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ACUTE MYELOID LEUKEMIA INDUCTION IN THE AGE OF NOVEL THERAPEUTIC AGENTS

Introduction

Acute myeloid leukemia (AML) is a malignant neoplasm of the myeloid lineage characterized by the uncontrolled proliferation of immature myeloid blasts in the bone marrow and peripheral blood. AML is a heterogeneous disease which occurs across the age spectrum, although with an increasing incidence with age. For decades, first-line, curative-intent therapy has been based on intensive therapy with anthracycline (typically daunorubicin or idarubicin) plus cytarabine (3+7), followed by additional consolidative chemotherapy and/or allogeneic stem cell transplantation. While improvements over the decades in overall survival have been observed, until recently this has been driven largely by advancements in supportive care leading to reduction in treatment-related mortality and allowing a greater proportion of patients (particularly older individuals) to safely undergo intensive therapy induction and consolidation. Despite this, five-year overall survival (OS) rates in older individuals are as low as 5% (age >70). Although OS for patients age 15-39 is now in the range of 50%-60%, a large portion of patients still succumb to their disease. Cytogenetic and molecular profiling has led to defined risk categories (**Table 1**), and complete risk stratification for all patients eligible for intensive therapy is

crucial to aiding in the selection of optimal induction and post-remission therapy. In recent years, an improved understanding of AML biology and genetics has led to the approval of a number of novel therapies for patients deemed fit and unfit for intensive therapy, which may finally be moving the needle beyond 3+7. This article will review a current approach to AML induction patients eligible for intensive therapy, with a focus on the utilization of available novel agents.

FLT3 Inhibition

FLT3 is a receptor tyrosine kinase that plays a crucial role in the pathogenesis of AML. Aberrations in FLT3 are present in approximately 30% of AML cases, with internal tandem duplication (ITD) generally associated with a poor prognosis in the majority of cases, and with tyrosine kinase domain (TKD) mutations having less certain impact on outcome. FLT3 has therefore become an attractive therapeutic target, and FLT3 tyrosine kinase inhibitors (TKIs) have emerged as adjuncts to AML induction, and as monotherapy for relapsed disease. Midostaurin is a multi-kinase inhibitor that targets FLT3, as well as other kinases involved in AML pathogenesis (including Src kinase, spleen tyrosine kinase, c-kit). The Phase 3 RATIFY trial randomized patients age 18 to 59 with newly

diagnosed AML and FLT3 mutations (either ITD or TKD) to receive standard induction therapy with daunorubicin and cytarabine and high- dose cytarabine consolidation, plus either placebo or midostaurin. The complete remission (CR) rate was improved by the addition of midostaurin (59% vs 54%), with a median OS of 74.7 months in the midostaurin arm and 25.6 months in the control arm. This survival benefit was seen in cohorts with both high- and low-FLT3 allelic burden. In the Phase 3 ADMIRAL clinical trial, gilteritinib, a more selective FLT3 inhibitor, was demonstrated to have superior efficacy vs salvage chemotherapy in patients with relapsed or refractory FLT3-mutated AML. CR or CR with incomplete hematologic recovery was reported as 34% in the gilteritinib arm and 15.3% in the chemotherapy cohort, with median event-free survival of 2.3 months versus 0.3 months. A clinical study comparing the addition of gilteritinib versus the addition of midostaurin to induction and consolidation is ongoing. Midostaurin is Health Canada approved in combination with standard induction and consolidation for newly diagnosed FLT3-mutated AML; gilteritinib is approved as monotherapy for patients with relapsed or refractory FLT3-mutated disease.

Gemtuzumab ozogamicin

Gemtuzumab ozogamicin (GO) is an anti-CD33 monoclonal antibody conjugated to calicheamicin with previous approval for relapsed/refractory (RR) AML. FDA approval was withdrawn in 2010 due to safety concerns (largely related to an increased risk of sinusoidal occlusive syndrome). However, it was reapproved by the FDA in 2017, and is Health Canada approved in combination with 3+7 for previously untreated CD33-positive AML (excluding acute promyelocytic leukemia [APL]). The ALFA-0701 clinical trial randomized patients to receive GO on Days 1, 4 and 7 of induction, as well as up to two consolidation cycles. The addition of GO did not appear to increase rates of CR (73% with GO vs 72% without GO), but resulted in a significant improvement in 2-year event-free survival (41% vs 7%). Although the ALFA-0701 trial did not show a statistically significant OS benefit with the addition of GO, a subsequent meta-analysis of five trials suggests that the addition of GO to standard therapy does provide an OS benefit for patients with favourable and intermediate risk CD33-positive AML, but not for adverse risk patients. In particular, for patients with core binding factor (CBF) AML, the addition of GO results in improved minimal residual disease (MRD) clearance, and may reduce the need for subsequent allogeneic stem cell transplant in this population.

IDH1 and IDH2 Inhibitors

Isocitrate dehydrogenase (IDH) mutations occur in approximately 20% of AML cases and are associated with an adverse prognosis. Inhibitors of IDH1 (ivosidenib) and IDH2 (enasidenib) have been developed. Both agents have monotherapy activity in RR IDH-mutated AML,^{10,11} and the

addition of ivosidenib to azacitidine resulted in improved response rates and EFS in newly diagnosed IDH1-mutated AML not eligible for intensive therapy. The ongoing HOVON study is evaluating the addition of ivosidenib and enasidenib to induction/consolidation and as maintenance in patients with IDH1/IDH2-mutated AML eligible for intensive therapy. Both agents are Health Canada approved for RR IDH1 and IDH2 mutated AML, respectively, although lack of provincial funding may provide barriers to their access.

Venetoclax

B-cell lymphoma-2 (BCL-2) is an anti-apoptotic protein which plays an important role in a number of hematologic malignancies, including AML. Venetoclax, a BCL-2 inhibitor, has been shown to improve OS when added to azacitidine (median OS 14.7 months vs 9.6 months) and low- dose cytarabine (in longer term follow-up, it has shown median OS of 7.2 months vs 4.1 months) in patients with newly diagnosed AML ineligible for intensive therapy (VIALE-A and VIALE-C trials, respectively). Both combinations are Health Canada approved. Venetoclax, in addition to 3+7 induction, resulted in high CR rates (91%, with 97% of patients achieving CR being MRD-negative) in a Phase II study, and an ongoing Phase 3 study is evaluating this combination in AML and advanced myelodysplastic syndromes (MDS).

Liposomal encapsulated daunorubicin and cytarabine

While “therapy-related” AMLs are now defined more by their predisposition for high-risk genetic profiles than by history of previous treatment exposure alone, the fact remains that the majority harbour adverse risk genetic abnormalities, and these leukemias are typically associated with a poor outcome. Likewise, AML arising from antecedent myelodysplasia or myeloproliferative neoplasms (MPNs) is also typically associated with adverse outcomes. The combination of liposomal encapsulated cytarabine and daunorubicin (CPX-351) was evaluated in older patients (age 60-75 years) with newly diagnosed high-risk secondary AML (defined in this trial as therapy-related AML, AML with antecedent MDS or chronic myelomonocytic leukemia (CMML), or AML with MDS-related cytogenetic abnormalities). Patients were randomly assigned to receive standard 3+7 induction and cytarabine consolidation, or up to two induction cycles and two consolidation cycles of the liposomal combination. Higher overall response rates (ORRs) were observed with CPX-351 vs standard therapy (ORR 47.7% vs 33.3%), and there was an OS benefit in the study arm (median OS 9.56 vs 5.95 months). Of note, patients who had received prior hypomethylating therapy did not appear to benefit in subgroup analysis, and patients with antecedent MPNs including primary myelofibrosis, essential thrombocytosis, polycythemia vera, and MDS-MPN overlap were excluded from the trial. Retrospective data presents conflicting evidence of benefit for younger patients treated with CPX-351, and further clinical studies are required to

Risk Category	Genetic Abnormalities
Favourable	t(8;21)(q22;q22.1)/ <i>RUNX1::RUNX1T1</i> inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/ <i>CBFB::MYH11</i> Mutated <i>NPM1</i> without <i>FLT3-ITD</i> bZIP in-frame mutated <i>CEBPA</i>
Intermediate	Mutated <i>NPM1</i> with <i>FLT3-ITD</i> Wild-type <i>NPM1</i> with <i>FLT3-ITD</i> t(9;11)(p21.3;q23.3)/ <i>MLLT3::KMT2A</i> Cytogenetic and/or molecular abnormalities not classified as favourable or adverse
Adverse	t(6;9)(p23;q34.1)/ <i>DEK::NUP214</i> t(v;11q23.3)/ <i>KMT2A</i> -rearranged t(9;22)(q34.1;q11.2)/ <i>BCR::ABL1</i> t(8;16)(p11;p13)/ <i>KAT6A::CREBBP</i> inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/ <i>GATA2, MECOM(EV11)</i> t(3q26.2;v)/ <i>MECOM(EV11)</i> -rearranged -5 or del(5q); -7; -17/abn(17p) Complex karyotype, monosomal karyotype Mutated <i>ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2</i> Mutated <i>TP53</i>

Table 1. European Leukemia Net 2022 AML Risk Stratification Schema²¹

define its optimal role in this patient population., CPX-351 is Health Canada approved for the treatment of adults with newly diagnosed therapy-related AML or AML with MDS-related changes.

Oral azacitidine

Patients with AML successfully completing intensive induction therapy require additional post-remission consolidation, either with additional chemotherapy (favourable risk disease) or allogeneic stem cell transplantation (most non-favourable risk disease). Review of patient selection for and outcomes of allogeneic stem cell transplantation is beyond the scope of this article; however, patients with non-favourable risk disease who are unable to proceed with allogeneic stem cell transplant typically have poor outcomes. The QUAZAR AML-001 randomized, placebo-controlled clinical trial reported that in AML patients in remission following intensive chemotherapy but unable to proceed to hematopoietic stem cell transplant, oral azacitidine maintenance therapy (administered Day 1-14/28 day cycles) improved median OS (24.7 months vs 14.8 months), as well as relapse-free survival. These results were evident in patients who did not receive any additional consolidative therapy post-induction. Oral azacitidine is Health Canada approved for maintenance therapy in adult patients with AML who achieved CR or complete remission with incomplete count recovery (CRi) following induction therapy who are not eligible for hematopoietic stem cell transplant.

Conclusion

After an extended period of limited progress in AML induction therapy, recent advances have led to the approval

of a number of novel agents for the treatment of AML in both fit and less fit patients, leading to improved outcomes for many of these patients. The optimal utilization of many of these agents remains to be defined, but prompt and complete molecular characterization of patients with newly diagnosed AML is more crucial than ever to ensure access to the most effective therapies. While novel agents have improved RRs and survival, many patients are still not cured of their disease. Numerous novel therapies, including small-molecule inhibitors (SMIs), immunotherapies and cellular therapies, are currently under investigation and offer hope for further improvements in long-term outcomes in the future.

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