

Optimal Post-Remission Consolidation Therapy in Patients with AML

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Abstract

Background: Despite recent advances, 40–85% of patients with acute myeloid leukaemia (AML) achieve complete remission after intensive chemotherapy. However, without optimal treatment after remission, the risk of relapse remains high. **Summary:** A variable number of consolidation cycles consisting of intermediate doses of cytarabine are the most commonly used regimens in low-intermediate-risk AML, while patients at higher risk of relapse should consolidate response by proceeding to HSCT. Different post-consolidation (maintenance therapies) have demonstrated their benefit in prolonging relapse-free survival, and others are still under investigation. Careful consideration should be given to which patients benefit most from each of these interventions, considering that the risk of relapse is dynamic.

Key Messages: Patients consolidated with chemotherapy should receive either 2 courses of HDAC or no more than 3–4 cycles of IDAC with dose reduction in patients over 60 years. Patients with mutated *FLT3* AML benefit from post-consolidation maintenance with *FLT3* inhibitors, and selected patients not fit for adequate consolidation may benefit from CC-468 maintenance.

Patients at higher risk of relapse should proceed to allogeneic SCT as soon as possible, opting for a more intensive conditioning in patients younger than 55 years. However, autologous HSCT may still have role in favourable-risk MRD-negative AML. Multiple treatment options targeting MRD are emerging, either as definitive treatment or as a bridge to allogeneic transplantation, and are likely to become increasingly relevant.

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Introduction

Curative approaches in acute myeloid leukaemia (AML) in fit patients are based on the delivery of intensive chemotherapy (IC) in order to eliminate leukaemic cells and restore normal haematopoiesis. Current protocols are based on an induction with one or two courses of anthracycline and cytarabine, which successfully induces a complete remission (CR) in 40–85% of patients depending on age [1–3]. In the late 1980s, it was established that induction alone was not sufficient to eradicate AML, and high relapse rates required the application of post-remission treatment [4, 5].

In the modern era, induction chemotherapy is frequently combined with a *FLT3* inhibitor in presence of *FLT3*-ITD or tyrosine kinase domain (TKD) mutations [6, 7] or gemtuzumab ozogamicin (GO) in CBF AML

with improved results in terms of relapse-free survival (RFS) and overall survival (OS) [8–11]. Despite these new and more effective induction regimens, without further consolidation or stem cell transplantation, the risk of relapse remains high. This highlights the need for consolidation for patients treated with curative intent. Here, we will review the current options for consolidation therapy, with the aim of clarifying which patient groups benefit most from each approach.

Which Post-Remission Therapy to Choose?

In fit patients, the decision between the post-remission therapies depends mainly on the risk-benefit ratio (non-relapse mortality [NRM] vs. relapse incidence). This will be mainly determined by cytogenetic and molecular features present at diagnosis [8]. However, the development of highly sensitive techniques to measure residual disease has allowed us to redefine the risk of relapse after induction and during treatment [8, 12]. Donor availability for related or unrelated allogeneic transplantation and patient fitness/co-morbidity are also critical factors for post-remission decision-making between transplant or not.

Chemotherapy

Patients with lower risk of relapse who achieve CR after induction (regardless of measurable residual disease – MRD status) are usually consolidated with intermediate or high doses of cytarabine (HDAC) [8, 13]. In 1994, the Cancer and Leukaemia Group B (CALGB) 8525 trial was the first evidence of the benefit of high-dose cytarabine. 596 patients in CR were randomised to receive four courses of cytarabine at $100\text{ mg/m}^2/\text{day}$, $400\text{ mg/m}^2/\text{day}$ (continuous infusion over 5 days), or 3 g/m^2 (over a 3 h infusion each 12 h on days 1, 3, and 5). Despite a high toxicity, there was a clear benefit of HDAC in terms of OS and DFS compared to lower doses of cytarabine [14].

In order to improve toxicity and reduce the risk of relapse, different groups have investigated the optimal dose of cytarabine for consolidation. The HOVON-SAKK trial compared intermediate (6 g/m^2 plus amsacrine) to high (16 g/m^2) total dose of cytarabine in the first consolidation after remission. They found no differences in OS nor incidence of relapse, with longer hospitalisation and a delayed neutrophil recovery in the HDAC group [15]. Also in 2011, the Study Alliance Leukaemia (SAL) in the AML96 study published a comparison of 12 g/m^2 versus 36 g/m^2 (total dose) of cytarabine as first consolidation. Again, there were no

differences in outcomes regardless of cytarabine dose [16].

Later, the UK MRC AML15 trial compared intermediate-dose cytarabine (IDAC) ($1.5\text{ g/m}^2/12\text{ h}$ on days 1, 3, and 5) to HDAC ($3\text{ g/m}^2/12\text{ h}$ on days 1, 3, and 5). They found a trend to a higher relapse incidence with intermediate compared to high dose (60% and 51%, respectively, $p = 0.06$), but there was no OS benefit from HDAC [17].

A 2017 meta-analysis of ten studies compared consolidation with low-intermediate (defined as a total dose lower than 20 g/m^2) against high-dose cytarabine. This review corroborated the similar outcomes regardless of cytarabine consolidation dose [3]. Thus, the intermediate cytarabine dose of 1.5 g/m^2 administered in 6 doses (total dose of $9\text{ g/m}^2/\text{cycle}$) was established as a less toxic schedule reporting similar outcomes [3, 8].

Regarding the potential benefit of HDAC versus IDAC in favourable-risk AML, there are inconsistent results across studies. The UK MRC AML15 trial did not find a significant benefit on OS of HDAC (HR: 0.68; 95% CI: 0.34–1.38) [17], although there was a trend for a reduced risk of relapse in patients with favourable-risk cytogenetics. In the Magnini et al. [3] meta-analysis, only favourable-risk AML appeared to benefit from HDAC with an improvement in RFS (HR: 0.57; 95% CI: 0.33–0.99) but not OS. These data are also supported from bigger retrospective studies such as the German SAL-AML registry, which did not find differences on outcomes regardless of cytarabine dose [18]. Some small retrospective studies report a benefit of HDAC over IDAC, with a significant benefit on 3-year OS (90 vs. 60%, $p < 0.01$), 3-year EFS (68 vs. 38%, $p < 0.01$) and a lower 3-year incidence of relapse (22 vs. 59%, $p < 0.01$) [19]. Overall, there is a lack of evidence on the optimal dose of cytarabine in favourable-risk AML (including *NPM1^{mut}* AML). Our own policy carried into the NCRI AML19 trial has been to apply 2 courses of HDAC as consolidation in these patients with excellent results [20]. As of writing, there is only one clinical trial registered (ClinicalTrials.gov Identifier: NCT02416388) comparing HDAC to IDAC in a multiple randomisation trial alone or associated with venetoclax or vosaroxin.

Days of Cytarabine

There is uncertainty about when IDAC should be optimally delivered. The most common schedule as defined in previous reports is the dose of $1\text{--}1.5\text{ g/m}^2$ every 12 h on days 1, 3, and 5 (total of 9 g/m^2) (HDAC-135).

Two studies evaluated a condensed schedule on days 1, 2, and 3 (HDAC-123) in patients younger than 60 years

old. The German-Austrian Acute Myeloid Leukaemia Study Group (AMLSG) was the first group to compare the condensed schedule against the standard cytarabine dose. The review included 568 patients from two prospective trials (the German AML Intergroup and AMLSG 07-04 protocols). They found no difference in any survival endpoint between HDAC-123 and HDAC-135, proving a faster neutrophil recovery associated to the HDAC-123 arm and pegfilgrastim administration [21].

A multicentre retrospective study compared a total dose of 18 g/m² delivered on 3 consecutive days (HDAC-123) to the 5 days schedule (HDAC-135) in 221 patients. They reported no differences in relapse incidence or OS, a reduction in hospitalisation stay (by 9 days) and length of neutropenia (by 4 days) in the HDAC-123 group [22].

More recently, the safety and efficacy of condensed intermediate (1.5 g/m²) dose cytarabine (AC-123) have been reported in a study that included 32/90 (33%) patients older than 60. Patients in the AC-123 arm had deliberately longer intervals between cycles than those in the AC-135 arm (6–8 weeks and 4–6 weeks, respectively). They reported no difference in survival between AC-123 and AC-135 when using G-CSF support but significantly quicker haematological recovery in the AC-123 group [23].

Number of Consolidation Cycles

As discussed earlier, the 1994 CALGB study first established the benefit of HDAC consolidation. The next question was: how many consolidation courses are needed? Delivering more courses may result in a deeper response and longer remission but may also cause greater toxicity. Since its publication, the four consolidation cycles used in the CALGB study have become widespread practice. Relatively few studies have sought to determine the optimal number of consolidation cycles. The Finnish group conducted a prospective study of 248 patients in CR after 2 inductions, comparing 2–6 consolidation courses. The shorter arm consisted of 2 HDAC courses, and the longer one had 3 HDAC courses and 3 with multiple drug combinations. Only 28/53 (52%) patients allocated to receive 6 consolidations completed them, with most withdrawals due to toxicity. Five-year DFS in the short consolidation group was 40%, compared to 35% in the long one [24]. This study was one of the first to highlight that fewer consolidation cycles could be sufficient to sustain remission.

In the following years, the CALGB 9222 study compared 3 courses of HDAC to an intensified regimen containing HDAC (1st course), etoposide and cyclophosphamide (2nd course), and diaziquone and mitox-

antrone (3rd course). 118/153 (77%) patients completed the 3 courses of HDAC, no differences in DFS or OS were found between groups. 5-year DFS was 35% (95% CI: 27–42%) in the HDAC group [25]. With similar results, the Japanese group described no differences in outcomes between 3 courses of HDAC (2 g/m² twice daily for 5 days) and 4 courses of multi-agent chemotherapy. They also report an improved 5-year DFS in the favourable cytogenetic group with HDAC (54% vs. 39%, $p = 0.05$) [26].

In the UK MRC AML15 trial, after completing two induction courses, patients were randomised to receive two or three cytarabine consolidation courses comprising HDAC × 2 or IDAC × 2; the third course was IDAC if randomised [17]. The 3rd course provided no survival advantage overall or for any subgroup and was possibly detrimental in older patients [17]. In a retrospective analysis, the 54 patients who received two FLAG-Ida inductions without consolidation had a similar survival to those who received two courses of DA and two consolidations [17]. These results are being tested in the NCRI AML19 trial (ISRCTN78449203).

In the subsequent NCRI AML 17 trial, non-adverse risk patients in CR after 2 courses of induction therapy were randomised to receive 1 versus 2 consolidation courses with either HDAC (3 g/m² × 6 doses) or multi-agent chemotherapy [27]. Patients given two courses (i.e., a total of four courses) had a reduced cumulative incidence of relapse and an improved RFS. Although there was a difference in favour of 2 courses of consolidation at 5 years (63% vs. 56%) with respect to survival, this was not statistically significant, but the trend to benefit of the 3rd was most clearly seen in those receiving HDAC. Patients with more favourable characteristics appeared to benefit from the 4th course, whereas those with intermediate-risk did not, although these were only trends for benefit [27].

More recently, results from the UK NCRI AML19 in *NPM1* mutated patients treated with 2 courses of FLAG-Ida-GO who were *NPM1* MRD negative in the peripheral blood [28] had a similar OS and RFS independently of the number of consolidations (zero, one, or two) in a non-randomised comparison [29].

It would therefore seem reasonable to deliver no more than two high-dose cytarabine consolidations (3 g/m²/dose), as more courses may cause additional toxicity. There is currently insufficient published evidence to establish the optimal number of IDAC (1–1.5 g/m²/dose) consolidation cycles required, although our approach is to limit to 2 courses, particularly in older patients [17]. An important consideration is that many of the studies

quoted here used double induction approaches, and care has to be given in extrapolating these findings to patients receiving a single induction [24, 30]. Indeed, the recent European *LeukemiaNet* (ELN) 2022 guidelines recommend 3–4 cycles of IDAC (1–1.5 g/m² every 12 h on days 1, 2, and 3), which can be reduced in patients older than 60 years to 0.5–1 g/m² [8, 30].

New Drugs Included during Consolidation

Low-Dose Chemotherapy

The combination of venetoclax both with azacitidine (AZA) or low-dose cytarabine (LDAC) has demonstrated good results in elderly patients, unfit for IC [31, 32]. Two retrospective studies have compared IC to azacitidine-venetoclax (AZA-VEN). In the first study, patients receiving IC had an improved OS compared to those who were treated with AZA-VEN. However, in a propensity score matching model, patients older than 65 years or those in the ELN adverse group benefited the most from AZA-VEN [33]. The second study highlighted that there are many confounding factors when making these comparisons. Patients treated with IC had a longer OS, but more adverse risk patients received AZA-VEN compared to IC (53% vs. 31%) [34].

These studies raise an important question: could some young patients benefit from a less intensive treatment or consolidation? As we have seen in the previous studies, not all patients initially fit to receive intensive chemotherapy are able to complete the entire consolidation. This may be due to accumulated toxicity, infections, or complications derived from therapy. There are some case reports about the efficacy of AZA in the treatment of patients becoming unfit for further intensive consolidation due to toxicity from prior induction chemotherapy [35]. The combination of venetoclax and low-dose chemotherapy has demonstrated remarkable efficacy in *NPM1*-mutated AML, with CR/CRi rates of 93% in first-line treatments and MRD negativity reached in 4/4 patients monitored [36]. In patients treated at MRD relapse, MRD negativity rates are between 78 and 92% [37–39]. These good results in favourable-risk patients (particularly *NPM1*-mutated *FLT3* wild type) [31, 40, 41] have motivated an ongoing clinical trial in this subgroup comparing intensive chemotherapy (DA + GO, DA and 2 HDAC consolidations) with 12 cycles of LDAC+VEN (EudraCT: 2020-000,273-24) [42]. Incorporation of venetoclax at consolidation combined with LDAC (50 mg/m²/12 h, days 1–5) is also being explored in the LAMSA2020 clinical trial (NCT04968015).

Maintenance Therapy after Intensive Consolidation

After achieving CR with induction and consolidation chemotherapy, relapse is the factor with the greatest impact on survival. Even after significant advances in recent years, relapse rates in patients over 60 years are still high [43, 44]. Allogeneic transplantation is a feasible option to reduce the risk of relapse, and in many cases, the risk-benefit balance favours it [45]. However, patients with comorbidities that make them unsuitable for allogeneic transplant after intensive chemotherapy may benefit from maintenance [44].

Previous studies [46] explored the efficacy of maintenance compared to consolidation, but the 1994 CALGB trial was the first to include a maintenance therapy (defined as a less toxic and time-limited treatment after induction and consolidation that aims to reduce the risk of relapse) [8]. This study used four cycles of standard-dose cytarabine (200 mg/m² on days 1–5) and a single dose of daunorubicin (45 mg/m²). 79% of the 383 patients completed all four courses, 26% of them requiring hospitalisation due to treatment-related complications. The ineffectiveness of this intervention led to its elimination from further trials [14].

Studies evaluating maintenance with interleukin-2 (IL-2) did not show a significant impact on relapse rates [47, 48]. However, a combination of low-dose IL-2 and histamine dihydrochloride was approved by the European Medicines Agency (EMA) in 2008 as an orphan drug. Improvement of leukaemia-free survival was reported with this combination, although no benefit on OS was demonstrated [49, 50]. Treatment-related adverse effects have been a pitfall in the development of other maintenance therapies, such as gemtuzumab ozogamicin [51].

AZA and Oral AZA (CC-486)

Following early results of AZA in the treatment of older adults with myelodysplastic syndrome and AML [52, 53], post-remission maintenance in this population was explored. Maintenance with subcutaneous AZA showed an improvement in DFS (AZA vs. observation; 2-year DFS: 44% and 32%, respectively; $p = 0.04$). However, the toxicity and lack of benefit on OS limited its application [54, 55].

The effectiveness of oral AZA (CC-486), which has a different pharmacologic profile than its injectable counterpart, was previously explored in AML and myelodysplastic syndrome [56, 57]. In the QUAZAR-AML-001 trial, patients not candidates for haematopoietic stem cell transplantation (HSCT) were randomised to maintenance with CC-486 versus placebo. Treatment was administered from days 1 to 14 in 28-day

cycles until more than 15% blast were present or unacceptable toxicity occurred. A survival benefit of CC-486 treatment was observed with a median OS of 22.7 months (vs. 14.8 in the placebo group, $p < 0.001$), irrespective of previous consolidation courses [58] and MRD status prior to maintenance [59]. A post hoc analysis evaluating the impact of *NPM1* and *FLT3* mutations revealed a particular benefit in patients harbouring *NPM1* mutation [60]. It must be noted that the adverse risk group may be underrepresented (14% in the trial) in a population of adults over 55 years of age, and patients with CBF AML were excluded [61].

Results from the QUAZAR-AML-001 trial must be interpreted cautiously, as the range of induction and consolidation cycles was heterogeneous to consider CC-486 as a maintenance. At least 20% of patients included did not receive any consolidation, and 76% received 1 or 2 cycles. A more recent sub-analysis of the clinical trial reports a significant benefit of CC-486 over placebo in patients who received no consolidation (HR: 0.55, 95% CI: 0.34–0.89) and only a trend toward a benefit in those who received any consolidation (HR: 0.76, 95% CI: 0.60–0.97) [62]. Overall, there is not enough evidence to recommend CC-486 as maintenance in patients who have received adequate consolidation [63].

Oral AZA (CC-486) received FDA and EMA approval as maintenance for patients in CR unable to complete intensive curative therapy. Under these terms, oral AZA represents a feasible maintenance treatment for selected populations, but it should not replace consolidation therapy in those patients who can receive it [64]. As of date, there are 2 ongoing clinical trials (NCT05413018 and NCT05197426) evaluating CC-486 as maintenance, both of them after induction or consolidation.

Post-Remission Therapy with FLT3 Inhibitors

Mutations in the *FLT3* gene are common in AML with internal tandem duplications (ITD) and TKD mutations present in 27% and 7% of patients, respectively, at diagnosis [28]. ITD mutations are associated with a high relapse risk and a worse OS [63], and TKD mutations have no impact on outcomes [61].

Midostaurin

In the RATIFY trial, patients younger than 60 were randomised to receive placebo or midostaurin (a tyrosine kinase inhibitor, TKI) plus standard chemotherapy, consisting of DA induction and 4 HDAC consolidations. 12 months of midostaurin maintenance was also given to patients not undergoing transplantation. 232/441 patients (53%) completed all consolidations of HDAC +/- mid-

ostaurin. Patients randomised to midostaurin had a significantly improved OS (HR: 0.78, 95% CI: 0.63–0.96) and DFS [6, 7]. The AMLSG 16-10 study confirmed the benefit of adding midostaurin in older patients compared with a historical control cohort. In this study, only 83/440 patients (19%) received at least one consolidation with HDAC, as allograft was intended in all patients achieving CR after induction [65]. Retrospective studies have shown the real-life benefit of the addition of midostaurin to intensive treatment in patients with *FLT3*-mutated AML [66, 67].

Two studies have evaluated the maintenance with midostaurin after consolidation, both of them previously mentioned. The RATIFY trial included per protocol a maintenance after consolidation, consisting of 12 × 28-day cycles. 120 out of 355 (36%) patients received midostaurin as maintenance, but the trial was not designed to determine the specific effect of maintenance [6, 8]. Although the RATIFY trial led to the approval of midostaurin by both the FDA and EMA during induction and consolidation, only the EMA granted approval for maintenance. A later analysis did not allow conclusions on the benefit of midostaurin maintenance [68]. In the AMLSG 10-16 trial, 35/83 (42%) patients received midostaurin maintenance after HDAC. Although tolerability was better after HDAC than after allograft, 36% of patients experienced grade 3 or higher toxicities [65, 69]. Midostaurin was, until the approvement of quizartinib, the only *FLT3* inhibitor approved by the FDA in induction and consolidation; however, other agents are in development and may soon become available in the clinical setting [6, 8].

Sorafenib

Sorafenib, a first generation type II *FLT3* inhibitor (which can inhibit activation in *FLT3*-ITD but not TKD mutations), showed promising results as an off-label compassionate treatment in relapsed/refractory AML [62, 70]. In patients younger than 60 years, the SORAML trial evaluated the benefit of adding sorafenib to standard chemotherapy and a later maintenance. This study demonstrated a significant benefit of sorafenib compared to placebo on RFS (HR: 0.61, 95% CI: 0.44–0.87) and EFS (HR: 0.57, 95% CI: 0.35–0.92), without a benefit on OS. More patients relapsed after 5 years in the placebo group (50%) compared to sorafenib (36%, $p = 0.087$), and 61/70 (87%) relapsed patients received allo-HSCT. A higher relapse incidence after HSCT in CR2 was reported in the sorafenib group (HR: 2.03, $p = 0.078$), explained by lower CR rates after salvage in patients previously exposed to sorafenib. The addition of sorafenib increased the

reported toxicity, limiting continuation of treatment in some cases. The clinically meaningful activity of *FLT3*i was demonstrated, although the results did not support the addition of this agent to first-line protocols [71, 72].

The SORAML trial included a 12-month maintenance with sorafenib or placebo only in those patients who did not proceed to HSCT. However, the final analysis could not determine the isolated effect of the maintenance phase on outcomes [71, 72].

Quizartinib

Recently, the QuANTUM-First trial demonstrated the efficacy of quizartinib in combination with standard chemotherapy. A major difference with the RATIFY trial was patient age: 216/539 patients (40%) were aged 60–75 years, adjusting cytarabine consolidations to a dose of 1.5 g/m² per dose in these patients. 187/539 patients (35%) were allografted. The study reported a benefit on OS in the whole cohort of adding quizartinib (HR: 0.78, 95% CI: 0.62–0.98). The post hoc subgroup analysis did not report a benefit on OS in patients older than 60 years, but the study was not powered to detect these differences between groups [73]. In the QuANTUM-First trial, a 36-month maintenance phase (called “continuation therapy” in the study) with quizartinib versus placebo was planned. 201/533 (38%) of patients initiated the continuation phase. Results regarding the efficacy of this intervention are yet to be published [73].

Other Therapies

Maintenance with other therapies such as androgens has led to some provocative results. The GOELAMS group conducted a randomised trial evaluating post-induction oral norethandrolone maintenance versus observation in patients older than 60 years. They reported a significant benefit of androgens on 5-year DFS (31.2% vs. 16.2%) and 5-year OS (26.3% vs. 17.2%) compared to observation. Maintenance with androgens was planned to last 2 years, possibly explaining the benefit in patients who were at CR after 1 year. No benefit was observed in patients presenting with a WCC >30 × 10⁹/L [74]. These findings would benefit from confirmatory studies. The combination of venetoclax and CC-486 is being evaluated as post-consolidation maintenance in patients not eligible to HSCT in the VIALE-M trial (NCT04102020).

Consolidation prior to Allogeneic Transplantation

An important question is how many consolidation cycles should be delivered prior to allogeneic transplantation. It should be noted that until haploidentical

transplantation became available, the difficulty in finding a compatible donor was greater, and few patients had a donor prepared after induction. Therefore, the option of 1 or 2 consolidation cycles prior to allo-HSCT may be necessary to prevent relapse while searching for a suitable donor. However, there is a balance between preventing relapse and avoiding excess toxicity which might in turn delay the transplant.

A retrospective study of patients transplanted in MRD-negative CR1 found a benefit of consolidation on OS and in reduction of relapse (HR: 0.50; 95% CI: 0.27–0.92) [75]. Other reports show that delivering a consolidation cycle compared to proceeding directly to allo-HSCT does not impact the outcomes, irrespective of conditioning intensity [76, 77]. A meta-analysis published in 2018 shows that post-remission consolidation prior to allogeneic transplant does not affect OS or relapse incidence [78]. Therefore, patients should proceed to allo-HSCT as soon as possible after reaching CR unless guided by MRD results [8, 78].

A key question is whether pre-transplant consolidation should be pursued or indeed intensified to try to achieve negative MRD prior to transplant [79]. There are discrepant results regarding the impact of intensified pre-transplant consolidation, and no studies to date directly address MRD; hence, no clear recommendation can be made about this issue.

Eradication of MRD prior to Allogeneic Transplantation

Multiple studies have concluded that pre-transplant positive MRD (assessed by multiparameter flow cytometry or RT-qPCR) is independently associated with a higher relapse incidence and lower survival [80–84]. There is a growing evidence that intervening MRD prior to haematological relapse may lead to better outcomes [37, 39, 85–88]. Some studies have evaluated the treatment of molecular failure (monitored by RT-qPCR for fusion genes or *NPM1*) including some patients prior to allo-HSCT [85].

Othman et al. [86] reported outcomes in 56 patients treated for molecular failure with *FLT3* inhibitors in monotherapy. Among them, 30% had received a prior HSCT, and 52% had previously been treated with *FLT3* inhibitors. A reduction in MRD was achieved in 32/53 (60%) patients and MRD negativity in 45%. Twenty-two patients were successfully bridged to allo-HSCT, with a 2-year OS in the whole cohort of 80% [86].

Recent evidence proves that detectable MRD in *NPM1^{mut}* AML can be successfully cleared with venetoclax combined with low-intensity chemotherapy (AZA, decitabine, or LDAC) [37, 87, 88]. In recent

reports, patients treated for MRD failure achieved MRD negativity rates of 71–92% [37, 85, 87], with venetoclax combinations being an interesting option as a bridge to allo-HSCT in molecular failure of *NPM1*^{mut} AML [85, 87, 88].

In the upcoming years, addressing of MRD and treatment options will be a relevant issue. The Australasian Leukaemia and Lymphoma Group (ALLG) AMLM26 INTERCEPT trial (ACTRN12621000439842) will explore a wide range of targeted drug combinations against MRD [89].

Stem Cell Transplantation

Autologous Stem Cell Transplantation

Autologous stem cell transplantation (ASCT) still has a role in some favourable- and intermediate-risk AML patients who achieve MRD negativity after induction [8, 90–93]. The main drawbacks of ASCT are the higher risk of relapse compared to allogeneic HSCT and that poor mobilisation after chemotherapy may compromise stem cell collection. ASCT has a NRM of less than 10% and, compared to consolidation with 3 cycles of HDAC, is associated with fewer hospitalisation days and better tolerability [94, 95]. In recent years, fewer ASCTs are indicated in AML as a consequence of increased donor availability due to haploidentical and unrelated transplants.

Allogeneic Stem Cell Transplantation

Allogeneic stem cell transplantation (allo-HSCT) is the post-remission therapy of choice for many patients with intermediate or adverse cytogenetic risk [8, 96]. It has been proposed and is widely accepted that allogeneic HSCT should be considered when based on cytogenetics and MRD clearance, the risk of relapse without transplantation is greater than 35–40% [97, 98]. In general, patients with favourable-risk and intermediate-risk disease with negative MRD can be consolidated with chemotherapy. However, the dynamics of MRD clearance have a clear impact on prognosis. Patients with *NPM1*^{mut} AML who have a reduction lower than 4 log of *NPM1* transcripts after induction or positive peripheral blood MRD assessed by RT-qPCR have a higher incidence of relapse and benefit from intensified treatment with allo-HSCT [28, 99]. Patients without adverse risk factors and *NPM1* wild type with detectable MRD assessed by multiparameter flow cytometry also benefit from transplant in first CR [100].

Regarding the most appropriate approach for intermediate-risk AML, in the ETAL-1, trial patients in first CR were randomised to consolidation with HDAC or allo-HSCT. Interestingly, patients had a similar OS irrespective of consolidation with HDAC or allo-HSCT (2-year OS of 84% vs. 74%, respectively). Nonetheless, allo-HSCT was associated with a lower 2-year relapse incidence than HDAC (20% vs. 58%, $p < 0.001$), but patients relapsing after HDAC consolidation were salvaged to IC and subsequent allo-HSCT, explaining the similar OS between consolidation and allo-HSCT in CR1. This study concludes that this population may not benefit from allogeneic HSCT in CR1 and may be salvaged at relapse but with higher cumulative chemotherapy toxicity. Importantly, transplants were reduced overall, proceeding to allo-HSCT 41/67 (62%) patients in the consolidation group [101].

After risk of relapse, NRM, influenced by the patient's comorbidities, is the other main factor limiting survival. To estimate transplant-associated NRM, we rely on tools that have been tested and validated in the allo-HSCT setting [102, 103].

Conditioning Intensity

Myeloablative conditioning (MAC) was associated with high treatment-related mortality in patients older than 40–50 years [104]. The development of reduced-intensity conditioning (RIC) has made allogeneic HSCT a feasible option for older patients and those with comorbidities. Theoretically, MAC has a higher treatment-related mortality than RIC, which would be offset by a lower relapse rate. Which conditioning is most appropriate for which patient is still a matter of debate. Major prospective randomised trials did not find a significant difference in relapse incidence or OS between RIC and MAC in patients with AML [105, 106]. Nonetheless, in the BMT CTN 0901 Clinical Trial, patients younger than 65 years who received RIC instead of MAC had a higher relapse incidence (HR: 4.06, 95% CI: 2.59–6.35), a lower OS and RFS but a significantly lower 4-year transplant-related mortality (9.9 vs. 25.1%) [107, 108]. Few studies have reported pre-transplant MRD, but retrospective data show that those patients in CR1 with negative MRD have similar outcomes irrespective of conditioning intensity [109–111]. However, RIC regimens appear less likely to clear a positive pre-transplant MRD than MAC [82].

In conclusion, randomised trials are needed to determine the optimal conditioning for the MRD clearance and the potential impact of MAC in this setting. Overall,

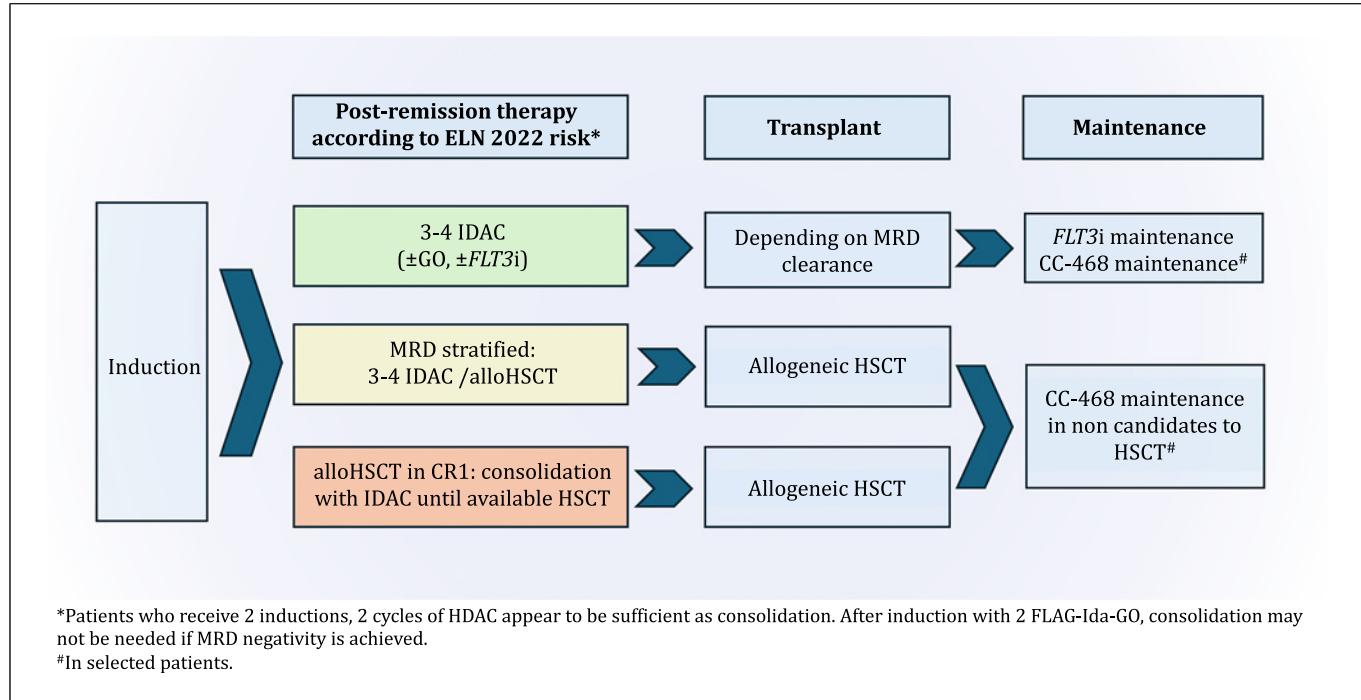


Fig. 1. Recommendations of post-remission therapy in fit patient candidates to IC.

MAC should be the preferred regimen for patients in CR1 younger than 55 years, and it should be prospectively addressed whether those who achieve negative MRD could avoid some toxicity by receiving RIC [98, 109]. Regarding allo-HSCT in patients older than 70 years, retrospective studies report the feasibility of this approach in selected patients in first remission, but prospective trials are needed to clarify the benefit in this population [112].

Conclusion

When considering the optimal post-remission treatment for patients with AML, careful assessment must be made of the risk of relapse and potential treatment-related mortality. These factors determine whether patients should receive consolidation with cytarabine or proceed to HSCT.

Those consolidated with chemotherapy should receive either 2 courses of HDAC or no more than 3–4 cycles of IDAC with dose reduction in patients over 60 years. There is no clear survival benefit for HDAC compared to IDAC in favourable-risk AML, although relapse appears reduced. For patients treated with double induction

protocols, 2 cycles of high-dose for those treated with intensified double induction, such as FLAG-Ida-GO, consolidation may not be needed at all for those achieving molecular CR (Fig. 1).

In recent years, multiple treatment options targeting MRD are emerging, either as definitive treatment or as a bridge to allogeneic transplantation. These options will be explored in the near future and are likely to become increasingly relevant.

Patients at higher risk of relapse should proceed to allogeneic HSCT as soon as possible, opting for a more intensive conditioning (MAC) in patients younger than 55 years. However, autologous HSCT may still have role in favourable-risk MRD-negative AML.

The benefit of maintenance after consolidation of midostaurin (in *FLT3*-mutated AML) has been established. Maintenance with CC-468 should be considered in selected patients not fit for adequate consolidation and should not replace the established consolidation cycles.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.J.C., R.D., and N.R. wrote and approved the final version of the manuscript.

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