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Acute myeloid leukemia in adults: where do we go from here?

Abstract Although 30–40% of newly diagnosed younger patients with acute myeloid leukemia (AML) can be cured with current approaches, the overall outcome has not improved in recent years. In addition, the outcome in adults >60 years of age remains dismal with <10% of patients achieving remission remaining alive and disease free. Results of randomized clinical trials in AML evaluating high-dose cytosine arabinoside, changes in anthracyclines, the use of hematopoietic growth factors, stem cell transplantation in first remission, and modulation of the multidrug resistance phenotype are reviewed. New directions for clinical trials include the use of nonmyeloablative allogeneic stem cell transplantation as a form of "immunotherapy", refinements in autologous stem cell transplantation, and possibly manipulations of neoangiogenesis in the bone marrow and incorporation of newer agents, such as gemtuzumab zogamicin into treatment regimens. It is likely, however, that future advances will be a consequence of a better understanding of the biology of leukemic stem cells, and issues related to such studies are discussed.

Keywords Acute myeloid leukemia · Stem cell transplantation · Hematopoietic growth factors

Introduction

A substantial fraction of adults with acute myeloid leukemia (AML) can be cured with combination chemotherapy based on anthracyclines and cytosine arabinoside (Ara-C). After complete remission (CR) is achieved, the hazard rate for relapse is maximal in the first 6–12 months, continually decreases over the next 2–2.5 years, and becomes relatively "flat" after a CR duration of 3 years [36]. Since the curves become stable only after 2.5–3 years, many observers feel that it is premature to publish studies with a shorter follow-up in younger patients in whom the goal of treatment should be long-term disease-free survival.

Approximately 40% of adults <60 years of age remain free of leukemia after completing postremission consolidation therapy [28, 36]. However, the median age of adults with AML is at least 55–60 years, and unfortunately the long-term results with these therapies applied to older patients are disappointing. At most, 10% of older patients who achieve remission remain disease-free and the remission rate in older patients is also lower, with CR being achieved in only 50–60% of patients >60 years of age [28, 36, 39]. There has been little increase in overall survival in the past two decades, with at least some of the improvements in treatment being related to better supportive care modalities, including more widespread availability of platelet transfusion, effective antiemetics, and a better understanding of infection treatment and prophylaxis.

Clinical trials addressing a variety of treatment approaches have been conducted in AML during the past two decades. The results of randomized trials evaluating these treatments have generally been remarkably consistent and are briefly summarized.

High-dose Ara-C

Enthusiasm for the use of higher doses of Ara-C developed following in vitro observations that increased doses could overcome mechanisms of drug resistance against it including deamination of Ara-C, decreased Ara-C transport across leukemia cell membranes, and inhibition of Ara-C phosphorylation [33]. Randomized trials

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demonstrated improved disease-free survival using high-dose Ara-C as consolidation therapy compared with conventional-dose Ara-C in younger, but not in older patients [28]. In some trials this favorable effect appeared to be most pronounced in individuals with more favorable cytogenetic findings, with less of an advantage in patients with more complex chromosome abnormalities, which are predictive of poor outcome [10].

As outlined in Table 1, the use of high-dose Ara-C in postremission therapy has produced similar outcomes in younger adults. Table 1 shows the results in control groups treated with chemotherapy alone in the randomized trials of high-dose therapy with stem cell transplantation as described below, and the large chemotherapy study conducted by the Cancer and Leukemia Group B (CALGB). Similar results appear to have been achieved using different doses and schedules of high-dose Ara-C, and there is no consensus on the optimal dose (1.5–3 g/m^2 per dose), number of doses, duration of infusion, and number of postremission courses. Randomized trials addressing these issues have not been conducted, primarily because the results achieved to date with even the more intensive programs are not sufficiently good and it is unlikely that attenuation of dosage could improve outcome. Hence, investigators have attempted to focus on questions that have greater potential for improving overall outcome.

Trials have also been conducted evaluating high-dose Ara-C as a replacement for standard-dose Ara-C during induction therapy. In general, the toxicity is greater with high-dose Ara-C, and two randomized trials have shown no improvement in complete remission (CR) rates [8, 41]. In addition, because of lingering toxicities from induction therapy, the use of high-dose Ara-C in induction often precludes its use as postremission consolidation therapy. Therefore most investigators utilize high-dose Ara-C in the postremission setting in younger patients.

Anthracycline modifications

Daunorubicin has been the standard anthracycline used in the treatment of AML for three decades. There have been many attempts to improve upon daunorubicin with other anthracyclines, particularly idarubicin and mitoxantrone. Both of these agents were approved for use in AML based on randomized trials showing similar, or in the case of idarubicin, slightly improved CR rates compared with those with daunorubicin, albeit with no improvement in remission duration or overall survival [3, 6, 40, 42]. The failure to make an impact on overall survival suggests that modest dose escalation of anthracyclines is likely to have little effect on AML outcome. Much steeper dose escalations of daunorubicin, such as a doubling from the "standard" 45 mg/m^2×3 doses to 90 mg/m^2×3 doses, as is feasible in younger patients, may merit further evaluation in the future [23].

Hematopoietic growth factors

Death from infection is a major cause of treatment failure, particularly in older adults with AML. As a consequence, multiple randomized trials comparing either granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) have been conducted in adults receiving initial induction therapy, often with placebo administered to the control group [14, 18, 22, 26, 27, 30, 34, 43, 46]. The overall results of these trials have been remarkably similar, and in retrospect one might wonder about duplications of effort. All trials demonstrated modest, 1–3 day, reductions in the duration of severe neutropenia (variously defined as ≤ 500 or ≤ 1000 neutrophils/μl), with no effect on CR rate or survival. Some trials demonstrated shortened hospitalization and slightly decreased antibiotic use, but these were inconsistent findings. More clinically relevant shortening of neutropenia was shown following postremission consolidation using growth factors, although there was no effect on remission duration or survival [21, 22]. Possible explanations for these somewhat disappointing results have been reviewed [35]. For many of the same reasons, thrombopoietic agents have also not been of benefit as adjuncts to therapy in AML patients receiving either induction or consolidation chemotherapy [2, 37].

Growth factors have also been evaluated as a means of increasing the sensitivity of leukemia cells to cell cycle-specific therapy, based on in vitro observations suggesting enhanced cytotoxicity of Ara-C against cells that

Table 1 High-dose Ara-C: results in randomized trials (*CR* complete remission)

Trial	4-year disease-free survival/overall survival (%)	Number of post-CR courses	Total number of high-dose Ara-C courses	Reference
US Intergroup	35/52	2	12	12
MRC	40/45	4	6[a]	11
GOELAM	40/55	2	8	20
POG	36/44	7	24	32
EORTC-GIMEMA	30/46	2	8[b]	46
CALGB	44/46	8	24	28

[a]Intermediate dose
[b]Plus 12 doses of intermediate dose

have been stimulated with growth factors [7]. Unfortunately, randomized trials evaluating pretreatment or simultaneous treatment of leukemia with growth factors and chemotherapy have failed to improve outcome [16, 27, 31].

High-dose therapy with stem cell transplantation

Following the demonstration of apparent cures following allogeneic bone marrow transplantation (BMT) in patients with advanced, refractory AML, vigorous controversy about the role of this approach in patients in first CR ensued. As summarized in Table 2, multiple randomized trials have recently been completed by adult and pediatric groups in the USA and Europe, randomizing younger patients in first remission to autologous BMT or high-dose Ara-C-based chemotherapy (see Table 1), with an allocation to allogeneic BMT for patients with histocompatible sibling donors [11, 12, 20, 44, 45].

With only minor inconsistencies among the trials, there were few statistically significant improvements in outcome with transplantation compared to chemotherapy alone. In general, the relapse rate was decreased in patients receiving allogeneic BMT, but overall survival was similar because of increased mortality related to graft-versus-host disease. However, the interpretation of the effect of autologous transfusion is complicated in all of the studies by the relatively low rate (50–60%) at which patients randomized to autologous BMT actually received this treatment modality. This is particularly true of the Medical Research Council (MRC) trial conducted in the UK in which approximately only one-third of eligible patients were randomized. This trial also differed from the others in that autologous BMT was performed at the end of all treatment and represented an "extra" course of therapy, whereas in the other trials it was intended that patients receive the same number of courses of treatment.

All of the studies appropriately presented their final results as an intent-to-treat analysis, but the results would certainly be "cleaner" if a higher proportion of patients had received the randomized treatment. Nonetheless, it is remarkable that the results of all of these trials were so similar, suggesting that it is difficult to make a strong recommendation for an individual patient using the transplantation approaches employed. Analyses of individual trials have been conflicting in terms of whether one therapeutic modality is superior for different cytogenetic subgroups. Since the number of patients in each subgroup in each trial was limited, a meta-analysis of the trials dealing with this question would be of considerable importance.

Modulation of p-glycoprotein-mediated drug resistance

Although there are countless papers describing different mechanisms of drug resistance in both cell lines and primary specimens from patients with leukemia and other types of cancer, perhaps none offered as compelling a therapeutic hypothesis as the demonstration of overexpression of the drug efflux pump mediated by p-glycoprotein in drug-resistant cancer cells from a variety of tumors. Importantly, this mechanism of multidrug resistance (MDR) could be overcome by concentrations of inhibitors that were safe and achievable in vivo. Although there remains some controversy about optimal methods of quantifying clinically relevant elevations of p-glycoprotein, there is a clear consensus that p-glycoprotein is overexpressed in leukemia cells of many patients with AML, with perhaps the most marked overexpression in cells from older patients or those with resistant leukemia and/or myelodysplasia [25]. As MDR inhibitors also affect drug disposition and metabolism due to effects on p-glycoprotein in biliary cells and renal tubular cells, randomized trials were preceded by often detailed phase I dose-finding studies combining chemotherapy and MDR modulators [24].

Preliminary results of four randomized trials comparing chemotherapy with or without the MDR-modulating agent PSC-833 have recently become available (personal communication; [4, 19]). PSC-833 was chosen

Table 2 Randomized trials of bone marrow transplantation (*BMT*) for AML in first remission (*OS* overall survival, *DFS* disease-free survival)

	POG	CCSG	EORTC	GOELAM	US	MRC
Reference	32	44	45	20	12	11
Chemotherapy alone						
No. of patients	117	160	126	134	117	191
OS (%)	44	59	46	53	52	45
DFS (%)	36	50	30	38	34	40
Autologous BMT						
No. of patients	115	150	128	75	116	190
OS (%)	40	45*	56	52	43	57
DFS (%)	38	40	48	48	34	54
Allogeneic BMT[a]						
No. of patients	89	140	168	88	113	–
OS (%)	~51	76	59	53	46	–
DFS (%)	52	70*	55*	44	43	–

*$P < 0.05$

[a]Allogeneic transplantation from HLA-identical sibling

for these trials because it appeared to be more active in vitro than its analogue cyclosporine A. Two trials using mitoxantrone and etoposide-based regimens were conducted in patients with poorer prognosis, many of whom were in relapse or had prior myelodysplasia. Two other trials were conducted in older patients with newly diagnosed AML receiving daunorubicin and Ara-C (with etoposide in one trial) with or without PSC-833. In all the trials, the doses of the anthracycline and etoposide were reduced by approximately one-third in the patients receiving PSC-833. Two of the phase III trials were ended prematurely because at the first interim analyses it was shown that the results were inferior in the PSC-833 arms [4, 19]. In one of those trials, significantly enhanced toxicity and mortality were seen in the PSC-833 arm, while in the other two trials the preliminary analysis suggested no advantage to treatment with PSC-833.

Although more detailed commentary will only be possible when the results of these trials are published in full, there are a number of possible explanations for the disappointing results, including many competing causes of treatment failure in patients with AML, such as infectious deaths. Thus all patients are not "informative" with respect to the endpoint of overcoming drug resistance. Partial responses (PRs), indicating less cytoreduction, are clinically irrelevant in patients with AML, but can be meaningful to patients with other tumors including multiple myeloma and various solid tumors. It may be that the need to achieve CR to judge an outcome meaningful in AML sets the bar too high, and that MDR modulation might be more fruitful in patients with other disorders.

The dose attenuation in the PSC arms may have resulted in underdosing for some patients in whom drug disposition may not have been significantly affected by the PSC-833. It is well known that there is marked variability in drug pharmacodynamics among patients. It is possible, and perhaps even likely, that MDR modulation would be of benefit only to the subset of patients with marked overexpression of p-glycoprotein. Correlation of in vitro results with clinical outcome are not yet available, and it is possible that more refined analysis might help address this question. Analysis may be complicated, however, because what constitutes clinically relevant positivity for MDR in the multiple assays that have been used to quantify p-glycoprotein expression and function remains unknown. Furthermore, it is probable that ultimate resistance is conferred by overexpression in the subpopulation of leukemic stem cells, and assays reliably quantifying p-glycoprotein and other proteins are not available for small subpopulations of cells.

Future considerations

In addition to the therapeutic goals, the trials described above included accompanying correlative science evaluations that have dramatically expanded our understanding of the cytogenetic, and more recently, the molecular genetic changes associated with the heterogeneous group of disorders grossly lumped under the rubric of AML. In addition, there are some clinical clues from these trials that can be capitalized upon in future studies. There is a huge challenge ahead and it is difficult at this time to design imaginative trials with the hope of producing large incremental gains. Some possible approaches are discussed below.

Allogeneic stem cell transplantation

Numerous recent observations have demonstrated that the major antitumor effect of allogeneic transplantation derives primarily from the immunologic attack of donor lymphocytes against host tumor, rather than the preparative regimens of chemo/radiation therapy [13]. A new era of nonmyeloablative or "mini transplants" is beginning in which preparative regimens are designed primarily to be immunosuppressive and permit engraftment of donor hematopoiesis and immune effector cells. Although graft-versus-host disease remains a serious consequence of this approach, there is excellent tolerance of the preparative regimen, permitting application of allogeneic transplantation to older patients or those with complicating medical problems.

There has also been considerable effort aimed at creating "smart" allogeneic lymphoid elements primed in vitro specifically to respond to leukemic cells expressing unique proteins resulting from the many well-characterized mutations and cytogenetic translocations in patients with AML. Whether such a targeted treatment will be safer than and as effective as more broadly reactive allogeneic lymphocytes will be a focus of research over the next decade, but it is clear that these immunologic approaches may provide the most powerful anticancer therapy available for many diseases.

Autologous stem cell transplantation

Almost all of the randomized studies have utilized bone marrow as the hematopoietic stem cell source. Many studies have shown that peripheral blood stem cells provide more rapid and reliable reconstitution of hematopoiesis following myeloablative therapy [5]. This in turn is likely to reduce morbidity and mortality from autologous stem cell transplantation, and new trials are in progress comparing peripheral stem cell transplantation with chemotherapy in first remission. While there may be some advantage in safety and tolerance, it is unlikely that the antileukemic effect will be substantially enhanced and the potential problem of reinfusion of clonogenic leukemia cells, even in patients in apparent remission, remains. Thus while important to evaluate, it may be predictable that this will not provide the great leap forward that one would desire.

New agents

"Hope breeds eternal" in oncology, and numerous chemotherapeutic and biological agents are under evaluation by pharmaceutical companies internationally in leukemia and other solid tumors. There is no particular new drug that stands out at the moment, although it is important to comment upon gemtuzumab zogamicin, which has recently been approved for the treatment of AML in relapse in the USA and Europe [38]. Gemtuzumab zogamicin consists of a potent cytotoxic agent, calicheimycin, linked to a humanized monoclonal antibody directed against CD33, an antigen expressed on blasts from ≥90% of patients with AML. After targeting AML blasts by binding to CD33, the calicheimycin is internalized and eventually results in DNA strand break and cell death. Phase I/II trials have demonstrated CR in 25–30% of older patients in first relapse after a first remission duration of 6 months, with somewhat lower response rates in younger patients [38]. Although the immediate side effects of antibody administration are well tolerated and there appears to be little mucositis compared to chemotherapeutic regimens, the duration of marrow aplasia after treatment has been prolonged with median times to platelet and granulocyte recovery of 30 to 40 or more days. There have been no long-term disease-free survivors using antibody alone, although that was expected in this patient population.

The targeting of CD33 has both advantages and disadvantages. CD33 is expressed on a high percentage of the blasts from most patients with AML and is not expressed on healthy hematopoietic stem cells. Nor, however, is it likely to be expressed on the leukemia stem cell [9], and therefore the antibody may not be capable of producing sustained remission when used alone. The drug is being used extensively at this time for relapsed disease, particularly in older patients, because of its putative safety profile. It remains to be seen whether it will be as active as chemotherapeutic approaches in this situation. It does, however, serve as a model of a new means of delivering more specific therapy and will be explored widely as a possible adjunct to induction chemotherapy and postremission consolidation.

Antiangiogenesis

The role of angiogenesis has achieved enormous attention recently in both scientific journals and the financial pages. Perhaps surprisingly, it has been demonstrated that neovascularization is substantially increased in the bone marrow of patients with AML, with increases in vascular endothelial growth factor in the total marrow population and myeloid blasts themselves [1]. It is unknown whether this has any critical relationship to leukemia cell proliferation and, in particular, whether compounds that modify angiogenesis might be of therapeutic benefit. Many such compounds are entering clinical trials, however, and could eventually be of use.

Stem cell biology

Stem cells from most organs are designed to supply a continual stream of cells capable of proliferation and maturation into more differentiated, functional effector cells. Since their survival is critical to the continued function of the organ, and hence the overall individual, stem cells tend to have overexpression of a variety of mechanisms designed to protect them against exogenous toxins. Overexpression of p-glycoprotein and other drug-resistance mechanisms in the hematopoietic stem cell are examples of this phenomenon.

The most drug-resistant variants of AML appear to derive from cells with characteristics similar to those of the multipotential hematopoietic stem cell (e.g. AML following myelodysplasia or myeloproliferative disorders, Philadelphia chromosome-positive disorders, French-American-British class M0 minimally differentiated AML). In addition, within a given patient, even though the morphology of the blasts may appear to be quite homogeneous, there are marked differences in the ability of these cells to survive in long-term culture and in animal models such as immunodeficient NOD-SCID mice. These clonogenic cells represent $\leq 1\%$ of the total cell population in patients with AML and have an immunophenotype ($CD34^+$, 38^-, DR^-) similar to the putative hematopoietic stem cell [9]. It has been difficult to study this small subpopulation of leukemia cells in vitro, but it is predictable that they may share many characteristics with healthy hematopoietic stem cells. It is possible that some of the inferences derived from studies of entire cell populations in patients with leukemia may be misleading, at least in terms of mechanisms of drug resistance and sensitivity. Virtually all studies have focused on mechanisms of drug resistance, with few studies evaluating mechanisms by which such cells are sensitive to the chemotherapeutic agents used currently. It is likely that greater understanding of the fundamental principles of stem cell biology will translate into new hypotheses on the treatment of leukemia and other cancers.

The interaction between leukemic and healthy hematopoietic stem cells is also of interest. It is generally agreed that leukemia occurs as a consequence of an acquired mutation that gives a proliferative and survival advantage to the affected cell compared to normal marrow cells. However, this does not provide an explanation for the profound reduction in the differentiated normal cell population that occurs as the leukemia cell population expands. This is not a physical phenomenon of "crowding out", but rather appears to represent suppression of normal hematopoiesis by the leukemic clone by unknown mechanisms. This is readily reversible in most patients with leukemia because as effective induction therapy is administered, normal

hematopoiesis recurs within 2–3 weeks of completion of chemotherapy. These factors may actually help to protect the normal precursors from the effects of therapy, and further investigation into this phenomenon might be fruitful in terms of improving overall tolerance of chemotherapy.

It has always been assumed that long-term remission represents elimination or profound suppression of the leukemia clone with the return of normal hematopoiesis. Some patients with AML in remission have clonal remissions in which the clone can be shown to have probably derived from the leukemic clone [17]. Thus in these patients, by mechanisms not understood, there may have been an elimination of the block in normal differentiation, which, rather than eliminating the leukemic clone, resulted in the appearance of normal hematopoiesis. Although there has been some controversy about this observation, further investigation to characterize the frequency and persistence of clonal remissions in AML would be of interest.

Finally, it has also been demonstrated that leukemia cells with the t(8;21) translocation can persist in small numbers detectable by highly sensitive polymerase chain reaction in patients in long-term, multiyear remissions who are almost certainly cured of their disease [29]. Whether this represents immunologic control of these cells or persistence of t(8;21) in cells incapable of further proliferation or differentiation is unknown.

Conclusions

It remains difficult to define the obvious next generation of studies in AML. The striking results achieved the specific tyrosine kinase inhibitor STI-571 in patients with chronic myeloid leukemia [15] provide a stimulus to the development of other small molecules specific for the critical mutations that define many subtypes of AML. Owing to the relative rarity of many of these disorders, it may be difficult to convince pharmaceutical companies to undertake the expensive clinical trials required to demonstrate the efficacy of such compounds. This practical consideration may be a real challenge in the development of targeted therapies for many malignant disorders in the future. Means by which such trials can be performed efficiently and rapidly must be developed.

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