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Current advancements and trends in treatments of acute myeloid leukemia

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Abstract

Acute Myeloid Leukemia (AML) is a cancer caused by the production of abnormal myeloid cells, a progenitor stem cell that matures into white blood cells, red blood cells, or platelets. AML is an aggressive cancer that creates a high production of unhealthy blood cells often forcing out healthy cells leading to infection, anemia, and/or bleeding. There are several different subtypes of AML based on the causative mutation including FLT3, c-KIT, and RAS genes. Even with recent advances in medicine and chemotherapies over the last 20 years, the overall 5-year survival rate for AML is low. There are several contributing factors for this low success rate including the fact that AML cannot be treated with a one size fits all approach, because different subtypes require differential treatment. Despite this, many physicians still approach treatment with the same chemotherapies that have been used for decades regardless of the mutations present, the main reasoning being there have been no new drugs approved for AML. The majority of patients diagnosed with AML go into remission after the first round of chemo, however, if the patient then relapses the survival rate drops drastically due to chemotherapy resistance. In this review, the current advancements in treatments for AML and promising prospective treatments to increase remission rates of refractory patients are explored by first surveying standard of care chemotherapy agents and then new drugs, alternative treatments, and combinatorial studies.

Introduction

Acute Myeloid Leukemia is not one disease with a singular cause. There are multiple subtypes that can vary in severity and prognosis. Based on current techniques of molecular genetic testing, there are four genes commonly associated with the development of AML, FLT3, NPM1, CEBPA, and KIT genes [1]. All of these mutations affect transcription of DNA directly or through epigenetic regulation, with most genetic abnormalities originating from chromosomal rearrangements or large genomic deletions [1]. Development of AML is a multistep process that requires at least two genetic abnormalities and can be classified as type I and type II [2]. Type I abnormalities confer a proliferation advantage of hematopoietic cells leading to increased production, while type II abnormalities impair hematopoietic differentiation [2]. Despite the heterogeneity that can exist among AML patients, the first line strategy with the majority is treatment with cytarabine and an anthracycline, termed induction therapy, which is aimed at getting rid of the bulk of cancer cells to put the patient into remission [3]. Given the rate of relapse and refractory disease with AML, it is clear that different subtypes may require differential treatment. However, many physicians still approach treatment with the same chemotherapies that have been used for decades regardless of the mutations present, the main reasoning being there have been no novel drugs approved for AML over the last 4 decades [4]. Thus, a homogenous approach to a heterogenous disease and the low rate of new, effective therapies are both major contributing factors for the unchanged treatment success of AML. There are, however, new treatment strategies including new FLT-3 inhibitors, assessing different drug targets such as anti-apoptotic proteins, use of drug combinations to exploit collateral sensitivity, and the use of new technologies.

First Line Chemotherapeutics to Treat AML

Cytarabine

The anchor drug used in the majority of AML cases is known as cytarabine [5] which has been the main treatment for AML for the last 47 years [6]. Cytarabine is a cytidine analog that is incorporated into the nucleotide salvage pathway through deoxycytidine kinase, leading to breaks in the replicated DNA [5]. This standard drug leads to 70-80% of patients achieving remission, but 80% of those relapse for which there is no standard secondary treatment regimen currently [5]. One of the biggest challenges that doctors face is the development of resistance to cytarabine during relapse. When chemoresistance emerges not only in AML but in many different types of cancer, very often the pathway targeted during initial treatment has been deactivated, rendering the relapsed cells resistant, termed refractory [7]. Specifically, cytarabine resistance comes from the inherent redundancy of nucleotide synthesis pathways in cells; the salvage pathway that cytarabine interferes with in cancer cells is not the only route for cytidine production.

Resistant cells show a loss of deoxycytidine kinase activity, rendering cytarabine ineffective [5] while the cancer cells are able to survive because cytidine can be produced through the de Novo

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synthesis pathway instead. Despite many AML patients experiencing relapse with refractory disease, there is no standard protocol leaving clinicians utilizing trial and error through the arrangement of known chemotherapies or enrolling the patients in emerging clinical trials [8].

FLT3 Inhibitors

FLT3 is a transmembrane type III receptor tyrosine kinase that regulates hematopoiesis through the phosphorylation of downstream proteins and activation of critical oncogenic pathways such as Ras/Raf/MAPK and PI3K/Akt/mTOR [9]. The FLT3-ITD mutation is the most common mutation found in AML patients consisting of about 30% of patients and is linked to the lower success rates with a complete remission rate between 30-40% [10]. The importance of therapy development for FLT3 mutations is high given that the use of FLT3 inhibitors as single agents has had very limited success. In a review done by Fujian Medical University they reviewed the use of multiple FLT3 inhibitors in preclinical and clinical studies including sorafenib, lestaurtinib, sunitinib, tandutinib, quizartinib, midostaurin, gilteritinib, crenolanib, cabozantinib, Sel24-B489, G-749, AMG 925, TTT-3002, and FF-10101 [10]. The current trends found when using these FLT3 inhibitors is a favorable response in AML patients, but a short response duration with a quick development of resistance [10]. These results indicate that alternative methods of treatment should be utilized to improve the success rate of patients with the FLT3 mutation [11]. Alternatively, given that this mutation is the most abundant in patients, new or improved FLT3 inhibitors are needed. New FLT3 inhibitors have begun to be investigated through organic synthesis. One study looked at a newly synthesized FLT3 inhibitor that showed potent inhibitory activity against several FLT3 mutations as well as high FLT3 selectivity over other kinases [12]. The synthesis and development of new FLT3 inhibitors with high potency and selectivity provides potential for new treatments with decreased resistance development. Another possibility is combining FLT3 inhibitors with other chemotherapeutic agents against other targets. In fact, clinical trials utilizing these FLT3 inhibitors show promise when used in combination with each other as well as with other chemotherapeutic agents [10]. Therefore, combining FLT3 inhibitors with other drugs potentially could increase their utility, especially if explored through the lens of collateral sensitivity (see below).

Up and Coming Chemotherapeutic Agents

Kinase Inhibitors

Much of the uncontrolled cell growth and replication found in cancer cells is due to overactive cytoplasmic tyrosine kinases [13]. A University of Pittsburgh study by Weir (2011) found three N-phenylbenzamide kinase inhibitors (TL02-59, TL8-133, and TL8-187) arrested growth in vitro and in vivo AML cells. This was also seen in pediatric AML with Janus tyrosine kinase inhibitors gemcitabine and cabazitaxel in a high throughput screening study to uncover effective chemotherapy options from already available medical compounds, that may or may not have already been categorized as having antileukemic properties [14]. Gemcitabine and cabazitaxel were the two drugs out of the panel of nearly 8000 compounds that demonstrated broad activity across multiple high-risk subtypes [14]. Thus, combinatorial studies utilizing both compounds should be conducted to further investigate their clinical usefulness. However, development of resistance to either of these drugs may arise, as they are both cytidine analogs and operate under the same mechanism of cytarabine. Nonetheless, more studies are necessary to determine if there is an increase or decrease in resistance development with these drugs such as in a long-term, low concentration study.

Venetoclax

B-cell lymphoma 2 (BCL-2) protein is an anti-apoptotic protein and key regulator in the intrinsic apoptotic pathway [15]. Orally active BCL-2 inhibitors such as ABT-199 (Venetoclax) have been clinically useful in the treatment of lymphomas [16], and multiple studies have demonstrated that AML blast survival depends in part on BCL-2 sequestering pro-apoptotic BAX, making it a potential target for treatment [17-21]. In fact, Venetoclax has demonstrated potency as a single agent both ex vivo with patient samples resistant to conventional therapies [19] as well as in patients with relapsed or refractory AML [20]. However, resistance to Venetoclax itself arises, due to upregulation of other anti-apoptotic proteins, and therefore it is used in combination cytarabine or hypomethylating agents, such as azacitidine and decitabine, as a first-line treatment for older AML patients who are ineligible for intensive chemotherapy [22-23]. In fact, favorable results were seen in a Phase 1b study of Venetoclax plus azacitidine or decitabine in the treatment of elderly, naive AML patients [24] and those combinations are currently in Phase 3 [25]. Therefore, Venetoclax has been added to the arsenal for treating AML and its use in combination with other chemotherapeutic agents continues to be explored both clinically. Additional preclinical studies combining Venetoclax with other drugs are also underway. For example, synergy of Venetoclax with CS005, an HDAC inhibitor, was investigated using relapsed/refractory AML samples, which may offer an alternative treatment strategy [26]. Clinical studies to follow up these results are needed, but the utility of BCL-2 inhibitors in treating AML is promising.

Other Advancements and Alternative Treatments

Advancement in detection of cancer cells and their mutations

In the last several years of the past decades there has been exponential changes and developments in both AML research and clinical practice. One of the advancements in determining relapse and treatment success is a more accurate measurement of minimal residual disease (MRD) or the approximation for how many cancerous cells remain after the treatment [4]. This measurement of MRD has been advanced with a multiparameter approach of using both flow cytometry and next-generation sequencing (NGS) [4]. Flow cytometry is a method of quantitative analysis of cells by passing a cell suspension at a high velocity through a laser beam to analyze the light scatter and fluorescence of the cells [27]. NGS refers to genomic sequencing that allows clinicians to analyze the genes of interest that most commonly lead to AML formation [28]. Utilizing both methods has increased the precision and accuracy of MRD levels as a quantitative measurement of the patient's success. Though it is noted that there is a need for continued randomized studies to show convincing evidence of the benefits of therapeutic intervention based on MRD levels [4].

The increased accessibility and use of gene sequencing have allowed clinicians to analyze mutational interactions of patients found with multiple mutations of different types. There has been an associated relationship found between biallelic mutations of the CEBPA gene and improved outcome for patients while this did not appear to be true for monoallelic CEBPA mutations [4]. Continued data on this relationship will allow clinicians to have a better understanding of a patient's potential survival and determine the method of treatment not just based on the patient's current AML condition but also on their potential outcomes based on their genomic mutations. Increasing the detection

of MRD and the advancement of the use of NGS will allow clinicians to develop detailed patient profiles that will allow for the application of personalized medicine that treats the patient based on their specific response to treatments and their risk factors associated with their genetic profile. In fact, very recently the effects of concurrent mutations and the influence of patterns of gene expression on drug sensitivity has been realized [29]. Consequently, either novel therapeutic agents or new combinations have been approved and/or are currently being explored in clinical trials over the past 3 years [30,31].

Understanding collateral sensitivity

Collateral sensitivity is a phenomenon where genetic alterations during treatment with one drug leads to the development of hypersensitivity towards another drug [32,33].

Taking advantage of collateral sensitivity may offer a potential solution to minimize the development of chemoresistance in many types of cancer [33,34] and therefore is an additional avenue for future investigation in the treatment of AML. One study from the University of Utah, using collateral sensitivity of breast cancer cells found that when treating ribociclib resistant breast cancer cells and non-resistant cells with a combination treatments of both Ribociclib and Adavosertib Chemotherapies, there was a synergistic results with antiproliferative effects and decreased selection for resistant cells [35].This approach shows promise in treating chemoresistant, heterogeneous cancers and should be a designated method of research for all cancers. By using a combination of drugs that inhibit different stages of the same cycles, apoptosis can be induced by effectively preventing the resistant cells from producing essential cell survival signals. Many studies have been done to analyze what combination of chemotherapies show promise in treating resistant AML in vitro, but many clinical trials are still in their early stages.

Current research is also investigating the use of collateral sensitivity by combining secondary drugs that interact with the same nucleotide pathways. One study from the Technion-Israel Institute of Technology analyzed two AML cytarabine resistant sublines sensitivity to hydroxyurea and azidothymidine [5]. Hydroxyurea attacks the de novo synthesis of DNA by inhibiting ribonucleotide diphosphate reductase that converts RNA nucleotides into DNA nucleotides while azidothymidine is an AIDS treatment that inhibits thymidylate kinase [5]. The study found high synergistic results in cytarabine resistant sublines and low toxicity in normal tissue indicating potential in hydroxyurea and azidothymidine combinatorial treatments for relapsed patients [5]. This shows promising results for treating AML that becomes refractory to cytarabine. Additional studies on the promise of the synergistic collateral sensitivity on cytarabine resistant patients should be conducted to offer a potentially successful treatment protocol for refractory patients that currently have low success in 5-year survival rates.

CAR T-cell Therapy

Chimeric antigen receptor (CAR) T-cell therapy (CAR T-cell therapy) is a newer method of cancer treatment that utilizes the patient's T-cells and modifies them to bind to commonly expressed antigens of the cancer cells being targeted, allowing the T-cells to bind and kill desired cancer cells [36]. CAR T-cell therapy has seen success in lymphocytic leukemias [37], although there are no currently approved treatment regimens in the treatment of AML. The possibility of successfully utilizing this method of treatment has been discussed, as AML cells express multiple differentiation antigens on the cell membrane that could be used to exploit CAR T-cells [31,38]. The difficulty in utilizing CAR T-cells to attenuate cancerous myeloid cells is that the differentiation antigens being targeted are also expressed in normal myeloid, which could potentially destroy all myeloid cells both healthy and unhealthy [38]. One possible solution suggested for future treatments of CAR T-cells is the use of attenuated Anti-AML T-cells that would only target cells with high expression of antigens such as CD123. The complications with this solution, however, is finding the right balance of activity that attacks AML cells but not normal myeloid cells [38]. A second potential use of CAR T-cell treatment is to utilize Anti-AML CART cells as a conditioning regimen for secondary treatments, such as allogeneic stem cell transplantation [38]. Research on the use of CAR T-cells to treat AML is still new and emerging, but continued focus could lead to potential treatment options in the future.

Tunneling Nanotubes

As the understanding of cellular biology increases, the importance of cellular components to cancerous cells is becoming better understood. In a study conducted by the University of Bergen in Norway, the role of tunneling nanotube formation in AML cells was investigated [39]. Tunneling nanotubes (TNTs) are plasma membrane embedded tunnel-like structures that interconnect cells and provide intracellular communication.

The exact cellular mechanisms that contribute to the formation of TNTs is not known, but they have an importance for cellular function [39]. In this study they looked at the effect of cytarabine and daunorubicin on the formation of TNTs using fluorescent microscopy and found that NF-kB activity is associated with TNT formation [39]. They further discovered that cytarabine alone and in combination with daunorubicin downregulated TNT formation and inhibited NF-kB expression. A previous study on TNTs that found that cancerous cells use TNTs to control their microenvironment and increase cytokine release for pro-survival in the presence of chemotherapies associating with chemo resistance [40]. Therefore, Gjertsen and Andersen (2016) investigated the effect of TNT downregulation of AML with FLT3-ITD mutation and NPM1 mutation and found that FLT3-ITD AML cells already have a lower expression of TNTs indicating a less dependence on their expression. Their results revealed the need for further investigation into therapeutic drugs that disrupt or change the expression and formation of TNTs in NPM1 AML. This is an example of how the treatment protocols must vary based on the mutation that causes AML, as TNT targeted treatments are more likely to be less effective with FLT3-ITD mutations.

Discussion

AML is a heterogeneous disease that can arise from different mutations, complicated by the fact that oftentimes during the course of treatment or during relapse cells become resistant. Therefore, the complexity of the disease and the variations that exist make it difficult to treat in a uniform manner. As the understanding of the disease and the factors that contribute to the development and growth of AML increase, so will the treatment protocols. For more than half a century AML has been consistently approached with a one size fits all treatment protocol. This has led to consistently poor results and survival rates. With the increase and efficiency of genetic profiling to identify potential cases and genetic alterations in patients, treatment should become more personalized and thus more effective. The use of the long-term staple drug of cytarabine is not necessarily ineffective, if utilized in combination with other therapeutic compounds to exploit the collateral sensitivities of the cancer. For example, utilizing current

chemotherapeutics with novel drugs such as Venetoclax can pave the way to more efficacious treatment leading to longer remission and overall survival. Moreover, use of drugs that have been previously used for other disorders and diseases such as HIV, such as azidothymidine, is an area warranting further investigation. Additionally, study of the effectiveness of new therapeutic combinations and regimens should be investigated alongside the study of the cytotoxic effects on normal tissue. Therapeutic strategies are only effective if they can treat the AML without disrupting other tissue types and cause more harm to the patient. As we develop better understanding of the mechanism and causation of AML from the mutations as well as the cellular components that assist its progression, such as TNTs, better therapeutics that target specific functions to disrupt the cell cycle of cancerous cells can be developed. Therefore, both in vitro and in vivo studies of currently available agents as well as progressing newly developed drugs and combinations to clinical trials is essential. Until the complete remission rate and the 5-year survival rate of AML is drastically increased to match other forms of cancer that are seen as heavily treatable, the work is not done.

Finally, as current treatments are refined and new ones added, advances in drug delivery could further revolutionize response, remission and survival. The potential for better drug delivery and targeting to assist in the reduction of cytotoxicity in non-targeted cells and tissues while at the same time increasing cancer cell response is yet another area where more studies are needed. The use of immunoconjugates where a chemical linker hooks together antibodies with a chemotherapy drug has shown promise [30,31,41]. The current treatment regimen is ineffective and should be revolutionized with innovative approaches to the many issues doctors face when utilizing current chemotherapies.

Authorship and Contributions

Connor Smith, an undergraduate research student of Victoria Del Gaizo Moore, Ph.D. at Elon University, compiled the resources and wrote the majority of this article under Dr. Moore's direction. This review paper is part of his larger research project investigating chemoresistance and sensitivity in AML. Dr. Moore's Ph.D. training is in Molecular Medicine and she was a postdoctoral fellow in Dr. Anthony Letai's lab at Dana-Farber Cancer Institute, where she worked on the mechanism of the BCL-2 inhibitor ABT-737.

She has been at Elon University since 2010, teaching biochemistry and running a cancer research lab. In 2018, she completed a year-long sabbatical in Dr. Kris Wood's lab at Duke University, learning chemotherapy resistance and collateral sensitivity techniques.

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