



How I Treat Adult Acute Myeloid Leukemia

Tapan K. Saikia¹

¹Department of Medical Oncology, Prince Aly Khan Hospital, Mumbai, Maharashtra, India Medical ,Oncology Prince Aly Khan Hospital, Mumbai, Maharashtra, India

Address for correspondence Tapan K. Saikia, MD, Medical Oncology, Prince Aly Khan Hospital, Nesbit Road, Mumbai 400010, Maharashtra, India (e-mail: tapan.saikia@gmail.com).

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Introduction

In the mind of a reader, the first query would be, do I need to read another review article written by an Indian physician when I get to read everything on the multiple platforms on the internet? Such reaction is a valid one, given the avalanche of information and limited time available to read. Nevertheless, on request of the editorial board I accepted the challenge, and have included some relevant Indian publications.

Acute myeloid leukemia (AML) is a heterogeneous disorder and a very challenging pathology, though not fully unraveled yet.¹⁻⁵ While nonrandom cytogenetic and molecular abnormalities have provided opportunity for a better classification, we still have a sizeable number of cases in whom the pathology is poorly understood, and they continue to receive old chemotherapy regimens and hematopoietic stem cell transplantation (HSCT) whenever possible. Additionally, incidence of Myelodysplastic syndrome (MDS) associated AML and therapy-related AML is not insignificant; a subset of patient pausing maximum challenge.⁶⁻⁸

Acute promyelocytic leukemia (APL) can now be treated very effectively with nonchemotherapy-based regimens and a small subset deriving added benefit from inclusion of chemotherapy drugs like daunorubicin, idarubicin, and antibody drug conjugate gemtuzumab ozogamycin (GO).⁹⁻¹² I will not discuss about APL in this review, as it needs a dedicated article.

Diagnosis

As a referral center, I always get to see a patient after a reasonably accurate diagnosis is done elsewhere. Hence, I immediately request following investigations, mostly on a marrow sample (rarely on peripheral blood, provided blasts cells are more than 20%, if the patient refuses to consent or only supportive care is the goal; ►Table 1). As frequent dialogues are necessary to arrive at a rapid and confirmed diagnosis, I

outsource sample to a laboratory where the hematopathologists are available for discussions to clarify doubts.

Morphology: As per the European LeukemiaNet (ELN) guideline and World Health Organization (WHO) classification, presence of 20% or more blasts after examining 200 leucocytes on a peripheral blood smear or 500 cells on marrow smear is necessary to proceed with further workup.^{1,13} However, in cases with t(15;17), t(8;21), inv(16), or t(16;16), even 10% or more blasts should be acceptable for confirming the diagnosis. Hence, awaiting these reports (takes ~3–5 days turnaround time) is worthwhile. Additionally, AML with monocytic or myelomonocytic differentiation, only monoblasts and promonocytes are to be counted to differentiate from chronic myelomonocytic leukemia (CMML).

Immunophenotyping: The full panel of cell surface and cytoplasmic markers (CD13, CD14, CD33, CD34, CD36, CD41, CD61, CD64, CD65, CD64, CD117, and Human Leucocyte Antigen DR [HLA-DR]) should be included and when necessary markers for mixed phenotypic acute leukemia panel [Mixed-phenotype acute leukemia (MPAL)—Myelo-peroxidase (MPO), Cluster of differentiation (CD) CD3, CD10, CD11c, CD14, CD19, cCD22, CD64, and CD79a] should be asked for.

Cytogenetics and molecular cytogenetics: It is crucial to ask for conventional karyotyping to detect all known nonrandom, random, or novel cytogenetic abnormalities to understand prognosis, therapeutic decision-making, and new information. Polymerase chain reaction (PCR) technology has become a boon for availing information on recurring abnormalities. For patients who understand and generate adequate funds for optimal treatment, we are now integrating next-generation sequencing (NGS), as it is an extremely powerful technique offering deeper insight into the disease biology.

For unified classification of various hematological neoplasms, currently WHO classification is followed by nearly all, the latest one published in 2016.¹

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Table 1 Tests performed for diagnosis and initial treatment

- Complete blood count (CBC) with full manual white cell count differential
- Bone marrow aspirate (trephine biopsy is optional—dry tap, research protocol)
- Immunophenotyping
- Cytogenetics: karyotyping
- Gene mutations and rearrangement: RT-PCR, NGS
- NPM1, CEBPA, RUNX1, FLT3, TP53, ASXL1, PML-RARA, CBF-MYH11, RUNX1-RUNXT1, BCR-ABL, any other as per ability of a specialized laboratory
- Demographics and medical history
- Family history
- Performance status
- Hepatitis B, C and HIV-1
- Blood chemistry: LFT, RFT, uric acid, LDH, electrolytes
- Coagulation profile
- Lumbar puncture, especially in children or on clinical suspicion
- Chest X-ray, ECG, 2DECHO/MUGA
- Biobanking
- HLA-typing (often at a later date), CMV-PCR, for patients potential candidates for allogeneic transplants

Abbreviations: FLT3, fms-like tyrosine kinase 3; NPM1, Nucleophosmin 1; CEBPA, CCAAT/Enhancer binding, protein alpha; RUNX 1, Runt-related transcription factor 1; TP53, Tumor Protein 53; ASXL 1, additional sex comb-like 1; PML-RARA, promyelocytic leukemia/retinoic acid receptor alpha; CBF-MYH11, Core Binding Factor Beta sub unit/Myosin Heavy Chain; BCR-ABL, Breakpoint Cluster Region-Abelson; 2D-ECHO, 2-dimensional echocardiography; MUGA, Multigated Acquisition scan; HLA, human leucocyte antigen; ECG, electrocardiogram; LFT, liver function test; LDH, lactate dehydrogenase; NGS, next-generation sequencing; RFT, renal function test; RT-PCR, reverse transcription polymerase chain reaction.

In larger institute, it should be a regular practice to bio-bank (following ethical and scientific process) the cells for further study. It is truly a valuable bank, and we were greatly benefitted by one at Tata Memorial Hospital.

The relevant workup for starting treatment that includes blood biochemistry, coagulation profile, electrolytes, viral markers (sometimes there could be need for extensive workup), surveillance culture (a debatable issue, we do not practice), chest X-ray (computed tomography [CT] scan of chest, abdomen and others, or magnetic resonance imaging [MRI]—in selected cases, based on justified clinical judgement) is completed.

Genetic stratification is becoming increasingly important to understand disease biology, prognosis, possible of drug toxicity, genetic counselling, and planned treatment (► **Table 2**).

Supportive Care

The first issue I try to solve before admitting a patient of AML is that, all necessary supportive care, antimicrobials, blood components, central venous device (CVD) care, nutrition, etc., are in place. This remains a challenge in many places in India. With a good reason, I am not a great proponent of prophylactic oral antibiotics; however, we now routinely use antifungal throughout the treatment course.¹⁴⁻¹⁷ For febrile neutropenia, our institutional practice at present is monotherapy, a carbapenem, based on microbiology data. Addition of colistin happens in a significant number. We have not used an aminoglycoside for a long period. Third-line antibiotic is vancomycin or teicoplanin.

Table 2 Genetic Stratification

Classification
Myeloid neoplasms with germ-line predisposition without preexpressing disorder or organ dysfunction
AML with germ-line CEBPA mutation
Myeloid neoplasms with germ-line DDX41 mutation
Myeloid neoplasms with germ-line predisposition and preexisting platelet disorders
Myeloid neoplasms with germ-line RUNX1 mutation
Myeloid neoplasms with germ-line ANKRD26 mutation
Myeloid neoplasms with germ-line ETV6 mutation
Myeloid neoplasms with germ-line predisposition and other organ dysfunction
Myeloid neoplasms with germ-line GATA2 mutation
Myeloid neoplasms associated with bone marrow failure syndrome
Juvenile myelomonocytic leukemia associated neurofibromatosis, Noonan's syndrome like disorders
Myeloid neoplasm associated with Noonan's syndrome
Myeloid neoplasms associated with Down's syndrome
Guide for molecular genetic diagnostics
Myelodysplastic predisposition/acute leukemia predisposition syndromes
CEBPA, DDX41, RUNX1, ANKRD26, ETV6, GATA2, SRP72, 14q32.2 genomic duplication (ATG2B/GSKIP)
Cancer disposition syndromes
Li Fraumeni syndrome (TP53)
Germ-line BRCA/BRCA2 mutations
Bone marrow failure syndromes
Dyskeratosis congenita (TERC, TERT)

Therapeutic antifungal is an echinocandin, amphotericin reserved for later use. For blood components, we followed the Association of American Blood Bank guidelines. Antivirals are not a part of routine therapy during induction; those are used only for allogeneic transplant cases. For CVD care, we have a dedicated nursing team. We do not use growth factor support—cerebrospinal fluid (G-CSF) in the induction phase but have been practicing during postremission therapy with high-dose cytarabine.¹⁸

Acute Myeloid Leukemia Directed Therapy

I try to take no half measures while managing a freshly diagnosed young patient with AML. Over multiple sessions, patients and families are explained and counselled about every aspect of the disease and management such as chemotherapy, biologicals, blood components, antimicrobials, need for stem cell transplants, donor selection, cost, prognosis and outcome, and duration of treatment. As it happens across India and other middle- and low-income countries (MLIC), only a small number can accept current standard of care. I follow ELN guidelines and most recent published updates.^{2,3,19-25}

Induction of Remission

Since the middle of 1980s, we have continued to use the 3 + 7 regimen of daunorubicin and cytarabine. We explored daunorubicin doses of 45 and 60 mg and 90 mg/m² daily for 3 days, finally settling down on 60 mg/m² dose.^{13,26-29} We used idarubicin very sparingly, given its high cost and nonsuperiority.³⁰ Cytarabine dose has always been 100 mg/m²/day continuous intravenous infusion for 7 days, although we are aware that 200 mg also could be used. We have not explored intermediate or high-dose cytarabine, as these are known to cause higher complications.²⁸ If the first cycle fails to achieve a morphological remission, we use high-dose cytarabine at a 1.5 to 3 g/m² in every 12 hours for six doses on 3 consecutive days or on days 1, 3, and 5.^{2,13,31} Addition of targeted agents, like FLT3 inhibitors, has not improved remission rate significantly but impacted event-free and overall survival (EFS and OS).^{32,33} However, promises are plenty for use of novel agents in induction and postremission phases.³⁴

Institution of chemotherapy is usually considered an urgency, if not an emergency, except in cases of APL; however, a recent report, the Beat AML study, has shown that a wait period of 7 days is safe, the time needed for turnaround of genetic information.³⁵

Postremission Therapy

I have tried to address the three approaches of postremission therapy as follows: (1) high-dose cytarabine-based chemotherapy, (2) allogeneic HSCTs and (3) autologous HSCT through case vignettes from our own experience. I have tried to include the issues of donor selection, minimal residual disease (MRD), and novel drugs.

Case 1: A 32-year-old female, was diagnosed to have AML with normal cytogenetics with NPM-1 mutation and FLT3 negativity in 2010. A complete remission was achieved with one cycle of 3 + 7 of daunorubicin 60 mg/m²/day × 3 days and cytarabine 100 mg/m²/day × 7 days. Subsequently four cycles of high-dose cytarabine at 4- to 5-week intervals were administered. She remains disease free till date with no long-term effects of therapy.

High-dose cytarabine is now administered in a dose varying from 1 G/m²/12 hours × six doses on consecutive or on alternate days to 3 G/m²/12 hours × six doses at 4-week intervals with no significant difference in outcome.^{28,29,31} We offer lower dose to patients over 50 years of age. All standard- and some intermediate-risk patients are eligible for this postremission therapy. Addition of anthracycline does not improve outcomes.

Case 2: A 39-year-old male, was diagnosed to have a poor-risk cytogenetics AML with trisomy 8 and mixed-lineage leukemia (MLL) translocations, when he presented with repeated febrile episodes and increasing fatigue in recent months. He received a 3 + 7 regimen of daunorubicin 60 mg/m²/day × 3 and cytarabine 100 mg/m²/day continuous intravenous for 7 days. He had a stormy postinduction phase that needed multiple antimicrobials. Although there was a morphologic remission, MRD was positive. Then he received one cycle of high-dose cytarabine, 2 g/m²/12 hours × six doses on days 1, 3, and 5. Within 3 months of initial therapy,

he received an allogeneic peripheral blood stem cell transplantation (PBSCT) from an HLA- and blood group-matched female sibling donor, following a melphalan and fludarabine conditioning chemotherapy. Posttransplant course was largely uneventful barring a brief neutropenic fever and minimal blood component requirement. There was no cytomegalovirus (CMV) reactivation or graft versus host disease (GVHD). There was no planned Donor Leucocyte Infusion (DLI) for patients who do not develop GVHD. Unfortunately, his disease relapsed 5 months after transplant. An attempt to induce a remission with the fludarabine + high-dose cytarabine + Granulocyte-Colony Stimulating Factor (FLAG) chemotherapy proved to be fatal.

This case raises the issues of outcome in poor-risk AML following current standard of care at 5-years.^{13,28,35} If a transplant is not feasible, the outcome is less than 15 and 35 to 45% following a transplant.²⁸ Should he have received a myeloablative conditioning regimen, Total Body irradiation (TBI) Fluorescent in-situ hybridization (FISH)-based or chemotherapy based? The issue remains unresolved with differing results from different trials.³²⁻⁴⁰

Logistically, MRD or measurable residual disease assessment following every phase of treatment should have an extremely powerful prognostic determinant and a base for clinical trials.⁴¹⁻⁴⁴ In B-precursor cell, the role of acute lymphoblastic leukemia (ALL) has been established and being actively used across the globe. AML being a biologically more heterogenous disorder and abnormalities detected with various techniques (cytogenetics, FISH, PCR, and NGS), not to mention the numerical burden of mutations makes MRD assessment more challenging. Currently, multicolor flow cytometry using minimum eight-panel antibodies is frequently used.⁴⁵ However, assessing individual abnormalities by molecular techniques have pertinent value. Nevertheless, it is a dynamic field and cannot be used in routine practice.

Case 3: A 27-year-old female, was diagnosed to have poor-risk AML (>10 abnormalities), following investigations for severe anemia. A 3 + 7 induction chemotherapy with daunorubicin and cytarabine could produce only a partial remission and a high-dose cytarabine therapy of 2 G/m² × six doses produced a morphological remission but with MRD positivity. She did not have a sibling donor; upon search, a 9/10-matched donor was found. While waiting for the transplant, she received another cycle of chemotherapy with single-agent cladribine and achieved an MRD negative status. She underwent matched-unrelated donors (MUD) transplant with melphalan + fludarabine conditioning and short methotrexate + cyclosporine for GVHD prophylaxis; 5-month post-transplant remains in graft and relapse-free survival (GRFS). It is still too early to realize whether the treatment has been curative!

This case emphasizes the importance of an allogeneic transplant from a suitable donor. MUD transplants appear to be safe and outcomes as good as sibling donor transplants if HLA match is 10/10 or 9/10 (50–52). However, the procedure is expensive and the challenge of finding a donor on time remains. Whether a haploidentical transplant could be more practical in an Indian setting, is a matter of discussion.

Donor selection for allogeneic transplant is important.^{28,46-48} While HLA-matched sibling donor is a first choice, lack of these donors for majority of eligible patients, alternative donors, namely, MUD, mismatched unrelated donors, and haploidentical donors are chosen. Outcome of such alternative donor transplants is improving. For MUD, 8/8 match is considered optimal; mismatch of one or more allele, the survival outcomes are inferior by 10% for each allele. Currently, most centers look for 10/10- or 9/10-matched donors.

Case 4: A 44-year-old female, was diagnosed to have an FLT3-internal tandem duplication (ITD)-positive AML and failed to achieve morphological remission with a 3 + 7 idarubicin and cytarabine + midostaurin induction therapy. Reinduction with high-dose cytarabine caused a prolonged neutropenic period lasting for more than 6 weeks. The marrow was hypocellular with no excess blasts. She was advised an allogeneic HSCT and her 42-year-old brother was found to be HLA identical. As she needed to raise funds for the procedure, she was advised to continue treatment with 5-azacytidine and sorafenib. She could receive 5-azacytidine but due to persistent neutropenia, sorafenib was omitted. She underwent transplant with busulfan + fludarabine conditioning and posttransplant cyclophosphamide (PTCY) for GVHD prophylaxis, a year after initial therapy. Posttransplant period was complicated by a short bacterial infection and need for moderate blood components. However, 4 weeks after post-transplant, she developed grade-IV thrombocytopenia and deranged liver function test (LFT). CMV copies were elevated to 1,350 copies/mL of blood. After being diagnosed as CMV hepatitis, she received a 3-week course of ganciclovir along with platelet support. CMV level returned to normal and LFT improved. Around the same time, skin rash was diagnosed as acute GVHD grade 1 and received methylprednisolone, followed by oral prednisolone. Her CMV and limited GVHD recurred and possibly BK virus-associated cystitis developed few months post-transplant and prednisolone, monitored by a local physician who is new to such care, we remain in constant touch.

Abnormalities in the FLT3 gene, either in the form of ITD in 15 to 25%, more common in younger population or mutations in the tyrosine kinase domain (D835TKD) in 5 to 10% of population. In last two decades, several targeted drugs and FLT3 inhibitors have been developed and clinical trials done.⁴⁹⁻⁵³ Currently, approved ones are midostaurin, quizartinib, crenolanib, and gilteritinib. Midostaurin used at a 50-mg twice daily dose included in the induction regimen and postremission phase and maintenance for a year, the phase-3 randomized RATIFY trial showed significantly improved EFS in younger patients.^{49,50} Clearly, more potent inhibitors are needed. Sorafenib, a multikinase inhibitor, showed its potential, but till date, no phase-3 has been published.⁵⁴ While it is somewhat easier to administer for chemotherapy-alone patients, these agents cannot be administered as smoothly following allogeneic transplants due to various complications like infections, GVHD, and hamper frequently.

At this point, I take the opportunity of mentioning novel drugs that have been approved or undergoing clinical trials

(► **Table 3**). It is beyond the scope of this article to mention details of each drug, clinical trials, and outcome. I request readers to refer to two excellent recent publications.^{51,53} Advent of these novel agents has brought about a revolution in treating elderly patients and some of relapsed cases. As time progresses, these will move onto treatment of newly diagnosed young patients.

Case 5: R.P., a 22-year-old male, was diagnosed with good risk t(8,20) AML with normal white cell count. A morphologic remission was achieved with a 3 + 7 regimen. Following a high-dose cytarabine postremission therapy, he was explained regarding further chemotherapy or a high-dose chemotherapy [Busulphan and Cyclophosphamide (BUCY) regimen] with autologous blood stem cell transplant (ASCT). He accepted ASCT and now 10 years later lives a normal life, married and father of a child. Long-term follow-up data from Electronic Bone Marrow Transplant (EBMT) Registry show that ASCT could be superior to intensive chemotherapy in good risk and intermediate risk cases.³⁶ In my opinion, ASCT remains a reasonable option if an experienced center has an extremely low transplant-related mortality rate.

Case 6: A 32-year-old female, presented with fatigue of two weeks duration. A complete blood count (CBC) revealed white blood cell (WBC) of $76 \times 10^9/L$ with 70% circulating blasts; hemoglobin, 6 g/dL; and platelets, $230 \times 10^9/L$. Immunophenotype confirmed AML with monocytic

Table 3 Novel drugs for treatment of acute myeloid leukemia (AML)

Drugs	Type of treatment	Studies
FLT3 inhibitors		
Midostaurin (oral)	Phase III	With chemotherapy (placebo controlled) RATIFY
Quizartinib		
Gilteritinib (oral)	Phase III	Vs. salvage chemotherapy ADMIRAL
IDH 1/2 inhibitors		
Enasidenib (oral)	Phase I/II	
Ivosidenib (oral)	Phase I/II	
BCL-2 inhibitor		
Venetoclax (oral)	Ib/II for adults ≥ 75 years old	Study M14-387
Hedgehog (Hh) pathway inhibitors		
Glasdesib (oral)	Phase II	Randomized BRIGHT
Chemotherapy		
CPX-351 (oral)	Phase III	Vs. 3 + 7 regimen
Gemtuzumab ozogamicin (GO)	Phase III	Vs. best supportive care EORTC-GIMEMA AML-19 Vs. 3 + 7 regimen ALFA-0701
Abbreviations: IDH1, isocitrate dehydrogenase 1; BCL-2, B-cell lymphoma-2.		

differentiation. A marrow aspirate was dry, apparently due to a packed marrow; a trephine was possible. Peripheral blood could be studied for karyotyping, a normal cytogenetics. NGS molecular diagnostics revealed NPM-1 mutation, IDH mutation and DNMT3 mutation; FLT3 mutations were negative. As per current prognostic criteria, she falls in the favorable group with 85% possibility of a cure with or without an HCT.⁵⁵ She received induction therapy with 3 + 7 regimen of daunorubicin 60 mg/m²/day × 3 and cytarabine 100 mg/m²/d civ × 7. Following required supportive care, her blood counts normalized on day 20. A marrow aspirate was easy this time; it showed morphological complete remission and MRD negative by eight-panel flow (sensitivity 3 log reduction). We are discussing with her regarding further care with three more cycles of postremission therapy or offer an allogeneic HCT if her only sister is HLA identical.

Treating Elderly Acute Myeloid Leukemia Patients

AML being disease of elderly, who are unable to tolerate aggressive therapy due to physiological decline in health and associated comorbidities, has been receiving only symptomatic care. However, with the availability of epigenetic therapy like 5-azacitidine and decitabine, currently a significant number of elderly patients receive these agents and some derive long-term benefit.⁵⁶ Intense research in this field has led to development of several novel drugs targeting pathways responsible for leukemogenesis. These have helped to treat a larger number of elderly patients.

Current trend is to offer a combination of 5-azacitidine and venetoclax for majority of elderly patients, if a molecular target has not been detected.⁵⁷ This combination calls for excellent supportive care as venetoclax produces deep cytopenia. The dose of this agent needs to be ramped up within 3 to 4 days, starting at 100 mg on day 1, 200 mg on day 2, 300 mg on day 3, and 400 mg from day 4 onward; there is no benefit in reducing the dose, rather a period should be allowed for marrow recovery.

Good-risk patients with good performance status, which comprise only approximately 10% of all elderly AML population, should be candidates for aggressive therapy as offered to the young patients. Of greater significance, development of novel drugs targeting various pathways responsible for leukemogenesis, such as FLT-3, IDH1/2, BCL-2, and immune checkpoints, have opened up the field for treatment of elderly patients; these agents are better tolerated; hence, outpatient care is feasible.^{51,53,58-63}

Maintenance Therapy

Studies have failed to show benefit of maintenance therapy in the form of chemotherapy, hypomethylating agents or biologicals, with or without a transplantation.⁶⁴⁻⁶⁶ However, investigators believe that research needs to be pursued in this area.⁶⁷ Till date, maintenance using midostaurin, the FLT-3 inhibitor has shown survival benefit in a subset in the RATIFY trial.^{49,50} Similarly, addition of dasatinib to chemotherapy for CBF AML in CALGB 10801 study has shown encouraging 3-year DFS and OS.⁶⁸ Of course, patients who have responded to epigenetic therapy or novel oral chemotherapy

drug, continue to receive treatment for a long period, a few for indefinite time.

The Indian Scenario

While managing a difficult disease that involves intensive therapy, team work and availability of resources in a low- and middle-income country (LMIC), the perineal issue of offering the best available therapy comes up, AML being one of the most difficult illnesses. As a result, there is dearth of publications, although many centers across the country can now offer standard of care. Nonetheless, the stark reality is that only small fraction of patients receive such therapy. While searching the PubMed for AML in India, there were 500+ articles, most on diagnosis and case reports.

Published reports discuss challenges of treating AML patients; however, the outcomes appear to be comparable with the international studies.⁶⁹⁻⁷³ A 2-year prospective study done at Christian Medical College, Vellore, in 380 newly diagnosed cases (excluding APL) revealed that median age was younger (40 years) and compared with the western world; only 29% of patients could receive standard of care.⁶⁹ Induction mortality was high (24.7%), occurred due to MDR gram-negative bacilli (44.5%) and fungal infections (44.5%). Median survival varied according to the age. The same group published encouraging results in the area of allogeneic stem cell transplantation.⁷⁰ A prospective multicentric study looked at invasive fungal infections following chemotherapy for acute myeloid leukemia.⁷¹ A couple of studies from North India (All India Institute of Medical Sciences [AIIMS]) and South India ([WIA] Adyar Cancer Institute) revealed issues in a real-world scenario.^{72,73}

Our data on selected patients ($n = 166$) using standard 3 + 7 regimen, followed by two cycles of high-dose cytarabine (15–18 G/m²) and four more cycles of lower dose outpatient daunorubicin and cytarabine showed (CR) Complete Response in 70%, early mortality in 16%, and 3-year relapse-free survival and EFS in 34 and 22%, respectively.⁷⁴

Some physicians have incorporated metronomic chemotherapy in the supportive care and have shown improved EFS and long-term survival in a small fraction of patients.^{75,76} These are phase-II trials in a selective cohort, not intent to treat; therefore, a meaningful scientific conclusion is hazardous. However, if we look beyond pure science, should we not offer such treatment to as many as possible for the ones who cannot afford intensive therapy? To be honest, even the best academic centers in the country do not fail to mention an oral agent like mercaptopurine (6-MP) along with supportive care in the discharge card. Hence, I will not be the jury here; I appreciate efforts of colleagues who are involved in acute leukemia care in very trying environments.

Resistance, Relapse, and Management

Treatment related mortality (TRM) is consistently coming down due to improving supportive care.²⁸ As a result, it is primary resistance, the incidence varying 10 to 40% depending on risk factors.²⁸ The long-term outcome in primary resistance cases is dismal, although some can be salvaged with an allogeneic SCT.⁷⁷⁻⁷⁹ Prognosis depends on time of relapse;

those who relapse with first 1 year have poor prognosis, as opposed to late relapses. Attempts to achieve a second remission with another chemotherapy regimen meets with varying success, usually less than 50% and remission duration is short. Some studies have shown that a favorable outcome could be possible if an allogeneic SCT could be done in early relapse cases. Clearly, newer approaches are needed for relapsed AML. Clinical trials using novel drugs, Chimeric Antigen Receptor (CAR) T-cell therapies⁸⁰ are to be explored whenever possible. I spend a sufficient time with patients and families explaining the situations.

More exciting is the development of numerous novel agents that have therapeutic targets. These agents have made it possible to treat relapsed cases, as well as elderly patients as a first-line therapy. ▶ **Table 3** shows a summary of these agents.

Conclusion

Our understanding of biology of AML has improved significantly. It remains a work in progress and much more remains to be understood, especially about the leukemia stem cells. Probably there lies the Achilles heel(s), emphasizing the need for development of more effective compounds. Current knowledge has helped to cure most of APL cases, given its unique biology of single molecular abnormality in more than 90% cases; exemplified by the Chronic Myeloid Leukemia (CML) model as well. However, cooperation of multiple mutations, some working as drivers of pathogenesis, makes treatment of all other types of AML hugely challenging. Hence, allogeneic transplants as a strategy to reduce relapse, continue to play an integral part of management for relapsed standard-, intermediate-, and poor-risk cases. Older AML patients who are not candidates for aggressive chemotherapy and/or allogeneic transplants, can now look for friendlier treatment approaches with tolerable therapy. Nevertheless, a cure still remains elusive for most of these people. A sober reminder, amidst all this excitement, survival improvement in younger patients remains modest; perhaps integration of novel biological molecules to chemotherapy agents will make an impact. We remain hopeful as the pace of progress in health science is painfully slow but the journey never stops.

Conflict of Interest

None declared.

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