Acute Myeloid Leukemia for Elders

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Acute myeloid leukemia (AML) is an aggressive hematologic malignancy affecting about 0.5% of people in their lifetime. Over the last few decades, a growing understanding of AML has revealed it to be a heterogenous disease with a widely variable prognosis. This is largely driven by disease biology, the ability to tolerate highly toxic multi-agent chemotherapy and, in most cases, undergo allogeneic stem cell transplantation to be cured of disease.

acute myeloid leukemia | older adult | frontline treatment

1. Introduction

Acute myeloid leukemia (AML) is an aggressive hematologic malignancy affecting about 0.5% of people in their lifetime. Over the last few decades, a growing understanding of AML has revealed it to be a heterogenous disease with a widely variable prognosis. This is largely driven by disease biology, the ability to tolerate highly toxic multi-agent chemotherapy and, in most cases, undergo allogeneic stem cell transplantation to be cured of disease. In the best of circumstances, this is a tenuous situation with life-altering implications. Our review will focus on the characteristics of AML in “older” patients and discuss frontline management approaches for this population that can range in terms of performance status from “fit” to medically “frail”. We also discuss future directions for treatment in this disproportionately afflicted, vulnerable population.

2. AML in “Older” Adults

In older adults, monosomal karyotypes, −5 and −7, as well as other adverse cytogenetic abnormalities, including 17p, 11q, +8, and complex karyotypes predominate, while favorable cytogenetic abnormalities are uncommon [1]. In a cytogenetic analysis of CALGB-8461 that compromised patients over 60 years with predominantly de novo AML (97.5%), a complex karyotype with ≥3 abnormalities (19% of patients) and “rare aberrations” (5% of patients) were associated with lower complete remission (CR) rates, while complex karyotype with ≥5 abnormalities (15% of patients) and “rare aberrations” were also associated with inferior disease-free survival (DFS) and overall survival (OS) [2].

Despite these patients being able to tolerate intensive chemotherapy, most patients did not fare well given their age and/or cytogenetic features [3]. Interestingly, in regards to non-trial data, an analysis of the SEER database found improvements in the response rates (RR) and 12-month survival with each decade from 1977–2006 for patients who were 65–74 years old but no improvement for their 75 years of age and older counterparts despite the approval of agents to treat older patients within this timeframe [4]. This variation in survival underscores a need to

discuss the prognosis and treatment of those between age 60 and 74 years old and patients 75 years old or more separately. Later in this review, we discuss the treatment of those between age 60 and 74 years old and patients 75 years old or more separately.

While not initially created for the assessment of oncology patients, they have subsequently been found to predict mortality and chemotherapy-related adverse effects [5][6]. AML and its treatment is among the most intensive stressors that a person can experience. Often, it evolves rapidly and may even require lengthy hospitalization and intensive supportive care. Several studies have gone on to assess the role and feasibility of geriatric assessments in patients receiving induction chemotherapy and even stem cell transplantation for AML in order to accurately depict the effect of induction chemotherapy on older patients [7][8][9][10][11][12][13].

In patients treated with “non-intensive” regimens, KPS < 80, an elevated fatigue index, and a diminished activity of daily living (ADL) index were associated with worse overall survival, which was seen in patients treated with best supportive care only or hypomethylating agents [10]. Utilizing the information obtained from GAs and combining it with cytogenetic and molecular information to optimally tailor individual treatment within this heterogenous group is under study and likely represents a step forward in the treatment of AML in older adults [14].

3. Consolidation Treatment

While most patients treated with induction chemotherapy have a complete remission, durability following treatment was an early issue with intensive therapy until post-remission, or consolidation, treatments were studied and found to be beneficial in sustaining these responses and potentially resulting in long-term cure. Consolidation is often achieved with either chemotherapy alone or with chemotherapy followed by hematopoietic stem cell transplantation.

However, given the complexity of the treatment schedule and multiagent approach, it is difficult to extrapolate these results to patients receiving single-agent cytarabine as a consolidation treatment. An alternative dosing schedule HIDAC has shown promise in young patients with quicker hematologic recovery, less days in the hospital, lower infection rates and no difference in survival with or without co-administration of peg-filgrastim compared with standard HIDAC dosing [15]. Further evaluation in additional randomized trials amongst older patients is needed. Notably patients treated with HMA and venetoclax do not typically undergo consolidation chemotherapy and instead remain on HMA/venetoclax as long as the response continues or toxicities are not seen.

Reduced-intensity conditioning provides an avenue for allo-SCT in older patients with lower TRM and LFS, higher relapse rates, and similar overall survival [16][17]. Allo-SCT with a HLA-matched donor, particularly from a sibling donor, appears to be a more effective consolidation method than autologous stem cell transplantation (auto-SCT) [18][19][20]. Although relapses are more common with auto-SCT, it is associated with lower treatment-related mortality and similar overall survival [18][19][20][21]. Auto-SCT remains a safe and effective consolidation approach in some older AML patients who do not have a readily available donor [22][23].

4. Measurable Residual Disease (MRD)

Measurable (previously minimal) residual disease has been a developing area of study over the last decade with significant clinical implications, and its assessment after completion of intensive therapy has even been included in recent guidelines [24][25]. Given the potential for sampling error or variation in bone marrow evaluation for morphologic evidence of persistent leukemia during or after treatment, more sensitive approaches were developed and studied [26]. The ability to detect the presence of minute numbers of cells (at least 1:10,000 and even 1:100,000) by one of three methods, multiparameter flow cytometry (MFC), next-generation sequencing (NGS), or reverse-transcriptase quantitative polymerase chain reaction (RT-qPCR) has been found to be prognostic and in other diseases (such as ALL) prompts initiation of specific alternate therapies [27][28][29][30][31][32].

Cytotoxic, targeted, and cellular therapies can lead to alterations and evolution in the molecular and genomic characteristics of any residual disease, emphasizing the importance of inclusion of NGS testing at some interval after these treatments to potentially guide future treatment options [33][34]. Additional studies are assessing combinations of these methods at various time points in the disease course and with different samples (peripheral blood vs. bone marrow) [35][36].

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