Primary Treatment of Acute Myeloid Leukemia (non M3) in Elderly: A Review

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Abstract

Treatment of acute myeloid leukemia (AML) in the elderly has always been a challenging task. Acute myeloid leukemia 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%. In spite of various available targeted therapies, the overall survival has not improved dramatically in the past decade. The ideal post remission regimen in this population has always been a matter of debate. Standard allogeneic bone marrow transplantation is too dangerous to be considered as a mean 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. The advent of non-myeloablative regimens has shown some prospects in select group of patients with good performance status. This review focuses on current therapeutic options available in this group of patients.

Key Words

Acute myeloid leukemia, Elderly

Introduction

The incidence of acute myeloid leukemia rises steeply after the age of 55. (Fig. 1) Any age criterion for "elderly AML" is arbitrary, patients are, for practical purposes, generally considered "older" if above age 55,[1] or 60.[2] At diagnosis, the important initial discussion with the patient focuses on determining whether standard AML treatment, investigational therapies in the context of a clinical trial, or palliative care might be the most appropriate option. Various groups have put forward many prognostic factors which may help to 'select out' patients who are suitable for standard treatment. Many studies have compared the option of best supportive care with that of induction chemotherapy for older patients with AML. Prospective non-randomized studies show trends toward improved survival when patients received chemotherapy in contrast to supportive care alone.[3] This may not, however, be true for the oldest subset of patients, those 80 years of age or older, who do not appear to benefit from the standard chemotherapeutic approaches that have been employed during the last two decades.[4] Cost is another important factor in deciding upon investigational therapies for the group of patients unfit for standard chemotherapeutic regimens.

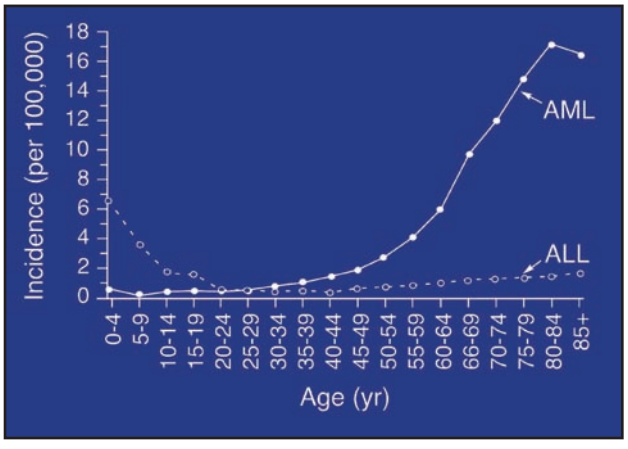

Fig. 1: Age related incidence of AML

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Defining Risk factors

The AML HD98-B trial of the German-Austrian AML Study Group correlated cytogenetic findings with outcome. They

identified 3 prognostic subgroups based on the influence of cytogenetic abnormalities on overall survival (OS): low-risk, t(15;17), and inv(16) in 25 of 361 patients (7%); standard-risk, normal karyotype, t(8;21), t(11q23), +8 within a noncomplex karyotype, and +11 within a non-complex karyotype in 208 of 361 patients (58%); high-risk, all other aberrations in 128 of 361 patients (35%). On multivariate analysis, high-risk cytogenetics (hazard ratio [HR], 2.24) and age above 70 years (HR, 2.34) were independent prognostic factors affecting OS, and stratification according to these parameters demonstrated that a large subgroup of patients (55%), characterized by age 70 or older or high-risk cytogenetics, or both, had very unfavorable treatment results despite intensive chemotherapy. Thus, karyotype and age are major determinants of outcome in elderly patients with AML. [5] In patients, in whom cytogenetic data is not available, the Penn Cytogenetic Surrogate Score designed by Andrea et al.[6], could be applied to make treatment decisions. This is a single-center study conducted to identify factors predictive of cytogenetic risk group in elderly AML patients. In multivariate analysis Hb < 100 g/L (p=0.005, OR=7.1, CI 1.82–27.30), CD7+ blast cells (p=0.033, OR=3.4, CI 1.09–10.27) and CD 34+ blast cells (p=0.003, OR=5.6, CI 1.80–17.53) remained significant predictors. Based on the odds ratios for CD7, CD34 and Hb, they constructed a simple scoring algorithm predictive of poor risk cytogenetic profile: entitled the Penn Cytogenetics Surrogate Score (PCSS).

The PCSS is defined as follows: CD7+ score =2, CD34+ score =3, Hb < 100 score =4. The total score is calculated at the time of diagnosis based on the patient's Hb and immunophenotype and is the summation of the individual scores for the subject. The probability of poor risk cytogenetics was 0.236 for patients with risk score of '0', whereas the probability was 0.763 for patients with risk score of '9'.[6] A recent French study indicated that in addition to the above mentioned factors, associated co-morbidities are independent factors that may influence achievement of complete remission (CR) in elderly patients with AML.[7]

Initial therapeutic options

A standard "3 + 7" induction regimen containing an anthracycline (often daunorubicin) and cytarabine may provide some benefit to some older patients. The median time from treatment with 3/ 7 regimens to death is 5 to 10 months. While CR rates are about 50%, the remissions are usually transient (rarely more than 12 months). The probability of remaining in remission 3 years after beginning treatment, beyond which time patients may operationally be considered "potentially cured," is less than 10%.[8] It is crucial to ascertain whether a particular patient, despite being elderly, may have a reasonable prospect of benefit from standard therapy in light of co-existing covariates that might mitigate the age effect. Chief among these are relatively young age (e.g., 55-65), good performance status, normal organ function, de novo presentation, "intermediate"—or "favorable"—cytogenetics and, most recently, lack of multidrug resistance gene (MDR) expression. [9] Data from Leith et al show the effect of these covariates in refining prognoses. Whereas the CR rate following treatment with a typical 3/ 7 regimen was 45% in all of Leith's 146 patients over age 55, it was 81% in the 27 of these 146 with de novo disease, intermediate or favorable cytogenetics, and "no" MDR expression.[10]

In the AML MRC 11 trial, patients with AML, more than 60 years of age were randomized between three induction regimens, DAT10 (Daunorubicin, cytosine and thioguanine-3+10+10) , ADE 10(Daunorubicin, cytosine and etoposide-3+10+5) and MAC (Mitoxantrone and cytosine-3+5). Patients who achieved remission had two more courses consolidation chemotherapy according to the randomization design. The complete remission rate was significantly better with DAT10 protocol (62%). However disease free survival and overall survival at 5 years were not significantly different between the three regimens. However, survival at 5 years with DAT was significantly better than ADE (12% vs 8%). [11]

Low dose cytosine

Various dose schedules were used and it has been debated as to whether the activity is mediated

by cytotoxicity or differentiation induction.[12] The UK MRC group recently completed a comparison of low dose Ara-C given in a schedule of 20 mg twice daily subcutaneously for 10 days every 4 to 6 weeks versus hydroxyurea for patients who were not considered fit for standard chemotherapy. Each arm was also randomized to receive All-trans-retinoic acid (ATRA) based on preclinical data that ATRA can sensitize AML blasts to Ara-C. This study recruited 217 patients. The independent Data and Ethics Monitoring Committee recommended premature closure of the trial because the remission rate and survival on the low-dose Ara-C arm was significantly superior. Eighteen percent of low-dose Ara-C patients achieved CR and the median duration of remission was 82 weeks. The overall benefit was entirely attributable to patients who entered CR, which reinforces the point that for survival benefit— even in the older patients—the main target for success is the achievement of CR. No clearly beneficial effect of the addition of ATRA was seen. [13]

On the basis of preclinical data suggesting a possible anti-angiogenic effect of arsenic trioxide (ATO), as well as clinical data showing activity of ATO in Myelodysplastic syndrome (MDS), a phase I/II trial of ATO in combination with LDAC (Low dose cytosine arabinoside) was initiated in IPSS-2 (International Prognostic Scoring System) MDS and newly- diagnosed, poor-prognosis AML patients. ATO was given at a dose of 0.25 mg/kg for days 1–5 and 8–12. LDAC was dose-escalated from 5 mg/m^2 subcutaneously twice daily (SC BID), to the target phase II dose of 10 mg/m^2 SC BID for days 1–14 (one treatment cycle). Patients who achieved CR after one treatment cycle were given a second, identical cycle, followed by maintenance treatment of 5 days of LDAC and 2 days of ATO every 28 days. Patients who did not achieve CR after one cycle were given a second cycle beginning between days 21–28, with the addition of ascorbic acid 1g IV within 30 minutes of the ATO infusion. CR was achieved in 11 out of 34 patients (39%), with follow-up 1–8 months. Six patients (55%) required 2 treatment cycles to achieve CR. There were no clinically significant drug-related arrhythmias. For AML patients, the combination of ATO and LDAC resulted in a CR rate comparable to conventional chemotherapy, with improved tolerability and induction mortality.[14]

Other chemotherapy regimen

Manoharan et al [15] treated elderly AML patients with cytosine, mitoxantrone and etoposide and most of the patients received at least two courses of chemotherapy. The duration of cytosine and etoposide were flexible according to the performance status and the response to the initial therapy.

Tsurmi et al [16] treated patients with low performance status with low dose cytosine and etoposide. If the performance status improved after induction chemotherapy, those patients had standard doses of consolidation chemotherapy. Those patients with improved performance status after induction showed a much better overall survival of 81% at one year, which confirmed the fact that performance status is an independent determinant of overall survival in the elderly population. Mori et al [17] showed that even very elderly patients of age more than 76 can be successfully induced with low intensity regimens (cytosine, 6 mercaptopurine and etoposide). Those achieving complete remission had an impressive overall survival of 22% at two years. Bashey et al [18] used FLAG regimen and showed that this regimen can be used safely in patients who pose contra-indications to the use of anthracyclines. The results are comparable and the induction mortality was only 12%. Those patients in complete remission had either consolidation chemotherapy, autologous or mini-allogenic transplant. However, Gert et al [19], in a phase III randomized trial showed that there was no difference in complete remission and overall survival when Fludarabine was omitted and with one group having only AG- cytosine and colony stimulating factors. Hartmann et al.[20] used two to three courses of divided dose etoposide along with cytosine and idarubicin.[15] This study and the one by Manoharan et al. included patients with both de novo and secondary AML.

Both of them showed that in these elderly patients there was no difference in complete remission or overall survival between both

groups. The results are summarized below [Table 1]. However, consideration must also be given to the fact that median age of patients with AML is in the mid-60s, and recruitment to trials in this age range is acknowledged to be selective so it is not easy to extrapolate the results from trials to the older AML population as a whole.

Antibody based targeted therapies

Antibodies against CD33 and CD45 are available for treatment in AML.

CD33 has emerged as the favored target, and although not leukemia-specific, it was expressed on the blast cells of 85% to 90% of cases.[21]

However, it is expressed on normal hemopoietic tissues but not on stem cells—at least at the level normally considered to give a designation of "positive." [22] As far as is known, no expression is found on nonhemopoietic tissue. Gemtuzumab ozogamicin (GO-Mylotarg; Wyeth, Philadelphia, PA) comprises a humanized anti-CD33 monoclonal antibody of the IgG4 subclass to which is chemically linked the powerful antitumor antibiotic calicheamicin. As free drug, calicheamicin is several logs more potent against leukemic cell lines than some clinically established drugs. It induces cytotoxicity by intercalation into DNA, and its potency excludes its use as a free drug. The key features of gemtuzumab ozogamicin are that the chemical linker to the antibody is only severed in the acidic intercellular environment of the lysosyme. Very little or no free drug is found in the product or patient's circulation. The second advantage is that when the antibody complexes with the CD33 epitope, the complex is rapidly internalized. This represents a theoretically advantageous drug delivery mechanism. [23] Developmental phase I and II studies were conducted in relapsed AML. The phase I study examined several dose levels from 1 to 9 mg/m^2. Saturation of CD33 receptors was maintained over several hours at doses from 4 mg/m^2, being maximal at 9 mg/m^2. CRs were observed at dose levels as low as 4mg/m^2.[24]

Mounzer et al.[25] treated 6 elderly AML patients with GO as a single agent upfront. The treatment consisted of Mylotarg 9 mg/m^2 on days 1 and 14.

Four of 5 evaluable patients (80%) achieved complete remission as documented by bone marrow evaluation. The treatment was well tolerated despite the neutropenic hospitalizations and all responders regained normal performance

Regimen	Number of patients	Age group	CR	OS at 1 year	Reference
FLICC[1]	25	61-78	52%	32% 64% for CR patients	14
Low dose cytosine and etoposide[2]	28	60-85	64%	22% vs 81%@	15
Cytosine, Daunorubicin and 6- Mercaptopurine[3]	65	>76	38%	22% at 2 years	16
FLAG[4]	24	>60	58%	-	17
DIVA[5]	42	>61	62%	Median survival 38 weeks, 51 weeks for CR patients	19

* All patients had poor performance status or co-morbidities.

@ 81% for patients whose performance status improved after induction and they received intensive consolidation.

1. Flexible Low Intensity Combination Chemotherapy – Mitoxantrone 6mg/m^2 x 3 days, Cytosine 10mg/m^2 twice daily 7-14 days, Etoposide 100mg orally once daily 7-14 days.
2. Cytosine continuous infusion 20mg/m^2 and Etoposide 50mg/m^2 x 10 days.
3. Cytosine 150mg/m^2 1-7days, Daunorubicin 30mg/m^2 1-3 days and 6 Mercaptopurine 100mg 1-7days.
4. Fludarabine 25mg/m^2 x 5days, Cytosine 1g/m^2 x 5days, G-CSF started 1 day before chemotherapy.
5. Cytosine 100mg/m^2 1-5 days, Etoposide 60mg/m^2 twice daily 2-5 days, idarubicin 10mg/m^2 1-3 days.

Table 1: Treatment outcome of elderly AML patients treated with various protocols upfront.

status. The AML MRC 15 trial has randomized patients to receive Mylotarg in the induction regimen. In the preliminary analysis in elderly patients the overall remission rate is 81%.[26]

Based on a study by Malgoa et al.,[27] which showed that addition of fludarabine was able to overcome multi drug resistance phenotype, an Italian study randomized elderly AML patients to receive FLAI (Fludarabine 30mg/m^2, Cytosine 1g/m^2, Idarubicin 5mg/m^2 on days 1-3) with or without Gemtuzumab (MY-FLAI). Patients on the GO arm received Gemtuzumab 3mg/m^2 on day 4. The complete remission rates were comparable between the two groups (52%). However, relapse free survival (40% vs 80%) and overall survival (14% vs 40%) were significantly higher in favor of MY-FLAI arm. [28]

Overcoming intrinsic resistance

High expression of the gene product of the MDR1 gene, P-glycoprotein (Pgp) correlates with increased age, adverse karyotype, a lower remission rate, and in some studies a higher relapse rate.[10] Other proteins are also associated with drug export and cell resistance such as MRP (multi-resistance protein), LRP (lung resistance protein), BCRP, and BCL2 .[29]

The efflux pumping function can be blocked by a number of agents, including quinine, cyclosporine, and the cyclosporine derivative PSC-833.

So far the overall strategy of modulation of drug resistance has been disappointing, particularly in older patients. The preclinical in vitro data were seductive. It is likely that subsets of patients could be identified where modulation can be shown to be beneficial. [30]

Transplant options

The optimal post remission treatment for elderly patients with acute myelogenous leukemia (AML) is presently unknown. Intensive consolidation courses do not offer therapeutic benefits as evidenced by the recent French (ALFA 9803) trial.[31] Trials with allogenic and autologous transplants have been carried out in the hope that eradication of minimal residual disease may offer 'cure' in this population. Allogeneic hematopoietic stem cell transplant (HSCT) using reduced-intensity conditioning regimens attempts to maintain the advantage of a graft-versus-leukemia effect while minimizing the toxicity of a fully ablative regimen.

Preliminary studies have demonstrated that durable complete remissions may be maintained with this treatment. One example is a recently published multicenter trial where low-dose (2 Gy) total body irradiation and fludarabine was used for the preparative regimen with cyclosporine and mycophenolate mofetil for graft-versus host disease (GVHD) prophylaxis in 122 high-risk AML patients where the median age was 57.5 years. Among a subset of these patients, 9 of 14 patients $\geq$ age 60 (range, 60-74 years) had durable responses. While GVHD remains a significant problem with this preparative regimen, clinical outcomes were encouraging. Among patients transplanted in CR1, the 2-year overall survival was 44% after HLA-related and 63% after HLA-unrelated HSCT, suggesting a stronger graft-versus-leukemia effect of the unrelated allogeneic graft. Overall, with a median follow-up of 417 days, transplant-related mortality was only 6.7%. [32]

In an M.D. Anderson study, couple of regimens were studied, Regimen 1 containing fludarabine, Ara C and idarubicin (FAI) and Regimen 2 which includes fludarabine/melphalan (FM), either 140 or 180 mg/m^2. There were 32 patients in arm 1 and 62 in arm 2. Median ages were 61 years in arm 1 and 54 years in arm 2. Of the patients in arm 1 and arm 2, 14 and 10 respectively were in remission. Arm 1 had exclusively sibling donors, whereas arm 2 had a mix of either unrelated or related donors.

Outcomes for the patients where the follow up was 54 months was 40% for the FAI and FM regimens. The data do not indicate significant superiority of one regimen over the other; however, there is a suggestion that FM may be superior. [33]

Lashkari et al. [34] evaluated the role of autologous transplants in AML patients $\geq$ 60 years of age. Twenty seven patients with newly diagnosed AML in first CR had chemo-radiotherapy preparative conditioning followed

by transplantation of peripheral blood progenitor cells procured after a single cycle of cytarabine-based consolidation chemotherapy as post remission therapy. The median follow-up from remission for surviving patients was 81 months (range 41.4-123.1 months). Seven patients are alive in continuous CR, 19 died from relapse, and 1 died as a result of treatment-related infection. Leukemia-free survival and overall survival are 10.3 and 13.4 months respectively. Actuarial leukemia-free and overall survival at 3 years are 25% ± 9% and 28% ± 9%, respectively.

Novel therapies

Cloretazine, a new alkylating agent has recently been shown to have efficacy in untreated older patients with poor-risk de novo AML, resulting in a 49% CR rate and DFS at 1 year of 27%.[35] Clofarabine is a new nucleoside analogue, which combines the advantages of fludarabine (incorporation into DNA) and cladrabine (inhibition of ribonucleotide reductase) and can be given orally. A recently reported phase II study that tested clofarabine in combination with cytarabine demonstrated an overall response rate of 60% in chemotherapy-naïve, high-risk AML patients > age 50. [36]

The UK MRC group initiated a trial using single-agent clofarabine as first-line treatment for patients not considered fit for an intensive treatment approach. A dose level of 30 mg/m^2 was chosen to try to avoid liver toxicity and possibly shorten the duration of cytopenia. Twenty-nine patients were recruited with a median age of 72 years (range, 61 - 82). Sixteen patients (53%) achieved CR after one course and a further two had marrow remissions without count recovery. The median duration of survival of patients who entered CR was approximately 26 weeks.[37]

FLT-3 is a member of the class III receptor tyrosine kinase family, which includes FLT1, FMS, PDGFR, and KIT. It is normally expressed on hematopoietic precursors and is over-expressed in unmutated form in AML cells. It appears to be the most common single mutation in AML, occurring as an internal tandem duplication (ITD) in the juxtamembrane domain of the receptor, in about 30% of patients so far reported. Farnesyl transferase (FT) is the enzyme responsible for the transfer of farnesyl to the cysteine residue of the C-terminal CAAX motif of RAS and other proteins—so-called prenylation. This allows RAS to anchor to the inner aspect of the cell membrane, facilitating binding with guanine nucleotides. Since RAS is widely expressed in various cancers, including AML, this process is of potential interest as a therapeutic target. Various agents causing Flt-3inhibition (SU5416, SU11248, PKC412,MLN518) and Farnesyl tranferase inhibitors such as Tipifarnib are under evaluation in Phase I and Phase II studies. [38]

Summary and conclusions

As the insights into disease pathogenesis continue to expand, the therapeutic options for these older patients who comprise the majority of AML cases will increase rapidly. A systematic approach to treatment of these patients proposed by Wendy et al. [39] seems logical with the current available studies. Newly diagnosed patients without bad prognostic factors such as increasing age (>75), performance status > 2, poor organ function, poor cytogentics, MDR1 expression, Flt3 mutation can be offered standard induction regimens and consolidation. Other chemotherapeutic regimens or novel agents can be incorporated in patients resistant to standard therapies.

Reduced intensity transplants are an option in these patients if they have matched sibling donors. Newer drugs are likely to be expensive, and it is reasonable to approach the problem by looking for new treatments that may produce a larger benefit rather than concentrating on large trials, which consume a lot of patients, designed to detect or disprove small differences.

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