trials with these agents was the concern that growth factor receptors on the surface of the leukemic cells would be stimulated and proliferation would ensue, thereby enhancing leukemia resistance. The myeloid growth factors granulocyte macrophage colony stimulating factor (GM-CSF) and granulocyte colony stimulating factor (G-CSF) have been used, albeit without much clinical benefit, to “prime” leukemic cells to proliferate so that S-phase specific chemotherapeutic agents such as ara-C (used afterwards) might be utilized to a greater

extent and subsequently might be more effective.^{40,41}

Nonetheless, early trials suggested that using either GM-CSF or G-CSF after chemotherapy to enhance recovery would be safe. Safety was similarly established via major prospective randomized trials mounted in the hope that myeloid growth factors would be effective supportive agents during induction chemotherapy. Except for one trial performed by the Eastern Cooperative Oncology Group⁴² that documented both a complete-remission rate benefit and overall-survival benefit to patients randomized to GM-CSF support, the majority of the trials were unable to demonstrate a clinically meaningful benefit beyond a reduction in the duration of neutropenia by a few days.⁴³⁻⁴⁶ The reason why a several-day reduction in the duration of neutropenia did not lead to an improvement in infectious mortality was probably because neither the neutrophil nadir nor the gastrointestinal toxicity of chemotherapy were affected. A trial performed mainly in younger adults showed that G-CSF after induction and/or consolidation reduced the duration of hospitalization suggesting a potential quality-of-life benefit.⁴⁷ G-CSF does have a similar benefit when given during induction therapy to the older adult with ALL.⁴⁸

Therefore the decision of whether or not to use growth factors in acute leukemia in the older adult rests more on economic factors rather than on clinical factors. In a small trial, megakaryocyte stimulating factor also failed to show any meaningful clinical benefit in terms of reduction in bleeding or use of platelet transfusions.⁴⁹

Other Issues in Supportive Care

In addition to ameliorating the duration of neutropenia as a means to decrease chemotherapy toxicity, it might be possible to consider decreasing transudation of bacteria from the gut into the blood stream, the presumed mechanism of both neutropenic

fever and nadir sepsis.⁵⁰ Agents that coat or protect the gastrointestinal lining have been tried without clear-cut results. Growth factors that could enhance recovery of gastrointestinal stem cells might be worth developing clinically.⁵¹

Secondly, the historic change from antibiotics with a great deal of nephrotoxicity such as amphotericin B to liposomal formulations of the same drug⁵² and aminoglycosides to broad-spectrum cephalosporins⁵³ has probably enhanced the ability of the older adult to tolerate induction chemotherapy. Hopefully, newer and better-tolerated antifungal agents such as caspofungin⁵⁴ and voriconazole⁵⁵ will become more widely applicable, even for empiric therapy. Nonetheless, though antibiotics have improved, the overall long-term disease free and overall survival results in older adults with AML have not appreciably changed during this time, again suggesting the importance of disease resistance relative to host factors as the major problem.

New Approaches

Because of the inferior outcome when standard therapy is administered to older patients with acute leukemia, efforts are underway to apply new therapies to this group of patients. The goal is to find less toxic and more specific approaches than the chemotherapy-based strategies available today. Although a detailed discussion is beyond the scope of this review, there are several different categories of new therapies under development: 1) targeting specific signaling molecules required for the maintenance of the leukemic state, such as tyrosine kinases; 2) targeting more indirect pathways that maintain leukemogenesis, such as angiogenesis or drug resistance; and 3) immunotherapy against either known or unknown targets.

One such strategy that has undergone significant testing specifically in older adults is the adjunctive use of agents thought to reverse the intrinsic drug-resistant characteristic of the

blasts from older adults with acute leukemia. Many drugs, including calcium channel blockers, phenothiazines, and cyclosporine (and its analogues), are known to inhibit the function of the drug efflux pump (MDR), previously mentioned as accounting for resistance in older adults with AML. If the pump can be inhibited, increased cytotoxic drug retention could lead to a more pronounced therapeutic effect.

Most of the trials with MDR modulators in AML have been done in patients with high-risk disease, either in relapse or in those over age 60. One prospective randomized trial performed by the Southwest Oncology Group study documented a survival benefit (from six to seven months median; $p < 0.05$) for the addition of a 72-hour infusion of cyclosporine A in patients (up to age 70) with relapsed AML receiving a novel regimen of bolus cytarabine and continuous infusional daunorubicin.⁵⁶ Several trials performed by the Cancer and Leukemia Group B have sought to develop a strategy in which the cyclosporine analog PSC-833 could provide a benefit to standard induction chemotherapy. The CALGB performed two Phase I^{25,57} and two Phase III²⁶ (one ongoing CALGB 19808) trials, one each for both younger and older adults with AML in which so-called equitoxic regimens of daunorubicin, etoposide, and cytarabine were developed in conjunction with and without PSC-833. A Phase III trial in older adults was prematurely stopped due to an unexpectedly high-toxic death rate in the PSC-833-containing arm.²⁶ Despite this disappointing result, it was suggested that those patients whose blasts extrude chemotherapy agents *in vitro* (a high-intrinsic level of functional drug efflux) actually benefited from PSC-833.²⁶ This subset analysis by no means proves the value of PSC-833, but does suggest that a more careful application of this strategy could be potentially useful.

Although specific leukemia antigens are difficult to identify, antibodies directed against CD33 have been developed for use in AML. CD33 is a membrane glycoprotein that is

expressed in blasts from 80 to 90 percent of those with AML, and is not expressed in non-hematopoietic tissues. Non-conjugated antibodies, which depend on antibody-dependent cellular cytotoxicity, have been associated with success in acute promyelocytic leukemia in which the CD33 antigen is strongly expressed.⁵⁸

Most importantly, the only new agent specifically approved for use among older adults with AML has emanated from this strategy: gemtuzumab ozogamicin, a humanized monoclonal antibody targeted against the CD33 antigen, which is conjugated to a highly potent toxin, calicheamycin. After gemtuzumab ozogamicin infusion, the calicheamycin is only released after intracellular internalization of the antibody-toxin complex into the acidic endosome environment. The approval of gemtuzumab ozogamicin as a drug for relapsed AML in older adults (blasts must express CD33 and the patient must not be a chemotherapy candidate) stems from a Phase II trial of 142 patients.⁵⁹ Patients received gemtuzumab ozogamicin at a dose of 9 mg/m² over two hours on days 1 and 14. Thirty percent responded. Half were standard complete remissions with disappearance of marrow and peripheral blood blasts and reconstitution of normal marrow function. About half the responses met all criteria except for not having a platelet count greater than 100,000. The approval of gemtuzumab ozogamicin has spurred the development of this agent in conjunction with induction chemotherapy and as a post-consolidation therapy. A report documenting veno-occlusive disease⁶⁰ associated with this agent has given caution with regard to its use.

In Summary

The current chemotherapy-based strategies for treatment of older adults with acute leukemia are disappointing. On the other hand, the need for more specific and targeted therapies does provide a fertile testing ground

for many of the new agents in acute leukemia. Linked to the development of novel therapeutic strategies for older adults are several difficult problems, not the least of which is the definition of older. Although most would consider those above age 60 with acute leukemia to be older, this is clearly an oversimplification. There are younger patients whose leukemias display biological characteristics resembling those typically seen in very old patients; some individuals in their eighth decade of life are fit and have leukemias having a favorable cytogenetic profile (suggesting that a good response to aggressive therapy is likely). Even though age is independently an adverse risk factor in most

studies, individualization of treatment recommendations are certainly appropriate.

Nonetheless at this time, both oncologists and primary care physicians are faced with the difficult task of advising the older adult with leukemia about the appropriateness of induction and post-remission therapy. To relay this information effectively, research is needed on effective communication strategies for this age group as well as on the quality-of-life impact of available therapies relative to the likelihood of a somewhat longer life expectancy. Indeed, acute leukemia in the older adult poses challenges spanning the gamut from molecular biology to doctor-patient communication issues. CA

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