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REVIEW OPEN ACCESS

First-Line Treatments for Patients with Acute Myeloid Leukemia: A Literature Review

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Abstract

Introduction: Acute myeloid leukemia (AML) is a type of cancer with a very low five-year survival rate (19%), which motivates research into numerous treatment options to improve survivability and remission rates. Here, some common treatments will be briefly discussed to provide a brief foray into AML treatment. As a very general statement, chemotherapy is the most common treatment for this condition. This is a general statement because different malignancies and multi-morbidities can heavily modify treatment options. These options each have their merits and critical differences, which should be discussed. Some significant medications are all-trans retinoic acid, interleukin II, lenalidomide, and colony-stimulating factors. Some targeted therapies would focus on FMS-like tyrosine kinase 3 inhibitors, isocitrate dehydrogenase 1 and 2 inhibitors, Gemtuzumab ozogamicin, B-cell leukemia/lymphoma-2 inhibitors, and hedgehog pathway inhibitors.

Methods: A literature review was performed to summarize all available research on the different categories and types of therapeutic options for AML. Patients at all stages of AML were considered, including newly diagnosed patients and those with relapsed or drug-resistant disease.

Results: Various treatments had their efficacy listed with information gained from various types of studies. The main "efficacy" focuses were remission rates and survivability over varied time periods (i.e., short-term versus long-term).

Discussion: This literature review provided insight into the current treatments of AML and noted that a direct comparison between every treatment type is not possible. Furthermore, several therapies are undergoing clinical trials in combination with chemotherapy, making it difficult to isolate their independent effects.

Conclusion: Treatment options for AML may be affected by the AML subtype, various prognostic factors, cytogenetics, and the patient's medical history. This review aids in accessibly summarizing essential information about AML and different therapeutic options including drug targets as well as identifying future areas of research.

Keywords: acute myeloid leukemia; chemotherapy; all-trans retinoic acid; lenalidomide; colony-stimulating factors; targeted drug therapy; FLT3 inhibitors; IDH inhibitors; BCL-2 inhibitors; HP inhibitors

Introduction

Acute myeloid leukemia (AML) is a heterogeneous group of clonal malignant myeloid disorders characterized by the overproduction of immature myeloblasts within lymphoblasts found in the bone marrow [1]. Circulating myeloblasts are vulnerable to lysis, cytopenia, and hematopoietic failure due to their immaturity [1]. Furthermore, immature myeloblasts lead to fatigue and weakness symptoms, hemorrhage, infection, and fever. In addition, this cancer can rapidly spread to the blood, after which it can continue to other body parts such as the lymph nodes, liver, central nervous system, and testicles [2].

In Canada, the annual incidence of AML from 1992 to 2010 is approximately 30.61 per 1,000,000 [3], increasing with age. The five-year relative survival rate is 21% [4]. Considering the overall lethality of this illness, it is imperative that better treatments be found to improve survivability. The estimates for AML in 2020 in America predicted that it would cause about 11,180 deaths (mainly in adults) [5]. As this is just in the United States, the global number would most likely be much higher, especially because 31% of adult leukemias are AML [6].

Treatment options for the illness are impacted by subtype, morphology, and cytogenetics [7], so every patient is different. AML is classified in different subtypes, which vary in symptoms and how they may respond to treatment, but they will share traits that are define AML (e.g. decreased blood cell levels). Myeloid is the most common subtype with some others being monoblastic and monoblastic. Acute promyelocytic leukemia is a specific subtype where cancer cells only mature until the progranulocyte stage, which is very different than the other subtypes. These differences affect treatment efficacies and need to be kept in mind. AML morphology is classified by the shape of the cancer cells. They are categorized based on the immature white blood cell that they most resemble. For instance, myeloid leukemia

cells look like immature neutrophils. Sometimes, AML can appear with red blood cell or platelet producers, being referred to as erythroid and megakaryocytic, respectively. In AML, cytogenetic changes are classified by how difficult they will be to treat (i.e. favourable, intermediate, unfavourable). These changes can inform patient treatment as they can change the behaviours and resistances of the cancer cells [8]. Chemotherapy is the most common treatment for AML [7]. Intensive treatment, such as high-dose therapy and stem cell transplantation, could improve survival among these patients but often is not possible because of age and co-morbidities [9].

This article will discuss certain treatments, medications, and targets. These include chemotherapy (induction therapy, stem cell transplants), stem cell transplants, surgery, all-trans retinoic acid (ATRA), interleukin II, lenalidomide, colony-stimulating factors (CSF), FMS-like tyrosine kinase 3 (FLT3) inhibitors, isocitrate dehydrogenase (IDH) and IDH2 inhibitors, Gemtuzumab ozogamicin, B-cell leukemia/lymphoma-2 (BCL-2) inhibitors, and hedgehog pathway (HP) inhibitors.

Therapeutic Options

Chemotherapy

This is the process of using various anti-cancer drugs to destroy/contain cancerous cells. The drugs can be administered via IV, sub-dermally, or into the cerebrospinal fluid. This form of treatment can spread around the body, making it effective against leukemias. It is the primary treatment for AML patients, although those with multi-morbidities may not be able to endure the intense treatment. Its value is due to the fact that it is a systemic treatment that can target cancer cells that have metastasized. Induction or first-line therapy aims to reduce the size of the tumour to make it more controllable for radiation therapy [10]. Stem cell transplants can also be added to help the body recover post-treatment [11]. This is especially important in cases where very high doses of chemotherapeutic drugs are used. The gold standard treatment follows the treatment regimen consisting of the combination of cytarabine (Cytosar-U) and an anthracycline drug [12], such as daunorubicin or idarubicin [13].

Surgery

This is an invasive process of removing cancerous tissue as its primary objective. Removing a tumour may not be feasible as leukemias can spread throughout both the blood and bone marrow. Prior to chemotherapy, surgery is performed to insert a central venous catheter into a large vein in the chest used to give intravenous drugs and reduce additional IV's during treatment. Allogenic hematopoietic stem cell transplantation (allo-HSCT) is a first-line treatment for (very/)-poor-risk AML patients [14], and it is a major use of surgical techniques for AML treatment as tumour excision is not a practical option [15].

All-Trans Retinoic Acid

This was initially used to treat acute promyelocytic leukemia (APL) and has been shown to inhibit Bcl-2 in AML cells, which is significant as ~84% of AML patients overexpressed BCL-2 survival at diagnosis [16]. It works by increasing retinoic acid induced gene-1 protein levels, increasing the production of Type 1 interferons. These type 1 interferons can then act to combat tumor cells in the body [17]. Furthermore, it has the added effect of promoting apoptosis. A recent primary study showed that ATRA maintenance therapy could be a feasible and effective choice for myelosuppression and hepatoxicity as the 5-year relapse-free survival rate was higher than ATRA monotherapy [18].

Lenalidomide

The T-cell proliferative effects of lenalidomide are 50 to 2000 times higher than that of thalidomide, and the effectiveness of T-cell interleukin (IL-2) and interferon-gamma (IFNγ) production augmentation is 300 to more than 1200 times higher [19]. This can slow/stop cancer cell growth. Also, it may reduce a patient's need for blood transfusions, reducing the overall resource cost of treatment. Likewise, lenalidomide is more effective in decreasing the production of tumour necrosis factor alpha [20], IL-1β, IL-6, and IL-12 than thalidomide [21].

Colony-Stimulating Factors

These are involved in white blood cell production, protecting the body from infection, which can be especially dangerous for an AML patient. A 2014 clinical trial strongly argues in favour of incorporation of CSF in frontline regimens for AML [22].

FLT3 Inhibitors

The FLT3 gene is part of the class III receptor tyrosine kinase family of enzymes which catalyzes the phosphorylation of tyrosine residues in target proteins [23]. Several genomic sequencing studies have indicated FLT3 as the most commonly mutated gene appearing in 25 – 30% of adult and pediatric AML patients [24]. Therefore, targeting FLT3 signalling via small-molecule inhibitors is essential as mutations can cause internal tandem duplication of the juxta membrane domain (25% prevalence) and point mutations in the tyrosine kinase domain. These can lead to patients facing higher rates of relapse and lower cure rates [25].

IDH1 Inhibitors

Isocitrate dehydrogenase (IDH) converts isocitrate to α-ketoglutarate within the mitochondria and mitochondrial matrix [26]. Recurring IDH1 mutations appear in ~20% of AML patients and results in neomorphic enzyme activity, increasing the accumulation of R-2-hydroxyglutarate to abnormal levels, promoting leukemogenesis [26]. In addition, AML patients with IDH1 mutations have inferior

overall survival and complete remission rate compared to patients without the mutations [27]. Thus, individualized treatment for IDH mutations is an important option for patients.

IDH2 Inhibitors

IDH2 is a different isoform of IDH and is located in the cytoplasm with a similar function to IDH1. Mutations in IDH2 appear in ~12% of AML patients and results in the hypermethylation of deoxyribonucleic acid and histone, subsequently halting cell differentiation [26]. Inhibitors selectively target IDH2 signalling and reverse the abnormal methylation of histones and DNA, leading to the differentiation of AML cells [28].

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody-related to calicheamicin [29]. After internalization and intracellular release, this highly toxic drug is targeted to CD33-expressing leukemic cells (>85% in patients) in mutations present (~30% of patients) in the nucleophosmin 1 (NPM1) gene that codes for the protein called nucleophosmin [29]. CD33 is a transmembrane surface receptor that is a common target for AML as is it is commonly expressed on hematopoietic cells and myeloblasts. GO enhances the anti-leukemic efficacy of chemotherapy and promotes cleavage in the lysosome, leading to apoptosis [30].

BCL-2 Inhibitors

The B-cell leukemia-2 family proteins are a critical part of the intrinsic cellular mechanisms of apoptosis [31]. BCL-2 inhibition is an established approach to therapy as AML cells express a high level of BCL-2 protein [32]. Inhibiting BCL-2 mutations allows the intrinsic apoptotic pathway to proceed, mutations that would otherwise affect the apoptotic pathway, increasing cancer cell survival [32]. Mutation of BCL-2 is estimated to have an incidence rate of ~20% in myeloblasts [33].

HP Inhibitors

The Hedgehog signalling pathway plays an integral role in embryogenic development, stem cell maintenance, and cellular proliferation [34]. Mutations causing differential Hedgehog pathway activity can be identified in 50% to 70% of myelogenous leukemia cases [34]. Small molecule inhibitors target the smoothened receptor expressed in CD34+ cells, resulting in apoptosis of AML cells and suppressed leukemic cell proliferation [35].

Methods

A literature review was performed to synthesize and analyze different treatment approaches to AML therapy. Searches were conducted in two databases of scientific literature, namely PubMed and Google Scholar. Abstracts were screened for eligibility by relevance and peer review status. Studies included in this literature review consisted of randomized controlled trials, case reports, and longitudinal studies. No restrictions were applied on gender or patient ethnicity. Individuals at all stages of AML were considered, including newly diagnosed patients and those with relapsed or drug-resistant disease. All approved therapeutic options and treatment routes were considered in the literature review. If patients withdrew from clinical trials or shifted to different treatments due to side effects, clinical data as reported in the study will be considered. Articles were included regardless of language and publication status, and date. Manuscripts of all animal studies were excluded.

Data Extraction

Study information and relevant outcome measures that were collected upon data extraction:

- *Interventions*: setting, dose, intervention, type of additional/comparator treatment, supportive treatment, intensity of regimen, number of cycles, duration of follow-up, cycles of chemotherapy
- *Outcomes*: disease-free survival, overall survival, event-free survival, treatment-related mortality, adverse events, and quality of life

Results

Below are various statistics from the different treatments mentioned in the introduction. This information can demonstrate the efficacy of each treatment.

Chemotherapy

This can be used in combination with many other treatments, which is partially why it may demonstrate a broad range of efficacy. For example, the standard treatment of daunorubicin + cytarabine ('7+3' modality) can lead to complete remission in 60-80% of adults, but most enter relapse later on [36]. A trial on 122 FLT3 patients found a median survival of 4.7 months and 12-month survival of 20% on chemotherapy patients [37]. The major side effects reported in clinical trials include febrile neutropenia, nausea and vomiting, lung infection, and pyrexia [34].

Surgery

As most surgery is rarely used for AML, allo-HSCT treatments will be the focus. A study evaluated the efficacy of allo-HSCT treating 147 out of 622 AML patients with it. The number of induction cycles required to attain the first complete remission were significantly reduced for Allo-HSCT patients. For the treatment group with daunorubicin/cytarabine, n=403 cycles for those without Allo-HSCT and n=130 cycles for Allo-HSCT patients [38]. The side effects of allo-HSCT treatments include lung infection, nausea, and Graft-versus-Host-Disease which is a leading cause of patient mortality.

ATRA

An *In vivo* study using TEX cells to mimic human AML cells found an observed early or late apoptosis in 55% of cells after a 4-day treatment with ATRA + 2d or tranylcypromine (TCP). There also was a small increase in p53-null HL-60 cell apoptosis [39]. Another study found that ATRA + TCP when used in 18 patients who could not undergo intensive treatment, had a response rate of 20% with two complete remissions and one partial response. The median overall survival was 3.3 months [40]. The clinical trial found that the most common adverse events were vertigo (n=7), hypotension (n=4), confusion/dizziness (n=4), and skin reactions (n=4).

Lenalidomide

A study evaluating lenalidomide maintenance in high-risk AML patients found an 18.7-month median remission for patients, concluding that the drug is safe and feasible as a maintenance strategy for high-risk patients who are not candidates for autologous stem cell transplantation (ASCT) [41]. A study found that in older patients (65+) with newly-diagnosed AML, one-year survival was 21% with high-dose lenalidomide, 44% with azacitidine + lenalidomide, and 52% with just azacitidine. This shows that high-dose lenalidomide was not tolerable for most patients, leading to changes in therapy [42]. Generally, lenalidomide is well-tolerated. The above clinical trial reported serious grade >3 adverse events in 13 patients (46%), including skin rash (n=5), thrombocytopenia (n=4), neutropenia (n=4), and fatigue (n=2) [40].

Colony-Stimulating Factors

The overall survival (OS) and relapse-free survival (RFS) probability at 3 years are 78% and 85% [22]. A study using clofarabine + high dose cytarabine + granulocyte CSF priming in relapsed or refractory AML patients found a complete remission of 46% (n=46) [43]. The study reported serious grade >3 adverse events: skin rash (n=5), hepatic transaminases (n=8), pulmonary infection (n=18), and hyperbilirubinemia (n=3) [41].

FLT3 Inhibitors

First-generation multi-kinase inhibitors (sorafenib and midostaurin) exhibit a broad-spectrum of drug targets, whereas second-generation inhibitors (crenolanib and gilteritinib) are characterized as more potent and specific FLT3 inhibition [25]. Therefore, the current standard for first-generation inhibitors is midostaurin in combination with chemotherapy whereas, gilteritinib is currently the primary second-generation inhibitor being tested.

The large-scale phase-3 trial of midostaurin in combination with chemotherapy reported a median OS of 74.7 months and complete remission rate of 58.9% [44]. The advantage of midostaurin in regard to event-free survival was found to be consistent across all subtypes of FLT3 mutations as well as patients had 21.6% lower chance of having an event than placebo. Notably, patients with midostaurin experienced more <3 adverse events: anemia and rash [44].

The phase-3 ADMIRAL study for gilteritinib reported significantly longer OS (9.3 months compared to 5.6 months with salvage chemotherapy [45]. 1-year survival rate was 37.1% and complete remission rate was 34%. The occurrence of grade >3 adverse events was 19.3 events per patient-year and included febrile neutropenia and anemia [45].

IDH1 Inhibitors

Ivosidenib was the first approved IDH1 inhibitor based on the compelling results of a phase 1/2 clinical trial [26]. The trial concluded monotherapy was well tolerated with a consistent safety profile. The complete remission rate was 21.6% with a duration of 93 months. Treatment related grade >3 adverse events occurred in 21% of patients and included leukocytosis and prolonged QT interval [26]. Mutation clearance occurred in 41% of patients and survival at 18 months was 50.1%.

IDH2 Inhibitors

Enasidenib is a selective allosteric inhibitor that exhibits more potent inhibitory effects on IDH2 than IDH1 [28]. The results from a phase 1/2 clinical trial indicated enasidenib monotherapy in AML is efficacious and safe. Overall response rate was 40.3% with average response duration of 5.8 months. 1-year survival among relapsed patients was 9.3 months [28]. Treatment-related grade >3 events occurred in 5% of patients, most commonly hyperbilirubinemia and IDH-inhibitor-associated differentiation syndrome.

Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin has been studied in several settings, both as a single-agent and in combination [46]. It was re-approved by the FDA after the results of a multicenter trial of 1,022 patients who were treated by GO in combination with chemotherapy [47]. It concluded event-free survival was significantly improved for all patients. The duration of first remission was 10 months and 26% of patients achieve complete remission. Treatment-related grade >3 events were similar between all study arms with an average 76% experiencing common events like cytopenia and gastrointestinal toxicities [47].

BCL-2 Inhibitors

The current standard BCL-2 inhibitor for therapy is venetoclax [48]. The Phase 2 trial studied venetoclax as a single-agent for relapsed AML patients [49]. The trial found venetoclax was well tolerated but had limited anti-leukemic activity in relapsed AML, with a leukemia-free survival and OS rates of 2.3 months and 4.7 months, respectively. The complete remission rate with incomplete haematologic recovery rates were 19%, with an additional

19% of patients exhibiting partial bone marrow response [49]. Treatment-related grade >3 events were reported in 85% of patients with febrile neutropenia as the most common.

HP Inhibitors

Glasdegib was the first FDA-approved HP inhibitor and is often paired with low-dose chemotherapy in AML treatment. In one particular study, AML patients who received low-dose chemotherapy with glasdegib had a reduced risk of death by 54%, compared to chemotherapy alone [35]. The Phase 1b trial assessed the novel Hedgehog pathway of Smoothened inhibitor in combination with standard chemotherapy and found it was generally well-tolerated and consistent with prior findings. The median OS was 27.2 months [50]. No dose-limiting toxicities were observed and overall, 31% of patients achieved complete remission. 87% of patients experienced treatment-related grade >3 adverse events with febrile neutropenia and thrombocytopenia being the most common [50].

Discussion

The results section presented data from every treatment type covered in this article, but direct comparison is simply not possible between treatments. AML can be present in varying severity in different patients, who may also have multi-morbidities to consider. Hence, every treatment has its place where it can be useful. Furthermore, many of these treatments are only used in combination, making it very difficult to isolate their effects as independent entities. The reality is that there are many aspects of patient survival and quality of life that a physician must consider when evaluating treatment plans, and there is no silver bullet that can fix every problem that a cancer patient has. The results will be published to elucidate the current treatments of AML and their general descriptions in a format that allows for easy digestion and comparison of information. This article aims to provide an accessible format for essential information about AML as an entry point for academic pursuits into leukemia.

Conclusions

AML is a heterogeneous group of clonal malignant myeloid disorders due to the overproduction of immature myeloblasts within the bone marrow. Treatment options and overall response rates for AML treatment are highly dependent on the subtype, morphology, and cytogenetics. Moreover, the patient's age and overall health must also be considered when discussing treatment options and possible side effects. Thus, individualized treatment is critical to treating the illness effectively. The standard for most types of AML is chemotherapy, along with a targeted selective inhibitor. This may be consequently followed by stem cell transplant. This paper aimed to summarize essential information about AML and different therapeutic options accessibly. However, throughout this literature review, a gold standard therapy is still unclear between the several selective inhibitors. Thus, future research should systematically review all the available primary studies on AML targeted drugs to evaluate and summarize the different categories of targeted inhibitors.

List of Abbreviations Used

ATRA: all-trans retinoic acid
CSF: colony-stimulating factors
FLT3: FMS-like tyrosine kinase 3
IDH: isocitrate dehydrogenase
BCL-2: B-cell leukemia/lymphoma-2
HP: hedgehog pathway
Allo-HSCT: allogenic hematopoietic stem cell transplantation
APL: acute promyelocytic leukemia
GO: *Gemtuzumab ozogamicin*
IL-2/1β/6/12: interleukin
IFNγ: interferon gamma
TCP: tranylcypromine
p53-null HL-60:
ASCT: autologous stem cell transplantation
OS: overall survival
RFS: relapse free survival

Conflicts of Interest

The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent

This study did not require ethics approval or participant consent since it is a literature review and did not involve humans, animals, or tissues in its completion.

Authors' Contributions

HN: Contributed to the research, drafting, and editing of the manuscript from start to finish.
AAGS: Contributed to the research, drafting, and editing of the manuscript from start to finish.

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