5 Therapy of Newly Diagnosed Acute Myeloid Leukemia (AML)

Anna B. Halpern and Elihu Estey

5.1 Pretreatment Disease Risk Stratification

Much progress has been made in identifying genetic features of AML that may predict resistance to classic cytotoxic therapy (and likely newer "targeted" therapies as well) and thus shape prognosis. These features encompass both classical cytogenetics and the mutational status of various genes. Further distinction is often made between de novo and secondary AML due to prior chemotherapy or following an antecedent hematologic disorder, as discussed in Chap. 3, although much of the prognostic relevance of secondary disease is accounted for by genetic risk [1]. The European LeukemiaNet (ELN) guidelines, most recently updated in 2017, are the most commonly used source for classifying risk of resistance, which even in patients in their 70s is the main cause of death in AML [2]. These guidelines group patients into "favorable," "intermediate," and "adverse" categories. The favorable category encompasses the core binding factor (CBF) leukemias, i.e., those with t(8;21)(q22;q22) resulting in the RUNX1-RUNX1T1 (AML1-ETO) gene and inv (16)(p13.1;q22) or t(16;16)(p13.1;q22) which creates the CBFB/MYH11 fusion gene. Patients with mutated NPM1 with wild-type FLT3-ITD or with FLT3 mutations with low allelic ratios (ratio of mutated to normal alleles <0.5) and those with biallelic mutations in CEBPA are also classified as favorable risk, regardless of other cytogenetic aberrations, although it now appears patients who have the NPM1+/FLT3-negative genotype but adverse cytogenetics have an adverse rather than a favorable prognosis. The intermediate risk category includes those with both a mutated NPM1 and FLT3-ITD with a high allelic ratio, those with wild-type NPM1 with a low-allelic ratio FLT-ITD, those with a t(9;11)(p21.3;q23.3) leading to the MLLT3-KMT2A fusion gene, and cytogenetic abnormalities not otherwise classified. Finally, the adverse-risk category encompasses those with TP53 mutations—perhaps the most dominant adverse-risk factor—the RUNX1 and ASXL1 mutations, along with complex and monosomal karyotypes and a few other gene specific cytogenetic abnormalities (e.g., monosomy 5 and 7). The National Comprehensive Cancer Network (NCCN) also published risk stratification guidelines whose recent 2017 update [3] are largely similar to the ELN 2017 guidelines, with a few differences in the classification of various FLT3-ITD mutated patients and CBF leukemia with the KIT mutation, who are placed in the intermediate-risk group.

A. B. Halpern (✉) · E. Estey
Division of Hematology, Department of Medicine, University of Washington, Seattle, WA, USA

Clinical Research Division, Fred Hutchinson Cancer Research Center/University of Washington, Seattle, WA, USA
e-mail: halpern2@uw.edu

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While the ELN 2017 guidelines are widely used, relatively easy to apply with currently available clinical genetic testing at most centers, and have been partially validated in subsequent studies (e.g., Japan Acute Leukemia Group Study patients [4]), there are some limitations. For example, age is not factored into these guidelines, although it does clearly play a role in prognosis, as Ostronoff et al. [5] found that patients aged >65 years with NPM1 mutations and wild-type FLT3-ITD (favorable risk) had poorer outcomes than younger adults in SWOG and MRC/NCRI trials. In addition to age, co-occurring mutations found on next-generation sequencing (NGS) likely interact with mutations in NPM1 and FLT3, for example, thus modifying prognosis. Eisfeld et al. [6] evaluated outcomes of 423 patients aged >60 years treated on Alliance protocols and found that while ELN favorable-risk patients did have longer survival than intermediate/adverse-risk patients, the intermediate and adverse risk had an indistinguishable prognosis. However, when they used an 80-gene NGS panel to more specifically attempt risk stratification, they were better able to risk stratify their study cohort. Similarly, Patel et al. [7] reported that both higher NPM1 mutation burden (measured as variant allele frequency) and the co-occurrence of DNMT3A mutations with NPM1 were associated with shorter EFS and survival.

These findings of the importance of gene–gene interactions demonstrate the significance of incorporating more comprehensive genetic data than what is included in the ELN 2017 guidelines when creating risk categories that then drive treatment decisions. The downside, however, of these large NGS panels is that while initial treatment decisions for AML therapy are usually made within the first few days after diagnosis, and often in community settings, these panels are not yet widely available beyond academic settings and results can take weeks to come back. Notably, however, multiple studies have demonstrated that delay in AML therapy often does not have a deleterious effect on outcome [8, 9]. Finally, although there has been a recent surge of drug approvals for AML, the majority of leukemia-associated mutations that have been identified are not yet targetable by available drugs. Even in cases where drugs are available for single mutations, the duration of response is relatively short, suggesting the future will likely see the use of such drugs in combinations with each other or with chemotherapy.

5.2 Pretreatment Patient Risk Stratification

In addition to the disease-associated factors noted above, patient-specific factors also play an important role in initial therapeutic decisions, especially whether to give an "intensive" or "less-intensive" regimen. With a recently expanding list of approved options with which to treat patients with newly diagnosed AML, in addition to many investigational agents, it is useful to have an "objective" or quantifiable approach to risk prediction. As described more fully in Chap. 4, there are a variety of scoring systems that have been developed whose goal is to identify patients at high-risk for "treatment-related mortality" (TRM) or early mortality following induction chemotherapy [10–14]. Some of these tools focus solely on patient-related factors, with recurring important predictive factors across tools including age, performance status, baseline leukocyte count, serum creatine, and antecedent hematologic disorder, while others combine both patient-specific factors and diseased-specific factors such as cytogenetics, which are more likely a predictor of efficacy rather than short-term toxicity [12].

While age is indeed a common variable in many of these models—and in real-world practice, it often is the primary factor used in treatment determination—the accuracy of each of these models seems to be improved when other covariates are added, underscoring the recommendation by both the ELN and NCCN that age should be considered in the context of other variables when deciding whether to proceed with intensive therapy [2, 3]. Further, with improvements in supportive care, intensive therapies have become safer and the overall TRM rate for AML has decreased over time [15]. In practice, however, even fitter older patients are

frequently offered less intensive therapy (commonly "hypomethylating agents" such as azacitidine or decitabine) rather than more intense therapy, based on the assumption that potential risks of intensive therapy are not commensurate with potential benefits. Indeed, records from large databases suggest that less than half of Americans aged >65 years with AML, and as few as 10–20% of those >80 years, receive intense chemotherapy [16, 17]. Data from population-based AML registries and one retrospective analysis from patients treated at five U.S. cancer centers support the use of intensive rather than low-intensity chemotherapy—in terms of disease-related and survival outcomes—in most AML patients up to age 80 years even with comorbidities [17, 18]. However, retrospective data should be interpreted cautiously since information on exact regimens is often not available and differences in supportive care and selection bias may confound the apparent benefit of intensive therapy. Further, although it is commonly assumed that quality of life (QOL) is better in recipients of non-intensive therapy rather than intensive therapy, recent data from a prospective observational study [19] in older AML patients comparing QOL measures between those treated with intensive vs. non-intensive therapy found QOL scores to be *higher* in the intensive group, supporting the notion that the benefits of better disease control can outweigh the detriment of treatment-related toxicities to QOL. There are data indicating that incorporation of formal geriatric assessment tools (such as the "Get-up and Go Test" and the timed 4-min walk test) into the evaluation of an older patient's health may provide a more nuanced picture of their medical fitness and tolerance of intensive chemotherapy [20, 21].

In sum the choice of therapy should take into account not only disease-specific cytogenetic and mutational data but also patient-specific features including (but not limited to) age, functional status, and organ function. These should ideally be quantified within a risk-prediction model. Taking these steps may help move us away from using age as our primary determinant of initial AML therapy.

5.3 Goal of Induction Chemotherapy

For younger and fitter patients (particularly those with intermediate and adverse risk disease), getting to allogeneic stem cell transplant (HCT), with as little disease and decline in functional status as possible, should be the goal; the intent being cure. For medically less fit, and potentially older patients, a more realistic goal is prolongation of life with the preservation of some measure of quality. But how to translate these goals into objective measures of drug efficacy for empiric evaluation in clinical trials is a challenge.

As in other malignancies, overall survival (OS) is likely the most relevant drug efficacy endpoint in AML. However, death is often delayed even when therapy is unsuccessful. This suggests the use of event-free survival (EFS) rather than OS as a measure of drug efficacy. Earlier-observed endpoints have also been suggested as a means to allow more efficient early-phase drug testing [22]. For many years, complete remission (CR) was regarded as such an endpoint. However, while achieving a CR appears necessary for long-term survival in AML, CR in itself is not sufficient to prolong survival [23, 24]. One potential explanation is that morphologically defined CRs vary widely in quality, with only "high quality" CRs translating into a survival advantage. In particular, the presence of measurable (formerly "minimal") residual disease (MRD) at the time of CR, or CR with incomplete hematologic recovery (CRi)—the latter likely more prone to relapse than the former—is associated with higher relapse and shorter EFS/OS—likely because MRD indicates a poor-quality CR [25, 26]. Indeed, once account is made for response (CR vs CRi) and presence/absence of MRD at CR, pretreatment covariates conventionally predictive of relapse (adverse cytogenetics, secondary AML, newly diagnosed vs. relapsed disease) lose much of their significance. Consequently, the goal of induction therapy in medically fit patients with AML should be attainment of a CR without MRD (with MRD defined by multiparameter flow cytometry and potentially per-

sistent cytogenetic abnormalities, with the contribution of mutational data to MRD evaluation remaining under investigation [27, 28]). The ability to demonstrate improved rates of MRDneg CR may be a more specific measure of efficacy when evaluating new induction regimens. Finally, speaking to the goal of induction therapy for medically less fit patients, there is some limited evidence that QOL is better for those who achieve a CR than those who do not (and thus are more likely to be transfusion dependent and at increased risk for infection and its sequelae); however, this is an area that requires further study.

5.4 Intensity of Induction Chemotherapy

Although 7+3 still remains the most commonly given induction regimen to newly diagnosed AML patients, many attempts have been made to "intensify" this backbone, both via increasing the dose of the anthracycline and the cytarabine, and via incorporation of a third agent—most commonly a nucleoside analog—into the regimen.

5.4.1 Anthracycline Dose and Intensity

There is no definitive evidence that higher doses of anthracycline (e.g., daunorubicin 90 mg/m^2 vs. 60 mg/m^2) is more efficacious, nor more toxic, than lower doses of anthracycline, although 90 mg/m^2 does appear superior to 45 mg/m^2. On the one hand, two well-controlled studies have indicated that escalated doses of anthracyclines given during initial induction chemotherapy can improve response rates and survival [29, 30]. Fernandez et al. randomized 657 adults aged <60 years to daunorubicin 45 mg/m^2 vs. 90 mg/m^2 as part of standard 7+3 and found higher rates of CR and improved OS in the higher-dose group, with similar rates of serious adverse events [29]. Similar results were found by Löwenberg et al. [30] in an older age group (age 60–83 years), although in this case higher remission rates in the higher-dose arm did not translate into a survival benefit. On the other hand, the UK NCRI AML17 trial randomizing 1206 patients treated with 7+3 to daunorubicin 90 mg/m^2 vs. 60 mg/m^2 found no difference in survival (except in the FLT3 ITD-mutated subgroup which appeared to benefit from the higher-dose arm), although there was higher 60-day mortality in the 90 mg/m^2 arm, which may have attenuated long-term benefit [31]. Ultimately, the lack of conclusive data on the benefit of anthracycline dose intensification largely stems from differences in designs of studies (e.g., choice of anthracycline and dose and differences in controls arms and consolidation strategies) that limit clear comparisons between studies.

5.4.2 Cytarabine Dose and Intensity and the Addition of a Nucleoside Analog

There are a few randomized studies asking whether increasing the cytarabine dose in combination with an anthracycline can improve outcomes. A large German study randomized 3375 adults to 7+3 vs. high-dose cytarabine containing therapy and found no difference in 5-year event-free or relapse-free survival (EFS, RFS) [32]. In the SWOG12033 trial (full results not yet published), 739 adults aged <60 years were randomized to standard dose 7+3 (with daunorubicin 90 mg/m^2) vs. idarubicin + high-dose cytarabine (IA; cytarabine dose 1.5 g/m^2 daily × 4 days) and IA + vorinostat (IAV). Although rates of CR were higher in the IA arm after the first course, there were no differences seen in EFS, RFS, or OS. As a limitation, patients receiving IA and IAV received less cytarabine with post-remission therapy than those given 7+3. Further, patients with favorable-risk AML actually did better on the control arm, although this outcome may also have been confounded by their post-remission therapy containing high-dose cytarabine rather than attenuated dosing of induction.

The MRC/NCRI AML 15 trial, on the other hand, involving approximately 3200 newly diagnosed patients with AML suggested that FLAG-Ida (fludarabine, high-dose cytarabine, G-CSF, and idarubicin) is a more effective anti-AML regimen than daunorubicin with standard-dose cytarabine (DA) or DA with addition of etoposide ([ADE]; 1268 patients participated in the direct comparison of FLAG-Ida vs. ADE [33]). This study found that patients randomized to FLAG-Ida had a lower cumulative incidence of relapse than the other regimens (at 3 years: 38% vs. 55%, $p < 0.01$), potentially reflective of more patients achieving CR after 1 course of therapy. Death in CR was more common with FLAG-Ida (17% vs. 11%), thus narrowing the difference in survival [15]. Despite a lack of unequivocal data, high-dose cytarabine containing regimens have, at some institutions, replaced 7+3 as the standard induction regimen for newly diagnosed AML, especially in light of improvements in supportive care and declining rates of TRM.

At the authors' institution, we use GCLAM (G-CSF, cladribine, high-dose cytarabine, and mitoxantrone) rather than FLAG-Ida based on data from the Polish Acute Leukemia Group and our own phase 1/2 trial [34, 35]. GCLAM differs from FLAG-Ida in the use of mitoxantrone rather than idarubicin and, primarily, in the substitution of cladribine for fludarabine. Cladribine is a more active single agent in AML than fludarabine; a Polish randomized trial in 652 adults aged <60 years found that while addition of fludarabine to 7+3 did not improve survival, however addition of cladribine to 7+3 did, with results principally due to superior outcomes in patients with adverse cytogenetics [35]. Single-arm studies from the Moffitt Cancer Center suggest that cladribine plus high-dose cytarabine is more effective than mitoxantrone, etoposide, and cytarabine (MEC) for relapsed/refractory disease [36], and the combination of cladribine, cytarabine, and mitoxantrone has also produced encouraging results in similar patients at Moffitt Cancer Center [37] and in Poland [38]. Nonetheless there are no randomized comparisons of GCLAM with FLAG-Ida or 7+3.

5.5 Newly Approved ("Targeted") Agents

In the past 2 years, the Food and Drug Administration (FDA) approved five new drugs for newly diagnosed AML (midostaurin, gemtuzumab ozogamicin, CPX-351, venetoclax, and glasdegib) along with another three in the relapsed/refractory setting (the IHD1 and 2 inhibitors ivosidenib and enasidenib and the FLT3 inhibitor gilteritinib) that may eventually move into the frontline setting. As the drug labels do not always reflect the populations in which these drugs were initially studied, there remains much to be learned about how to best integrate these drugs into our current treatment pathways, in which areas they might make the most impact, and how best to monitor response.

5.5.1 Midostaurin

Midostaurin—an oral tyrosine kinase inhibitor that is active against the FLT3 internal tandem duplication (ITD) and tyrosine kinase domain (TKD) mutations—was approved by the FDA in 2017 for the treatment of adults with newly diagnosed AML who are positive for the FLT3 mutation, in combination with standard cytarabine and daunorubicin induction and cytarabine consolidation. FLT3 ITD mutations occur in about 25% of patients aged <60 years and in about 15% of older patients, with mutations in the TKD occurring in another 5–10% [39]. Approval was based on a large randomized study by Stone et al. [40] comparing 7 + 3 + Midostaurin to 7 + 3 + placebo in 717 patients aged <60 years with a FLT3 mutation. Midostaurin was dosed at 50 mg orally twice daily (BID) on days 8–21 of induction and consolidation (cytarabine consolidation given at the commonly used dose of 3 g/m^2 BID on days 1, 3, 5) and then as maintenance at the same dose for 1 year. Although CR rates were similar, OS and EFS were longer in the midostaurin group compared to placebo (hazard ratio for death 0.78 for both; $p = 0.009$ for OS and $p = 0.002$ for EFS). Results were not affected by censoring at HCT. Midostaurin was superior regardless of

ITD allelic ratio (high vs. low) or type of FLT3 mutation. The benefit of the maintenance portion of this regimen remains unclear (maintenance therapy has been approved in Europe but not the United States) [41]. Regardless, the addition of midostaurin to 7+3 is now standard therapy for adults aged <60 years with newly diagnosed AML and a FLT3 mutation, although the FDA approval is not age-limited, despite a lack of data in older patients. Notably, while potentially more specific for the FLT3 domain than other multikinase inhibitors [42], midostaurin does inhibit kinases other than FLT3, and thus its multikinase properties could be inhibiting other growth pathways in cancer cells, plausibly providing benefit in patients without this mutation. Rollig et al. [43] demonstrated that the addition of the multikinase inhibitor sorafenib to 7+3 improved EFS compared to placebo in patients aged <60 years, regardless of FLT3 ITD mutation status. It remains to be worked out whether more "potent" and specific inhibitors of FLT3 (e.g., quizartinib and gilteritinib) provide more benefit or whether the less specific multikinase inhibitors are ultimately more effective due to ability to limit the development of resistance to a single mechanism.

5.5.2 Gemtuzumab Ozogamicin

Gemtuzumab ozogamicin (GO, Mylotarg), a CD33 targeting antibody–drug conjugate which delivers a DNA-damaging calicheamicin derivative into the cell, was initially approved in 2000 for CD33+ AML patients aged older than 60 years in first relapse, but then removed from the market in 2010 after a large phase 3 study from SWOG comparing induction with 7+3 vs. 7+3+GO (at a dose of 6 mg/m^2 on day 4) demonstrated a higher induction mortality in the combination arm without improvement of CR rate, disease-free survival, or overall survival [44]. Following the withdrawal, four more randomized trials were done: MRC AML15, ALFA-0701, NCRI AML1642, and GOELAMS AML2006IR [45–47], which demonstrated survival benefit with the addition of GO to induction therapy. In particular, the ALFA-0701 trial, which randomized patients aged 50–70 years to 7+3 with or without GO in fractionated doses of 3 mg/m^2 on days 1, 4, and 7, and demonstrated improvement in EFS from 9.5 to 17.3 months [47], and the NCRI AML17 trial compared GO doses of 3 and 6 mg/m^2 and found lower rates of veno-occlusive disease (VOD) in the lower dose arm without decrement in survival or higher relapse rates [48]. Further, meta-analyses have suggested particular benefit in favorable-risk disease [49]. Correlative studies attempting to identify genetic predictors of response—such as having the rs12459419 CC splice variant of CD33 as demonstrated in the pediatric phase 3 trial AAML0531 [50]—are ongoing.

This large body of data subsequently led GO to be re-approved by the FDA in 2017 for the treatment of both newly diagnosed and relapsed/refractory CD33-positive AML in adults and pediatric patients (Mylotarg prescribing information, 9/2017). It was approved in induction in combination with daunorubicin and cytarabine dosed at 3 mg/m^2 on days 1, 4, and 7 and in consolidation at a dose of 3 mm/m^2 given on day 1. It was also approved as a single agent given as 6 mg/m^2 on day1 and 3 mg/m^2 on day 8 of induction or in "continuation" at 2 mg/m^2 every 4 weeks for up to eight courses.

However, GO is not necessarily the "magic bullet" antibody therapy we have been looking for to revolutionize AML treatment for a variety of reasons. Mechanisms of resistance to GO include low and variable CD33 expression levels on AML, making CD33 a difficult target, part of a broader problem in AML contributing to the lag in development of antibody-based approaches compared to other leukemias such as acute lymphoblastic leukemia (ALL) and some lymphomas [51]. Further, GO is a first-generation antibody–drug conjugate, with technology that was not perfected, and thus about half of the antibody molecules are not labeled with the toxin leading to binding site competition with unconjugated CD33 antibody. Additionally, CD33 is only slowly internalized, leading to limitations in bringing the toxin into the cell, and AML blasts frequently express drug transporters

able to successfully expel the toxin. These shortcomings have led to active development of newer generations of antibody–drug conjugates targeting CD33, such as SGN-CD33A [52], and bispecific antibodies targeting CD33/CD3 such as AMG330 [53, 54], which are being designed to overcome these limitations. Novel and investigational therapies in AML will be further addressed in Chap. 8.

5.5.3 CPX-351

In 2017, the FDA-approved CPX-351 (Vyxeos) for the treatment of newly diagnosed therapy-related AML (t-AML) or AML with myelodysplasia-related changes (AML-MRC). It is a liposomal formulation of cytarabine and daunorubicin at a fixed 5:1 molar ratio that leads to prolonged exposure of AML blasts to the drugs. The approval was based on a randomized trial of 309 patients aged 60–75 years with therapy-related, secondary, or de novo AML with MRC to CPX-351 or standard 7+3 [55]. CR/CRi rates were higher with CPX-351 (48% vs. 33%), there was longer EFS and OS in the CPX-351 arm (HR 0.74, $p = 0.021$ and HR = 0.69, $p = 0.005$, respectively) and similar toxicity and 60-day mortality were observed between arms (13% with CPX-351 and 21% with 7+3). More CPX-351 patients went to HCT (34% vs. 25%) and were more likely to be in CR prior to HCT. Further, transplanted CPX-351 patients had better post-HCT survival than the 7+3 group [56], although this may only reflect that a higher proportion of these patients entered transplant in a CR or that more of them were actually MRD-negative, although MRD rates were not reported in the study. Notably the benefit for CPX-351 vs. 7+3 was limited to patients who had not received prior hypomethylating agents (HMA), although that is a likely frequent past therapy for patients with secondary AML or AM-MRC. Further, although the trial was limited to patients aged 60–75 years, the FDA approved the drug regardless of age. Thus, further evaluation of this drug in expanded clinical scenarios is warranted, including its use in patients who are medically unfit or as a backbone in combination with some of the newer targeted agents (e.g., midostaurin or venetoclax). However, despite the limitations of this initial trial, CPX-351 is currently a reasonable option for fit older patients with newly diagnosed secondary AML.

5.5.4 Venetoclax

Venetoclax is a selective oral inhibitor of B-cell lymphoma 2 (BCL-2), an anti-apoptotic protein that is thought to play an important role in survival of AML blasts and promote resistance to typical AML therapy. In 2018, the FDA approved Venetoclax in combination with azacitidine, decitabine, or low-dose cytarabine (LDAC) for the treatment of newly-diagnosed AML in adults aged >75 years or who have "comorbidities that preclude use of intensive induction chemotherapy." This approval, however, was based on only two non-randomized, single arm, open-label studies. The first, by Wei et al. treated 82 adults aged 60 years and older with untreated AML (prior HMA allowed) who were ineligible for intensive chemotherapy with venetoclax 600 mg daily in combination with LDAC 20 mg/m^2 daily for days 1–10 [57]. They demonstrated a CR rate of 26% and CRi rate of 28% with a median duration of remission of 8.1 months and median OS for all patients of 10.1 months. The 30-day mortality rate was 6%. Similarly, DiNardo et al. [58] evaluated venetoclax at doses of 400–1200 mg daily in combination with either azacitidine or decitabine in 145 patients aged >65 years and ineligible for standard induction chemotherapy for reasons such as: age >75 years, cardiac disease, prior anthracycline use, secondary AML, and "high probability" of treatment-related mortality. They demonstrated a CR rate of 37% and CRi rate of 30%, with 29% of patients achieving MRD negativity at at least one time point. Median time to first response was 1.2 months (range 0.9–13.5) and to best response 2.1 months (range 0.9–13.5), with median duration of response of 11.3 months. With a median follow-up 15.1 months, the median OS was 17.5 months. Similar response rates were seen with either

azacitidine or decitabine and at either venetoclax 400 or 800 mg daily.

Despite the FDA approval, several questions remain about in which settings the drug should be employed. Although patients in both the Wei and DiNardo studies were required to be "ineligible" for intensive therapy, they were required to have a performance status of 0–2 and adequate renal and hepatic function in the DiNardo study, and 71% and 84% of patients enrolled respectively in each study had a PS of 0 or 1. Therefore, it is worth assessing this regimen in an objectively unfit population, as it is likely to be used in real-world situations. Further, it might be worthwhile to evaluate venetoclax in combination with higher intensity therapies such as 7+3 or FLAG-Ida in patients at low risk of TRM or in the consolidation or MRD-positive settings.

5.5.5 Glasdegib

Glasdegib, an oral inhibitor of smoothened (SMO), a key regulator of the Hedgehog pathway, was also approved by the FDA in 2018 in combination with LDAC for newly diagnosed AML patients aged over 75 years or who have comorbidities that preclude intensive induction chemotherapy. This was based on a study by Cortes et al. [59] randomizing 132 patients to Glasdegib 100 mg daily in combination with LDAC (n = 88) vs. LDAC alone (n = 44) and demonstrated CR + CRi rates of 24% in the glasdegib/LDAC arm compared to 5% in the LDAC arm, with a median duration or CR in the combination arm of 9.9 months. Overall survival (the primary endpoint) was found to be longer in the glasdegib arm at 8.8 months compared to 4.9 months in the LDAC-alone arm (hazard ratio 0.51, $p \leq 0.01$). Criticisms of this study include an open-label design without a blinded, placebo-controlled arm, short duration of exposure to LDAC on the LDAC-alone arm, and lower than expected response rates observed in the LDAC-alone arm compared to prior studies. Since randomized trials have shown that LDAC is associated with shorter survival than azacitidine or decitabine, it is possible that the proper control arm for glasdegib + LDAC should be azacitidine or decitabine rather than LDAC. Further, like the venetoclax studies noted above, about 50% of enrolled "unfit" patients actually had performance status of 0–1. Therefore, more studies are needed before the role and true benefits of glasdegib in AML can be determined.

5.6 Overall Recommendation for Initial Induction Therapy

Favorable-risk disease: A 37-year-old, previously healthy woman presents with a leukocyte count of 38 × 10^3/μL with 54% blasts, platelets of 40,000/μL and hemoglobin of 7.8 g/dl. Cytogenetics revealed a t(8;21)(q22;q22) in 20 cells, and NGS testing is unremarkable, including negative for c-KIT.

> We would favor induction with 7+3+GO in this patient, without plan to transplant in CR1 as long as she achieves >3-log reduction in RUNX1-RUNX1T1 transcripts after induction [60].

Intermediate-risk disease: A 55-year-old man with diabetes mellitus and hypertension presents with a leukocyte count of 81 × 10^3/μL including 70% blasts*, platelets of 12,000/μL and hemoglobin 8.4 g/dl. Bone marrow confirms AML. Cytogenetics show a normal male karyotype, and NGS testing reveals a FLT3-ITD, NPM1, and DNMT3A. The FLT3 ITD allelic ratio is 1.2.*

> We would give this man 7+3 (with daunorubicin dosed at 90 mg/m^2) for induction in conjunction with midostaurin, along with midostaurin and high-dose cytarabine for post-remission cycles. We favor allogeneic HCT in CR1 with midostaurin maintenance following HCT [61].

Adverse-risk disease: A 78-year-old female with a history of invasive ductal carcinoma of the left breast, who received doxorubicin, paclitaxel and cyclophosphamide, presents with progressively worsening cytopenias down to a leukocyte count of 1.5 × 10^3/μL*, platelets of 20,000/μL and hemoglobin 6.7 g/dl. Bone marrow confirms AML with MRC, cytogenetics reveal a complex karyotype in 16 cells and normal karyotype in four cells, and NGS testing demonstrates a TP53 and*

STAG2 mutation. Medical history includes hypothyroidism, hyperlipidemia, and osteoporosis. She lives in a nursing facility and walks with a walker.

> This patient has poor-risk disease and is likely to do poorly with standard chemotherapy, and thus we recommend participation in a clinical trial if possible. One of the more interesting investigational agents in myeloid neoplasms is APR-246, which has been shown to reactivate mutant and inactivated p53 protein. By restoring wild-type p53 conformation and function, the drug is able to induce apoptosis, and a small, early phase clinical trials in humans showed the drug to be very efficacious in combination with azactidine [62]. If the patient did not have access to clinical trials, a hypomethylating agent (azacitidine/decitabine) or LDAC in combination with venetoclax or glasdegib would be a reasonable option.

5.7 Conclusion

Where is the future of therapy for newly diagnosed AML headed? Despite advances in NGS techniques leading to a deeper understanding of AML pathogenesis and prognosis, cytotoxic chemotherapy remains the standard of care for inducing remission in most patients with newly diagnosed AML. However, refinements of this cytotoxic backbone are finally coming to fruition with the expansion of drug options targeting specific mutations and drug resistance pathways. Now that we have many new therapeutic options for this disease, the next challenge is to—through rigorously designed, prospective controlled clinical trials—evaluate in which situations and patient populations they will provide most benefit. Further attention needs be paid to a more precise evaluation of "ineligibility" for intensive chemotherapy and evaluating the benefits of less intense vs more intense therapy in medically less fit patients. And finally, we need better understanding of how genes interact in AML pathogenesis to allow us to more precisely combine our growing arsenal of therapeutic options to translate short-duration remissions into genuine long-term gains in survival.

Conflict of Interest The authors declare no competing financial interests.

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