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Review Article

Strategizing the Treatment Approach to Acute Myeloid Leukemia

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ABSTRACT

For decades acute myeloid leukemia, the primary acute leukemia affecting adults, had limited treatment options. Since 2017, we have seen discovery and development in cytogenetic and molecular classification of acute myeloid leukemia, improved understanding of cell signaling pathways, and development of new treatment for acute myeloid leukemia. These new treatments include novel combinations of agents and therapy targeting molecular alterations improving rates of remission and overall survival. Treatment discovery provides therapeutic opportunity to older patients and populations previously excluded from intense induction chemotherapy. In this review, we discuss the timing of first therapy, non-intense treatment regimens achieving remission, and new targets for directed therapy. We reference key clinical trials to expand our discussion of newly approved agents for acute myeloid leukemia. In this review, we highlight the discovery of treatment strategies to improve patient outcomes and ongoing research in leukemia.

Introduction

Despite extensive efforts to understand the biology and mechanisms of leukemogenesis, the backbone of treatment for acute myeloid leukemia (AML) had not changed since the 1970s, since the introduction of cytarabine and anthracycline-based intensive induction chemotherapy (often referred to as "7+3"). Advances in survival have been largely driven by improved risk-stratification, management of disease and treatment-related complications and treating eligible high-risk patients with stem cell transplant [1, 2]. Much has changed in the approach and treatment of AML in the past 3-4 years. AML is an aggressive malignancy resulting from driving molecular mutations and chromosomal alterations [3]. Risk stratification takes into account cytogenetic (karyotype) and molecular categories of prognosis, usually defined as good, intermediate or poor risk [1].

Since the median age at diagnosis is 68, many patients are not sufficiently fit to receive intensive induction chemotherapy [4]. While lower intensity options, such as hypomethylating agents (HMA) and low dose cytarabine (LDAC), may offer some benefit, there remains a large unmet need for many patients for longer disease-free and overall survival. Between 2017 and 2020, the Food and Drug Administration (FDA) approved at least ten new therapeutic agents or combinations for the treatment of AML. These agents utilize unique molecular or cell cycle signaling targets and provide treatment options to patients who historically had a limited therapeutic profile. These new agents show the potential to reach rates of remission comparable to intense induction chemotherapy. Updated methods for cytogenetic and molecular classification of AML have in part facilitated a deeper understanding of the underlying mechanisms of AML, including driver mutations and therapeutic resistance while permitting treatment discovery. We present a summary of these agents and their utilization to strategize treatment of AML.

Diagnosis and Time to Treatment

AML was historically considered a medical emergency due to its acuity and rapid progression. The treatment approach included immediate therapy to achieve optimal outcomes. This concept was supported by research demonstrating shorter survival in patients age ≤ 60 years in whom treatment was delayed by greater than 5 days [5]. With advances in cytogenetic and molecular tests as well as advances in therapeutic options, need for immediate treatment is now challenged. The premise of a treatment regimen best tailored to patient disease characteristics provides optimal outcomes. This involves delaying initiation of therapy while waiting for bone marrow aspirate cytogenetic and molecular results.

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A large retrospective analysis of 2263 patients showed that time to treatment did not significantly affect disease remission or survival [6]. The main complications contributing to early mortality after diagnosis are neutropenic infections, bleeding complications and leukostasis, with a median survival of 17 weeks if untreated [6, 7]. Improvements in management have decreased mortality related to these complications allowing for an increase in time from diagnosis to treatment. Improved understanding of microorganisms causing neutropenic infections and direct antibiotic therapy help decrease mortality [8]. Supportive care with transfusions helps prevent complications of anemia and thrombocytopenia [9]. Hydroxyurea prevents complications of hyperleukocytosis, while the utility of leukapheresis is questionable [10, 11]. Better understanding of how to manage disseminated intravascular coagulation and tumor lysis syndrome has also improved outcomes [12, 13]. By preventing mortality related to these conditions, physicians can delay initiation of treatment while waiting for results that guide therapeutic options without sacrificing disease remission or overall survival (OS). As well, patient comorbidities can be appropriately assessed and medically optimized during this time period preparing patients for intense or targeted therapy. All patients should also be offered palliative care at diagnosis for symptom management, advanced care planning, and discussion of goals of care [14].

With AML being a complex and dynamic disease, delay in treatment is worth the wait. Cytogenetic and molecular alterations are excellent prognostic markers for response to treatment and relapse risk. These alterations allow for early disease classification and planning the framework of treatment. The European Leukemia Net is the most referenced cytogenetic and molecular risk classification system, continually refining prognosis as targets are discovered [1]. Favourable classification suggests patient response to intense induction chemotherapy, while adverse classification suggests current regimens would not provide any response and instead, clinical trials should be considered. AML classification gives physicians an idea of whether early donor search and allogeneic stem cell transplant are needed. Classification also allows for the use of novel therapies targeting specific cytogenetic and molecular alterations. Prognostic markers such as age and performance status allow both physicians and patients to evaluate the best path forward, creating an informed and shared decision.

New Role of Intense vs. Non-Intense Induction

Complete remission (CR) remains the cornerstone of management of newly diagnosed AML [15]. The initial approach to treatment is to evaluate whether a patient is a candidate for intense induction chemotherapy. Age ≥ 65 is often used to determine whether a patient will tolerate intense chemotherapy and is a predictor of treatment-related mortality [1]. There are multiple patient and disease-related factors that determine a patient's candidacy for intense chemotherapy. These include performance status, presence of comorbid conditions, higher WBC, de novo AML vs. secondary AML and cytogenetic or molecular risk classification [15]. Age should not be used alone [1]. Historically, the prognosis of elderly patients unable to receive intense chemotherapy has been poor. However, recent studies with lower intensity regimens, including HMA and venetoclax combinations show favourable outcomes in these patient populations [15, 16].

For patients ≤ 65 years with newly diagnosed AML deemed fit for intense chemotherapy, the standard of care for induction therapy is the "7=3" regimen of 3 days of an anthracycline (daunorubicin or idarubicin) and 7 days of standard dose cytarabine. This is associated with a 60-80% CR rate in younger patients and 40-60% in older patients [1]. Intense chemotherapy requires prolonged hospitalization associated with myelosuppression and increased risk of infection and hemorrhage. This may translate into early treatment related mortality [15]. A new delivery method for "7+3", CPX-351 or liposomal cytarabine and daunorubicin, was studied in a randomized phase III trial, including patients age 60-75 years with untreated AML and a history of secondary AML or antecedent myelodysplasia. Patients were randomized to receive CPX-351 or 7+3. CPX-351 was associated with better OS and complete remission and/or complete remission with incomplete hematologic recovery (CR/CRi) rates [17]. It is worth noting the control arm in the trial used a lower dose of cytarabine (100 mg/m^2) and daunorubicin (60 mg/m^2). One advantage of CPX-351 is the ability to administer in the outpatient setting in an experienced cancer center.

Patients who are ineligible to receive intense chemotherapy due to age, comorbidities, poor performance status, or adverse cytogenetic or molecular alterations are candidates for lower intensity therapies. Options include HMAs decitabine, and azacitidine, LDAC or HMA or LDAC in combination with venetoclax or LDAC in combination with glasdegib. Of these lower intensity options, HMA combination with venetoclax is a preferred combination [2]. BCL-2 is an antiapoptotic protein overexpressed in AML cells. Venetoclax is an oral BCL-2 inhibitor approved in combination with either HMA or LDAC for the first line treatment of AML [18]. A multicenter phase Ib study of venetoclax in combination with either decitabine or venetoclax revealed a CR/CRi rate of 73% with venetoclax 400 mg daily [16]. A phase II trial of venetoclax 600 mg daily in combination with LDAC showed a CR/CRi of 54%. Median OS was 10.1 months. The main adverse events were febrile neutropenia (42%) and thrombocytopenia (38%) [19].

In the double-blind, randomized phase III VIALE-A trial, patients ineligible for intense chemotherapy received either azacitidine and venetoclax or azacitidine alone. OS was significantly higher in the combination arm (14.7 months) than the control arm (9.6 months). The CR/CRi rate for combination therapy was 66.4% vs. 28.3% in the control arm. Responses with venetoclax are rapid with a median time to first response of 1 month for combination and 2.6 months in the control arm. Improvement in survival was noted in many subgroups, including primary and secondary AML, intermediate cytogenetic and molecular risk and IDH1 or IDH2 mutations. The main grade 3 or higher adverse events in the combination arm were thrombocytopenia (45%), neutropenia (42%), and febrile neutropenia (42%). GI side effects of any grade were also common, including nausea, constipation, diarrhea, and vomiting [20].

Glasdegib, a hedgehog pathway inhibitor, was studied in combination with LDAC vs. LDAC alone in a randomized phase II trial in patients with AML or high-risk MDS who were ineligible for intense chemotherapy. Median OS was 8.8 months in the combination arm and 4.9 months in the LDAC arm. CR rate was also higher in the combination arm (17%) than the LDAC arm (2.3%). Grade 3/4 adverse events included pneumonia (16%) and fatigue (14%) [21]. Patients intolerant to

HMA or combination therapies should be screened for treatment with targeted agents.

Approaching P53 Disease

TP53 mutation occurs in 10-15% of AML cases and is associated with an extremely poor response to intense induction chemotherapy. 70-80% are missense mutations and tend to involve the DNA binding domain. Classically OS for TP53 mutated AML patients is short at 5-9 months [22]. Ten-day cycles of decitabine resulted in responses in patients with TP53 mutations [23]. Even five-day schedules of decitabine led to response rates of 62%. However, decitabine does not induce deep and durable remissions, so additional combination or consolidation therapy is necessary.

APR-246 (eprenetapopt) in combination with azacitidine was approved as a breakthrough therapy for MDS with TP53 mutation. This is a small molecule drug that reactivates mutant and inactivated p53, which reactivates pro-apoptotic and cell cycle arrest function in cancer cells. APR-246, in combination with azacitidine, was studied in patients with TP-53 mutant MDS and AML. The median age of patients enrolled in the study was 74; 19 patients had AML, and 34 patients had MDS. The overall response rate (ORR) was 76%. For AML patients with low blast count ORR was 78%, including 33% CR. The median OS for all patients was 12.1 months. 51% of patients who had at least received three cycles of treatment achieved mutant TP53 negativity by next-generation sequencing [24]. A phase III trial assessing combination of azacitidine and TP53 is underway. There is also a phase I study (NCT04214860), studying the combination of APR-246 plus azacitidine and venetoclax in TP53 mutated myeloid malignancies.

Magrolimab is a monoclonal antibody that targets CD47, a macrophage checkpoint inhibitor designed to interfere with recognition of CD47 by the SIRPa (signal regulatory protein alpha) receptor on macrophages. This mechanism helps to block a “don’t eat me signal” on the AML cell surface [25]. Azacitidine is synergistic with magrolimab in eliminating leukemic stem cells; so the combination approach was studied in a Phase Ib trial. Sixty-eight patients were treated with magrolimab and azacitidine at the time of data cut-off; this included 29 patients with previously untreated AML. Common treatment-related adverse events (AE) included anemia (38%), fatigue (21%), neutropenia (19%), thrombocytopenia (18%), and infusion reaction (16%); only one patient discontinued therapy due to treatment-related adverse event. 56% of patients with AML became red blood cell transfusion independent with therapy. No immune-related adverse events were noted on magrolimab. For AML patients, 64% achieved an objective response. In TP53 mutated AML, 75% of patients achieved a CR/CRi [26]. The median duration of response and median OS were not reached in MDS, AML or TP53 mutated AML, with a median follow-up of 5.8 months, 9.4 months, and 8.8 months respectively.

Targeted Therapy

I Gemtuzumab Ozogamicin (GO)

Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody conjugated with cytotoxic agent calicheamicin. It’s the first FDA approved antibody-drug conjugate for AML. Initial approval was for patients age ≥ 60 in the setting of first relapse [27]. About 30% of patients who received GO obtained remission [27, 28]. GO was removed as therapy in 2010 after SWOG 0106 showed the lack of benefit in CR, DFS or OS in the induction and post-consolidation treatment [29]. GO gained new approval in 2017 after several studies including, MRC AML15 and meta-analysis of NCRI AML16, ALFA 0701, GOELAMS AML2006 IR, SWOG 0106, and MRC AML15 showed benefit in combination with intense induction chemotherapy. The meta-analysis of over 3000 patients showed improvement in OS at 5 years and reduced risk of relapse. It also found GO in induction combination was most beneficial in patients with favourable-risk cytogenetics [30, 31]. For patients who are intense induction candidates, the standard of care for CD33+ disease with favourable or intermediate-risk cytogenetics includes GO with induction chemotherapy [2]. For patients who are not intense induction candidates, single-agent GO was shown to have acceptable OS and CR compared to standard of care [32]. There are ongoing trials for GO, including combination therapy with venetoclax (NCT04070768), CPX-351 (NCT03904251), or talazoparib (NCT04207190).

II FMS-Like Tyrosine Kinase 3 (FLT3)

FMS-like tyrosine kinase 3 (FLT3) is a class III receptor tyrosine kinase. FLT3 plays an integral role in stem cell hematopoiesis by regulating proliferation and apoptosis. The two most common FLT3 mutations are tyrosine kinase domain (TKD) and internal tandem duplication (ITD). FLT mutations are the most common molecular mutations in AML; ITD mutations found in 35% and TKD mutation in 10% of patients [33]. Since discovery FLT3, several medications have been developed and approved in both induction and relapsed disease settings. Midostaurin was first shown to decrease peripheral and bone marrow blast percentage significantly in a phase II study [34]. CALGB 10603 phase III study showed in patients 18-59 years of age, with newly diagnosed FLT3 mutated AML addition of midostaurin to induction chemotherapy, consolidation and maintenance increased OS and event-free survival (EFS) when compared to placebo [34, 35]. The median OS in the midostaurin group was 74.7 months compared to 25.6 months in the placebo group. There were no differences in CR noted between the two groups [35].

At this time, midostaurin is the only FDA approved FLT3 inhibitor used in the induction and post-induction consolidation setting. There are many ongoing trials evaluating second generation FLT3 targeted medications, including a phase II study comparing midostaurin versus gilteritinib when combined induction and consolidation chemotherapy in newly diagnosed patients (NCT03836209) and phase III study comparing standard induction chemotherapy to CPX-351 with gilteritinib (NCT04293562). Studies are comparing crenolanib versus midostaurin after induction chemotherapy and combination of GO, midostaurin and induction chemotherapy (NCT03258931, NCT03900949). Quizartinib, a second generation FLT3 inhibitor, is being studied in combination with induction chemotherapy and HMAs (NCT04047641, NCT03661307). There are also trials looking at gilteritinib in combination with HMA in patients not eligible for intense induction chemotherapy (NCT02752035).

There is only one FLT3 inhibitor approved in the relapsed/refractory (R/R) setting. Initial phase I and II testing with gilteritinib showed an increase in ORR with acceptable tolerability [36]. In the phase III ADMIRAL study, gilteritinib significantly increased OS compared to conventional salvage chemotherapy (9.3 months versus 5.6 months) [37]. It also improved EFS (2.8 months compared to 0.7 months) and improved CR rates (34% to 15.3%) [37]. This study led to FDA approval in late 2018 for the use of gilteritinib in the R/R setting. Quizartinib, studied in the QuANTUM-R phase III trial in the R/R setting showed significant improvement in OS, though it did not gain FDA approval in 2019 due to concerns over trial design [38].

III Isocitrate Dehydrogenase (IDH1/2)

Isocitrate dehydrogenase is an enzyme involved in the Krebs cycle converting isocitrate to alpha-ketoglutarate. Mutation in this enzyme leads to the accumulation of R-2-HG, an oncometabolite, which promotes leukemogenesis [33, 39]. Currently, there are no IDH inhibitors approved in combination with intense induction chemotherapy. However, IDH inhibitors are approved with low-intensity treatment. Ivosidenib is an IDH1 inhibitor approved for the first line treatment in newly diagnosed AML in patients older than 75 years or otherwise not eligible for intense induction chemotherapy [40]. Study AG120-C-001 was a phase I study that showed ORR of 58.8% and CR/CRi rate of 41.2% [40]. Enasidenib, an IDH2 inhibitor, does not have FDA approval in the newly diagnosed setting, though NCCN guidelines support its use as monotherapy after sub-study data within the Beat AML Master trial [2, 41] This sub-study showed a CR/Cri in 43% of patients, though the sample size was small (n=23) [41].

Venetoclax is an indirect IDH inhibitor, and recent publications show efficacy in IDH mutated AML [16]. Combination of venetoclax with HMA therapy showed a median survival of 24.4 months and a CR+CRi of 71% [16]. The data behind the utility of IDH inhibitors is ever changing, and there are many ongoing clinical trials. HOVON150AML is combining either enasidenib or ivosidenib with induction and maintenance chemotherapy (NCT03839771). Ivosidenib gained approval in July 2018 for use as monotherapy in R/R AML after data showed a CR rate of 21.6% with a median response duration of 9.3 months, ORR of 41.6%, and median response time of 6.5 months [42]. Enasidenib was approved in August of 2017 in R/R AML after the phase I/II Study AG221-C-001 showed 23% of patients obtained CR/CRi with a median response duration of 8.2 months. The study also showed an improvement in transfusion requirements and acceptable median time to response of 1.9 months [43].

IV Maintenance Therapy

While CR rates are 40-55% after intense induction chemotherapy, median DFS is only 6-13 months. Significant interest in maintenance regimens exists after intense induction chemotherapy or stem cell transplant to decrease rates of disease relapse. A phase II study with decitabine maintenance in younger patients with AML in first CR did not show better DFS compared with historical controls [44]. Until the QUAZAR Phase III trial, there was no known maintenance therapy that significantly improved OS. CC-486 (oral azacitidine) is an oral HMA hypothesized to be effective as post-remission maintenance through continuous exposure to the drug.

Prior to the advent of oral azacitidine, HOVON97 was a Phase III trial conducted in patients ≥ 60 years with AML or MDS, in remission after at least two cycles of intense chemotherapy. Patients were randomized to either observation or azacitidine maintenance. The 12-month DFS was 64% for the azacitidine group and 42% for the control group; these differences held for poor-risk cytogenetic groups. OS did not significantly differ between groups (84% vs. 70% at 12 months, p=0.69), even when censoring for stem cell transplant [45]. Criticisms for HOVON97 trial were inadequate power to detect differences in OS and duration of azacitidine therapy was limited to 12 cycles.

QUAZAR AML-001 was a phase III international, randomized, double blind, placebo-controlled study evaluating maintenance treatment following intense induction chemotherapy in patients ≥ 55 years who were not stem cell transplant candidates and achieved first CR. These patients had de novo (91%) or secondary AML, intermediate (86%) or poor-risk cytogenetics (14%), and ECOG PS of 3 or lower. Within four months of achieving CR, patients were randomized to receive CC-486 300 mg or placebo. Treatment continued indefinitely until the presence of > 15% blasts, unacceptable toxicity or stem cell transplant. At median follow-up of 41.2 months, CC-486 had a significantly higher median OS at 24.7 months compared to 14.8 months in a placebo group (p=0.0009). Median RFS was also higher in the CC-486 arm at 10.2 months compared to 4.8 months in placebo arm. (p=0.0001). OS and RFS benefits were noted regardless of baseline cytogenetic risk, number of prior consolidation cycles received, and CR/CRi status. CC-486 did not adversely affect the health-related quality of life compared to placebo [46]. CC-486 is the first approved maintenance therapy for AML after intense chemotherapy.

Conclusion

As we further understand the mechanisms of cell signaling and biology of cytogenetic and molecular markers that drive AML and promote leukemogenesis, additional targeted therapies and combinations of therapy will be discovered. The treatment strategy of AML is changing for the first time since the 1970s. These discoveries include the timing and intensity of therapy required to achieve remission. Patients now have treatment options in addition to, instead of, or following intense chemotherapy that improves OS. Targeted treatment now changes prognostic models as mutations of poor prognosis can be subdued with therapy. Outcomes of ongoing clinical trials are intriguing for the potential to achieve durable remission in AML without the use of intense chemotherapy and preserving patient functional status and quality of life.

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