Update on Optimal Management of Acute Myeloid Leukemia

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Review

Update on Optimal Management of Acute Myeloid Leukemia

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Abstract: Acute myeloid leukemia (AML) represents a malignant accumulation of immature myeloid cells in the marrow, presenting with impaired hematopoiesis and its attendant complications, including bleeding, infection, and organ infiltration. Chromosomal abnormalities remain the most powerful predictors of AML prognosis and help to identify a subgroup with favorable prognosis. However, the majority of AML patients who are not in the favorable category succumb to the disease. Therefore, better efforts to identify those patients who may benefit from more aggressive and investigational therapeutic approaches are needed. Newer molecular markers aim at better characterizing the large group of intermediate-risk patients and to identify newer targets for therapy. A group that has seen little improvement over the years is the older AML group, usually defined as age ≥ 60. Efforts to develop less intensive but equally efficacious therapy for this vulnerable population are underway.

Keywords: AML, management, prognosis

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Introduction

Acute myeloid leukemia (AML) is a clonal malignant proliferation of myeloid blast cells in the marrow with impaired normal hematopoiesis. AML occurs at an approximate rate of 3 cases per 100,000 individuals per year, causing 1.6% of cancer deaths. According to 2006 estimates, there were 11,930 new cases of AML and 9,040 AML-related deaths in the United States. The median age of individuals with newly diagnosed AML continues to increase and averages 66–68 years. There generally is no identifiable predisposing cause of AML. However, there are an increasing number of AML cases following exposure to cytotoxic therapy to treat carcinomas or benign conditions (termed therapy-related AML). In addition, AML can arise as the terminal phase of antecedent hematological disorders, such as myelodysplastic syndromes or myeloproliferative disorders. This fact, coupled with an increasing age at diagnosis, can pose significant challenges in the management of AML.

AML Classification

The French-American-British (FAB) system of AML classification, proposed in the late 1970’s, relied on morphologic features, which were not consistently predictive of clinical behavior. The World Health Organization (WHO) proposed a more relevant classification scheme, which focused on characteristics with prognostic value. WHO categories include AML with recurrent cytogenetic abnormalities, those with translocation (15;17), the core binding factor leukemias [(CBF), translocation (8;21), inversion 16, or translocation (16;16)], and translocations involving the mixed lineage leukemia (MLL) gene on chromosome 11. AML with dysplasia with or without an antecedent myelodysplastic syndrome, treatment-related AML and AML not-otherwise-specified constitute the remaining categories. 2 Other major differences between the FAB and the WHO classifications are the threshold for AML diagnosis (30% vs. 20% blasts, respectively) and the fact that acute promyelocytic leukemia (APL) and CBF AML are defined as AML based on the chromosomal abnormality regardless of the blast percentage. Although the FAB classification is still utilized in some clinical trials, it has been largely supplanted by the WHO classification.

Predictors of Prognosis

Karyotype

Cytogenetic abnormalities remain the most powerful predictors of outcome and are essential in guiding AML treatment decisions. The importance of chromosomal abnormalities in AML was established by the Medical Research Council (MRC) AML 10 trial, which included cytogenetic information at diagnosis on 1,612 children and adults up to 55 years of age with newly diagnosed AML. This data was recently updated by Grimwade et al, based on analysis on 5876 patients treated on the MRC 10, 12, and 15 trials. Specifically, their report clarifies the significance of rare re-occurring chromosomal abnormalities in a large cohort of patients age 16–59. The South Western Oncology Group (SWOG) and the Medical Research Council (MRC) cytogenetic risk groupings are the most commonly utilized risk categories in the United States. Table 1 describes the differences between these systems. The core binding factor leukemias and APL comprise the favorable risk group with an estimated 10-year overall survival (OS) of 55%–81%. Those in the intermediate risk category had a 10-year OS of 30%–40%, and 10-year OS for the adverse risk category was 8%–20%. In addition, the poor impact of monosomal karyotype on AML prognosis, as defined by Breems et al, was also demonstrated in recent trials.

Molecular markers

Much attention has recently been focused on incorporating molecular markers into the prognostic classification of AML. A few of these markers have been incorporated into the routine evaluation of newly-diagnosed AML, as knowledge of the presence or absence of these markers allows clinicians to better identify patients at increased risk of relapse who may benefit from more intensive and curative treatments, such as early allogeneic bone marrow/stem cell transplantation or inclusion onto clinical trials of molecularly targeted agents. These mutations may also play a role in the early detection of minimal residual disease during treatment and follow-up of AML. C-kit is a proto-oncogene that encodes a transmembrane tyrosine kinase receptor and has been implicated in leukemogenesis. Mutations in the c-kit gene are detected in approximately 20%–40%
of CBF AML. In addition, they occur most frequently within exon 17, which encodes the activation loop in the kinase domain, and in exon 8, which encodes the extracellular portion of the kit receptor. Finally, their presence portends a poor prognosis for patients with CBF AML.13–15 Specifically, among patients with t(8;21), kit mutations were associated with higher marrow blast percentage, shorter overall survival (OS), event-free survival (EFS), and shorter time-to-relapse than those without kit mutations. The 5 year OS for adult patients with t(8;21) harboring exon 17 c-kit mutations was shorter than for those without mutations (27% vs. 61%).15 The prognostic effect of kit mutations among pediatric CBF AML has not been clearly established.15,16 Among patients with inv(16), data on the prognostic impact of c-kit mutations has been less consistent.14,15 Therefore, it is reasonable to recommend a risk-adapted approach to the management of AML with t(8;21) based on the presence or absence of c-kit (exon 17) mutations.

Among the cytogenetically normal group of AML (CN-AML), several molecular abnormalities have prognostic implications. Those include point mutations or internal tandem duplication (ITD) in the FMS-like Tyrosine Kinase 3 (FLT3) gene, which confer a prognosis similar to that of AML with adverse risk cytogenetics.17–19 Isolated mutations in the nucleophosmin (NPM1) gene and the CCAAT/enhancer binding protein α gene (CEPBA) confer a favorable prognosis.20,21 Among CN-AML, compared to NPM1 wild type, NPM1 mutations (in the absence of FLT3 mutations) independently predict for higher CR rates (84% vs. 48%, P < 0.001), longer DFS (23% at 3 years vs. 10%, P = 0.004), and longer OS (3 year rates of 35% vs. 8%, P < 0.001).22 CEBPA mutations were also identified as independent indicators of favorable prognosis, even after adjusting for cytogenetics and FLT3 status, with an estimated 5-year OS of 53% vs. 25% for unmutated CEBPA (P = 0.04).23 Patel et al reported the prognostic relevance of integrated genetic profiling in samples from 398 patients treated on the ECOG E1900 phase 3 clinical trial.24 In this trial, when compared to standard-dose daunorubicin (45 mg/m²), high-dose daunorubicin (90 mg/m²) improved the rate of survival among patients with mutated DNA (cytosine-5)-methyltransferase 3A (DNMT3A), NPM1, or MLL translocations.24 The use of mutational profiling is leading to re-classification of the subgroup of patients defined as having intermediate-risk AML, based on chromosomal analysis, and reassigns a significant number of them to the favorable or unfavorable-risk subgroups. Such efforts aim to more precisely define the heterogeneous group of AML patients with intermediate-risk cytogenetics and to better select those who may benefit from allogeneic transplantation in 1st complete remission as curative therapy. A summary of selected reported mutations to date is in Table 2.25–27 Evaluation of these molecular markers should be incorporated into the management of newly diagnosed AML.
The achievement of PCR negativity following induction therapy identified patients with an incidence of relapse of 6.5% at 4 years and an OS of 90%, compared to 53% and 51% for those with positive NPM1 mutations (detected by PCR) respectively ($P < 0.001$). Overexpression of the Wilms tumor (WT1) gene in AML has led to its use as a potential marker of MRD. However, its utility has been hindered by variability in performance of the assays evaluated to date. The European Leukemia Net (ELN) undertook a systematic evaluation of a range of published WT1 assays and established the basis for a highly sensitive assay, which could predict reduced relapse risk among subjects with greater WT1 transcript reduction after induction chemotherapy.

Detection of MRD is likely to become a standard endpoint in clinical trials.

Age and AML prognosis

The prognostic significance of age at the time of AML diagnosis has been well described. Most trials of induction and post remission therapy have focused on patients younger than 60 years of age, with good performance status. However, given that the age at diagnosis of AML is increasing, attention is shifting toward a focus on the older AML population. The combination of poor performance status and older age identifies a group of patients with extremely high induction-related mortality, while the effect of performance status tends to be less pronounced among the younger AML population.

Other prognostic factors

The white blood cell (WBC) count at time of AML diagnosis has variable prognostic significance. Patients with a white cell count exceeding 100,000 tend to have a higher risk of complications during induction therapy but a similar overall outcome when compared to patients with a WBC count less than 100,000 cells/mcL. In addition, hyperleukocytosis (WBC > 100,000) has been identified as a risk factor for central nervous system (CNS) involvement with AML. The significance of CNS involvement with AML has been debated, with some authors reporting a worse prognosis and others reporting no effect on AML prognosis. Pediatric regimens routinely utilize CNS prophylaxis while adult protocols do not. However, sampling of cerebrospinal...
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Risk stratification and management of AML

fluid and intrathecal prophylaxis should be considered in patients with AML and hyperleukocytosis. Extramedullary disease (EMD) in general has been associated with lower rates of CR and inferior long-term prognosis in adult AML when compared to those presenting without EMD. The development of AML in the setting of an antecedent hematological disorder or prior exposure to chemotherapy or radiation therapy has been associated with less favorable prognosis when compared to de-novo AML; however, this group of AML patients also tends to have less favorable cytogenetic abnormalities.

Obesity has been found to be a negative prognostic factor in pediatric AML. The Children’s Oncology Group (COG) found that body mass index (BMI) > 95th percentile was predictive of worse outcomes, with lower complete remission (CR), EFS and OS. However, the same effect has not been consistently demonstrated in adult AML. In fact, in a recent report, increased BMI was evaluated among 63 newly-diagnosed AML patients receiving induction chemotherapy. In that cohort, 33% of patients were obese (≥130% ideal body weight [IBW]). The authors found no significant effect of obesity on CR, OS, count recovery, or rates of non-hematological toxicity. In addition, CR rates were not significantly different between patients whose chemotherapy doses were not adjusted for IBW and those with dose adjustments (CR = 86% vs. 67%, P = 0.55). Le et al evaluated whether obesity affected outcomes of 329 adult patients who received high dose cytarabine-based regimens for induction. In this study, in which doses of chemotherapy were administered according to actual body weight, 1/3 of patients were obese, and BMI did not have a negative impact on OS or treatment-related complications.

Treatment Strategies

The treatment of AML has not significantly evolved over the last 2 decades, with curative treatment still dependent on effective induction therapy to achieve a complete remission and subsequent risk-adapted consolidation therapy to prevent relapse. Response to induction chemotherapy is substantial, with over 2/3 of younger adults and approximately 1/2 of older adults achieving complete remission. The challenge remains in keeping patients in remission, as relapse is expected in most of the responding patients, especially those without favorable cytogenetic/molecular features. The increased age at diagnosis of AML and the higher likelihood of the patient population to be frail, with borderline performance status makes delivering what is considered standard induction therapy more challenging. Thus, there is a predilection to divide therapy into intensive versus non-intensive regimens when approaching the older AML patient.

Induction therapy

Early trials by the Cancer and Leukemia Group B (CALGB) in the 1980’s established the “7 + 3” regimen consisting of cytarabine at a dose of 100 mg/m²/day by continuous infusion for 7 days and daunorubicin at a dose of 45 mg/m²/day for 3 days, as the standard induction regimen for newly diagnosed AML in the United States. This regimen led to remissions in 60%–80% of younger adults and 40%–60% of older adults. A decade later, we learned that idarubicin at 12/mg/m² was superior to the standard dose of daunorubicin for AML induction, especially among younger patients. The MD Anderson group performed a large retrospective analysis to compare the relative activity of combinations containing cytarabine and idarubicin without fludarabine or topotecan (IA) and those containing cytarabine with either topotecan (TA) or fludarabine (FA). This analysis included 1,279 patients treated for newly diagnosed AML, refractory anemia with excess blasts (RAEB) or RAEB in transformation (RAEB-t) at their center. Despite the limitations of a retrospective study, this large study revealed that IA combinations generally led to higher CR rates and better overall outcomes than the TA and FA combinations, albeit in a very heterogeneous population of patients.

Different modifications of the 7 + 3 regimen have been carried out, including intensifying the dose of cytarabine, changing the type or dose of anthracycline, and adding additional chemotherapeutic agents (Table 3). The Acute Leukemia French Association (ALFA) 9000 study was a randomized comparison of control “3 + 7” induction (daunorubicin 80 mg/m²/d for 3 days and cytarabine at 200 mg/m²/d by continuous infusion for 7 days), double induction (3 + 7 followed by mitoxantrone 12 mg/m²/d on days 20–21 and cytarabine at 500 mg/m² every 12 hours on days 20–22), and timed-sequential induction (daunorubicin 80 mg/m²/d and cytarabine at 500 mg/m²/d...
by continuous infusion on days 1–3, followed by mitoxantrone 12 mg/m²/d on days 8–9 and cytarabine at 500 mg/m² every 12 hours on days 8–10. Consolidation was similar, but dose was stratified according to patient age. Among 592 subjects, 449 (76%) patients obtained complete remission. EFS at 2 and 5 years was estimated at 20.5% and 19.4% respectively and OS was estimated at 45.4% and 29.8% at 2 and 5 years, with no significant difference among the 3 treatment arms.52

The subsequent ALFA-9801 evaluated the effect of high doses of daunorubicin (DNR at 80 mg/m²×3 days) or idarubicin (IDA4 at 12 mg/m²×4 days) with standard doses of idarubicin (IDA3; 12 mg/m²×3 days) for remission induction in patients with AML age 50–70. The complete remission rates were significantly higher for the Idarubicin groups when compared to the high dose daunorubicin group (83%, 78%, and 70% in the IDA3, IDA4, and DNR arms, respectively; P=0.04); however, no significant differences were observed in relapse incidence, EFS, or OS among the 3 arms.53 The MRC AML 12 trial addressed the question of optimal anthracycline for induction in pediatric AML and reported a remission rate of 92% (73% CR after Course 1 and 20% after Course 2) with no difference among treatment groups when using mitoxantrone or daunorubicin with cytarabine and etoposide. 10-year EFS and OS was 54% and 63% respectively and relapse risk was estimated at 35%. There was a benefit for using mitoxantrone with regard to relapse rate (32% vs. 39%; Hazard ratio (HR) 0.73) and disease-free survival (DFS; 63% vs. 55%; HR 0.72), but this benefit did not translate into better EFS or OS.54 The ECOG investigators recently published results of the E1900 clinical trial comparing daunorubicin at 90 mg/m² with the standard 45 mg/m² dosing for AML induction in patients age 18–60 years. The results revealed better OS in the favorable and intermediate cytogenetic groups with the higher doses of daunorubicin, with complete remission rates in 70% versus 57% respectively (P<0.001).55 In the unfavorable cytogenetic group, the overall survival was similar between the 2 dosing schemas. In AML patients, older than 60 years of age, escalating the dose of daunorubicin to 90 mg/m²/dose, with the entire dose administered in the first induction cycle, lead to a higher response rate (CR of 64% vs. 54%, P=0.002) when compared to the conventional (45 mg/m²/dose) dose, without additional toxicity. However, survival outcomes did not differ between the 2 dosing groups.56

### Post-remission therapy

It has been recognized since the 1970’s that additional chemotherapy is required in order to sustain initial remissions in AML.57,58 In the early 1980’s, the ECOG investigators conducted a randomized trial (EST 3483) comparing the effect of continuation of chemotherapy (consolidation or prolonged maintenance) with no further therapy in AML patients after the achievement of complete remission. Accrual to the “no further therapy” arm was halted after the interim analysis discovered that all the patients in the “no further therapy” arm had relapsed by a median of 4 months.59 Subsequently, the final analysis of the EST 3483 trial revealed that a single course of consolidation or allogeneic transplantation (patients...

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**Table 3. Treatment regimens for AML.**

<table>
<thead>
<tr>
<th>Study group</th>
<th>Regimen</th>
<th>Patients</th>
<th>CR (%)</th>
<th>Survival (m)</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALGB135</td>
<td>ARA-C/dauno 45–60 mg/m²</td>
<td>668</td>
<td>68</td>
<td>10</td>
<td>1987</td>
</tr>
<tr>
<td>ECOG136</td>
<td>ARA-C/ida (7 + 3)</td>
<td>214</td>
<td>70 vs. 59</td>
<td>12.9 vs. 7.8</td>
<td>1992</td>
</tr>
<tr>
<td>SWOG137</td>
<td>HDAC + dauno vs. DA</td>
<td>665</td>
<td>55 vs. 58</td>
<td>NR</td>
<td>1996</td>
</tr>
<tr>
<td>MRC AML 1572</td>
<td>Standard induction ± GO</td>
<td>1115</td>
<td>85 vs. 85</td>
<td>NR</td>
<td>2006</td>
</tr>
<tr>
<td>ECOG 190055</td>
<td>Dauno 90 vs. 45 + ARA-C</td>
<td>657</td>
<td>70 vs. 57.3</td>
<td>23.7 vs. 15.7</td>
<td>2009</td>
</tr>
<tr>
<td>HOVON/SAKK138</td>
<td>HDAC vs. ARA-C</td>
<td>860</td>
<td>82 vs. 80</td>
<td>42 vs. 40*</td>
<td>2011</td>
</tr>
<tr>
<td>ECOG 3489139</td>
<td>Post remission HIDAC</td>
<td>740</td>
<td>83 vs. 74 vs. 56</td>
<td>19</td>
<td>1998</td>
</tr>
<tr>
<td>CALGB 9222140</td>
<td>Post remission multiagent chemo vs. HIDAC</td>
<td>474</td>
<td>72</td>
<td>13 vs. 12</td>
<td>2005</td>
</tr>
</tbody>
</table>

**Abbreviations:** CALGB, Cancer and Leukemia Group B; ECOG, Eastern Cooperative Oncology Group; SWOG, Southwest Oncology Group; MRC, Medical Research Council; HOVON/SAKK, Hemato Oncology Foundation for Adults in the Netherlands/Swiss Group for Clinical Cancer Research; NR, not reported. *= % survival at 5 years.
age ≤ 40) were superior to 2 years of maintenance therapy for AML in first remission, and that consolidation with high dose cytarabine (3 gm/m² IV over 1 hour every 12 hours for 12 consecutive doses, days 1–6) and amsacrine (100 mg/m²/d IV for 3 days, days 7–9) was extremely toxic for patients aged ≥ 60 years (early mortality of 57% for age ≥ 60 vs. 13% for <60 years old).60 Consolidation regimens have included intensive chemotherapy, non-intensive regimens, allogeneic and autologous transplantation. The choice of consolidation therapy is guided by baseline cytogenetic and molecular markers, with allogeneic transplantation in first complete remission being potentially curative for the unfavorable cytogenetic/molecular subgroup. The MRC AML8 trial randomized AML patients in complete remission following 2 courses of induction therapy with daunorubicin, cytarabine, and 6-thioguanine (DAT) to consolidation with 2 vs. 6 further courses of DAT. Overall outcomes (OS and EFS) were not different between the 2- and 6-course groups. However, 6 courses of DAT consolidation resulted in a reduction in the number of relapses that occurred beyond the first year after randomization.61 This large trial also found no significant advantage to central nervous system (CNS) prophylaxis with intrathecal cytarabine and methotrexate, and no benefit for late intensification vs. continued maintenance chemotherapy.62 The Cancer and Leukemia Group B (CALGB) evaluated 3 dosing schedules of cytarabine (3 gm/m² twice daily on days 1, 3, and 5 vs. 400 mg/m² or 100 mg/m² daily for 5 days) for 4 cycles in consolidation (followed by maintenance) for AML in first remission. This trial established the commonly used high dose (3 grams) Ara-C (HiDAC) regimen62 for AML in first CR, with a higher probability of remaining in continuous CR at 4 years for the HiDAC group compared to the lower doses of Ara-C (44% vs. 24% and 29%).62 The benefit of HiDAC consolidation was greatest for younger patients with CBF AML, and to a lesser degree for those with intermediate risk cytogenetics.63 Of note, interim analysis of this trial revealed that the regimen was prohibitively toxic in patients age 60 and older and that fewer than 50% of the patients older than 60 had received the intended number of cycles of HiDAC.62 Our experience using a modified HiDAC schedule (2 gm/m² daily for 6 days and daunorubicin 45 mg/m² daily for 3 days) for induction and consolidation revealed promising remissions (69%) and <10% 30-day mortality in patients age 60 and older with newly-diagnosed de-novo AML.64 The US intergroup Study, E3489/S9034, compared 1 cycle of high-dose cytarabine with allogeneic and autologous transplantation for patients with AML in first CR and did not reveal a difference in OS.65 However, when analyzed according to cytogenetic grouping, patients with unfavorable cytogenetics had better outcome with allogeneic transplantation.7 Similarly, the German AML Cooperative Group study group (AMLCG) reported a landmark analysis of patients younger than 60 years with AML and high-risk cytogenetics in CR1, treated on the AMLCG 99 who underwent allogeneic transplantation as consolidation therapy. When compared to patients who received continued consolidation chemotherapy, those who received allogeneic transplantation experienced superior 5-year OS (48% vs. 18% respectively, \(P = 0.004\)) and RFS (39% vs. 10% respectively, \(P < 0.001\)).66 The MRC AML 10 trial aimed to assess the benefit of high-dose therapy followed by autologous or allogeneic bone marrow transplantation (BMT) in patients age < 56 in first CR after receiving 4 courses of intensive chemotherapy. In that trial, patients received up to 2 cycles of induction chemotherapy. Patients who achieved CR received 2 further courses of chemotherapy and those who had an HLA-matched sibling went on to allogeneic BMT after the 4th course of chemotherapy. Patients who lacked an HLA-matched sibling went on to autologous BMT after the 4th course of chemotherapy. In that trial, the relapse rate was significantly lower for patients who received autologous BMT compared to those who received allogeneic BMT (37% vs. vs. 58%, \(P < 0.001\)), but this did not translate into a benefit on OS, likely due to an excess of death in CR for the autologous BMT group vs. the no-further-treatment arm.67 There was a significant reduction in relapses for the autologous BMT group when compared to the no-further-treatment arm (37% vs. 58%, \(P < 0.001\)), but this did not translate into a benefit on OS, likely due to an excess of death in CR for the autologous BMT group vs. the no-further-treatment arm.67 Similarly, in that trial, the relapse risk was reduced in the donor arm (36%) when compared to the no donor arm (52%; \(P = 0.001\)) and the disease-free survival (DFS) was also improved for the donor vs. no donor arm (50% vs. 42% respectively; \(P = 0.01\)). However, OS was not different (55% vs. 50%) at 7 years.68
Gemtuzumab ozogamicin (GO) is an anti-CD33 immunoconjugate that is worth mentioning due to its recent media coverage. GO was granted approval in 2000 under the FDA’s accelerated approval program, for patients ≥ 60 years of age with AML in first relapse, not considered candidates for standard cytotoxic therapy, based on its activity in the relapsed setting. Subsequently, GO was voluntarily withdrawn from the US market in 2010 after the confirmatory study designed to assess improvement in survival for the addition of GO to standard chemotherapy in previously untreated AML showed no improvement in clinical benefit, as well as an increased 30-day mortality for patients who received GO compared to those who received chemotherapy alone. The phase III SWOG “S0106” trial randomized patients aged 18–60 with newly diagnosed AML to induction with daunorubicin and cytarabine (‘3 + 7’, AD) chemotherapy +/- GO at 6 mg/m² on day 4. Patients who achieved CR received 3 cycles of consolidation with high dose cytarabine, and those who remained in CR after consolidation were eligible for a second randomization between either 3 doses of GO at 5 mg/ m² every 28 days, or observation. The interim analysis revealed almost identical CR rates (66% for AD + GO vs. 69% for AD), no difference in relapse-free or overall survival, and a significantly higher rate of fatal adverse events for the AD + GO group (5.8%) vs. the AD group (0.8%, P = 0.002). These results led to the closure of the S0106 trial by the SWOG DSMC on August 11, 2009 and the voluntary withdrawal of GO from the market. It is postulated that the non-fractionated dosing schema that was used may have led to the increase in GO-associated toxicity. European investigators have explored fractionated, lower doses of GO in an attempt to reduce GO-associated toxicity, and have found promising results. The randomized MRC AML15 trial showed that the addition of GO at 3 mg/m² on day 1 of the first and third courses of chemotherapy did not add any advantage over chemotherapy alone in terms of relapse, relapse-free survival, or overall survival. However, a prespecified analysis according to cytogenetic grouping revealed a significant benefit of GO in the younger, favorable-risk patients, with a 79% OS for GO vs. a 51% OS for the control group, with no added toxicity. Recently, investigators from the Acute Leukemia French Association conducted a study (ALFA-0701) designed to compare the addition of low, fractionated doses of GO to standard frontline chemotherapy in 280 patients age 50–70 years with previously untreated de novo AML. Patients were randomized 1:1 to standard chemotherapy (“3 + 7”) +/- 5 doses of GO administered at 3 mg/m²/ dose on days 1, 4 and 7 during induction and on day 1 of each of 2 consolidation chemotherapy cycles. They found no difference in rates of CR (81% for GO and 75% for control); but at 2 years, the estimated EFS was 40.8% in the GO group vs. 17.1% in the control group (hazard ratio [HR] 0.58; P = 0.060), OS was 53.2% vs. 41.9% (GO vs. control, respectively; HR 0.69; P = 0.0368), and RFS 50.3% for GO vs. 22.7% for the control arm (HR 0.52; P = 0.0003) all in benefit of the GO group. Hematological toxicity, particularly persistent thrombocytopenia, was more common in the GO group than in the control group (16% vs. 3%; P < 0.0001), without an increase in toxic deaths (9/139 [6%] for GO vs. 5/139 [4%] for control). The MRC AML16 trial showed that the addition of GO to low dose Ara-C, in older patients with AML, doubled the CR rate but did not improve OS. However, in the AML16-intensive trial, adding GO at 3 mg/m² on day 1 of the first course of chemotherapy in older patients with AML did not affect the CR rate, but a benefit was seen in terms of cumulative incidence of relapse (CIR; 3-year CIR 68% for GO vs. 76% for control arm; P = 0.007), RFS (21% vs. 16% at 3 years; P = 0.04), and OS at 3 years (25% vs. 20% for GO vs. control arm respectively, P = 0.05). A meta-analysis of the 2 large trials (AML 15 and AML 16) confirmed the benefit of adding GO to upfront AML therapy, with a reduction in relapse (HR, 0.82; 95% CI, 0.72 to 0.93; P = 0.002) and improved survival (HR, 0.88; 95% CI, 0.79 to 0.98; P = 0.02). These trials support a role for GO administered at 3 mg/m² in combination chemotherapy for the upfront treatment of AML.

AML adults older than 60 years

Reasons for the poorer prognosis of AML in older adults relate to patient-related factors such as advanced age, comorbidities, and poor performance status, leading to early induction-mortality. In addition, disease-related factors, such as lower incidence of favorable cytogenetics, higher incidence of unfavorable cytogenetics, higher incidence of
secondary AML, and higher expression of the multi-drug resistance gene lead to a more resistant disease when compared to younger AML. There may also be physician-related factors that limit treatment options in the aging AML population. Indeed, among over 2500 AML patients of medicare age, chemotherapy was given to only 30 percent of the population. The median survival for treated patients was 7 months versus 1 month for the untreated patients.

Enrollment of patients older than 60 years onto AML clinical trials was curtailed in the early 1990s due to high induction-mortality, despite the fact that intensive induction regimens have led to higher rates of complete remission (Table 4). The search for less intensive chemotherapy regimens is ongoing. Current non-intensive regimens include hypomethylating agents such as azacitidine and decitabine. These agents appear to have a favorable toxicity profile and promising remission rates in the range of 20%–50%. Clofarabine, a next generation nucleoside analogue, has shown promising results that await phase III confirmation. In a randomized comparison, low dose cytarabine (20 mg subcutaneously twice daily for 10 days on 4–6 week cycles showed a better remission rate (18% vs. 1%) and better overall survival compared to hydroxyurea in AML patients considered unfit for induction chemotherapy. Low-dose cytarabine has since become a standard comparator arm for randomized trials for newly diagnosed, older, unfit, AML patients. Clinical trials with combination regimens of non-intensive agents are ongoing.

### Table 4. Treatment of Older AML patients ≥ 60 years of age.

<table>
<thead>
<tr>
<th>Study group</th>
<th>Regimen</th>
<th>Patients</th>
<th>CR (%)</th>
<th>Early death (%) (within 30 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMLCG</td>
<td>TAD9 induction and consolidation +/- maintenance</td>
<td>511</td>
<td>51</td>
<td>27–34</td>
</tr>
<tr>
<td>BMRC</td>
<td>DAT induction and consolidation</td>
<td>636</td>
<td>46–48</td>
<td>30–52</td>
</tr>
<tr>
<td>CALGB</td>
<td>Standard or intensified 7 + 3 +/- maintenance</td>
<td>556</td>
<td>41–47</td>
<td>31–54</td>
</tr>
<tr>
<td>SECSG</td>
<td>Idarubicin vs. daunorubicin + cytarabine</td>
<td>111</td>
<td>53</td>
<td>20</td>
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<tr>
<td>EORTC/LCG</td>
<td>Mitoxantrone vs. daunorubicin +/- LDAC³</td>
<td>489</td>
<td>38–47</td>
<td>6–15</td>
</tr>
<tr>
<td>MDAC</td>
<td>Cytarabine-based intensive induction</td>
<td>430</td>
<td>45</td>
<td>36</td>
</tr>
<tr>
<td>Clofarabine</td>
<td>Clofarabine monotherapy</td>
<td>112</td>
<td>38</td>
<td>10</td>
</tr>
<tr>
<td>Emory</td>
<td>Modified HIDAC induction/consolidation</td>
<td>59</td>
<td>69</td>
<td>10</td>
</tr>
</tbody>
</table>

**Abbreviations:** AMLCG, AML Cooperative Group; BMRC, Behavioral Medicine Research Center; CALGB, Cancer and Leukemia Group B; SECSG, Southeastern Cancer Study Group; EORTC, European Organisation for Research and Treatment of Cancer; HOVON, Hemato Oncology Foundation for Adults in the Netherlands; MDAC, MD Anderson Cancer Center.

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**Acute promyelocytic leukemia**

APL is a distinct subtype of AML characterized by a unique reciprocal translocation, t(15;17) (q22;q11-12), leading to a fusion between the promyelocytic leukemia (PML) gene on chromosome 15 and the retinoic acid receptor-α (RARA) gene on chromosome 17. This results in a blockade in the differentiation of granulocytic precursors. The PML-RARA fusion gene is detectable in over 95% of APL cases, while variant rearrangements have been detected in the remainder of cases. APL cases with these variant rearrangements do not have the same clinical behavior as typical APL and are treated similar to non-APL AML due to their resistance to all-trans retinoic acid and arsenic trioxide.

Due to the profound bleeding diathesis that is characteristic of APL, the mere suspicion of APL diagnosis by morphologic evaluation should trigger a reflexive mechanism of treatment and supportive care strategies, including frequent transfusions with fresh frozen plasma, cryoprecipitate and platelets to treat disseminated intravascular coagulation and prompt initiation of all-trans-retinoic acid (ATRA), due to its ability to control APL-associated coagulopathy and to decrease the risk of bleeding. The following step should be confirmation of the APL diagnosis in bone marrow or peripheral blood at the genetic level, by demonstration of the t(15;17) or the PML/RARA gene by chromosomal analysis, fluorescence in-situ hybridization (FISH), or reverse transcriptase polymerase chain reaction (PCR) since the efficacy of ATRA and arsenic trioxide depends on its presence.
Early recognition of the retinoic acid or differentiation syndrome, which presents with dyspnea, fever, acute renal failure, and pulmonary infiltrates, together with a rising white blood cell count, usually after initiation of targeted or cytotoxic therapy, should prompt the rapid institution of dexamethasone (10 mg twice daily). Some authors advocate preemptive dexamethasone in APL patients at risk for the syndrome due to presenting WBC > 5–10,000 cells/mL.

**APL therapy**

Once a diagnosis of APL has been confirmed, induction therapy should be promptly started. While ATRA alone induced remissions in the majority of APL patients, the risk of relapse was high. Subsequently, several groups worldwide have confirmed the superiority of ATRA in combination with anthracycline-based chemotherapy for APL, with remissions in approximately 95% of patients. Three APL risk groups have been identified, based on the presenting WBC count and platelet count at diagnosis, with those presenting with WBC > 10,000 cells/mL being considered high risk, those with presenting WBC ≤ 10,000 cells/mL and platelets ≤ 40,000 cells/mL being intermediate, and those presenting with WBC ≤ 10,000 cells/mL and platelets > 40,000 cells/mL considered to be at low risk of relapse. Based on this distinction, risk-adapted therapy has become the standard, providing more therapy for those who are at high risk of relapse, and less therapy and therefore potentially fewer treatment-related complications for those who are at lower risk of relapse. The most recent update from the Programa Español de Tratamientos en Hematología (PETHEMA) and Hemato-Oncologie voor Volwassenen Nederland (HOVON) investigators, the LPA2005 trial, found a significantly lower 3-year relapse rate (11% in the LPA2005 vs. 26% in the LPA99 trial) with the addition of cytarabine for high-risk patients and reduced duration of cytopneas and hospital stay for low- and intermediate-risk patients after a reduced dose of mitoxantrone in the second consolidation without sacrificing efficacy.

The European Acute Promyelocytic Leukemia Group (APL93 and 2000 trials) showed a benefit to escalating the dose of cytarabine and adding intrathecal therapy to the ATRA–anthracycline combination, especially for high-risk patients, in addition to confirming the role of maintenance therapy in APL. Of note, the APL 93 and 2000 trials utilized daunorubicin, instead of idarubicin, which was used in the PETHEMA trials. The role of low-dose oral maintenance therapy has also become standard, although authors have questioned the utility of maintenance therapy in low-risk APL. It is not advisable to adapt or mix and match portions or different regimens. Indeed, the expert panel on behalf of the LeukemiaNet support the use of maintenance therapy with protocols in which maintenance was shown to confer a benefit.

The role of arsenic trioxide (ATO) is being expanded from the relapsed setting into the upfront setting. With a median follow-up of 5 years, the EFS, disease-free survival, and OS were 69%, 80%, and 74% respectively for 72 patients with APL treated with single-agent ATO for induction, consolidation, and maintenance. It should be noted that anthracycline was allowed at induction for patients with rapidly rising WBC. Data on 197 newly-diagnosed APL patients from Tehran treated with single-agent ATO daily until CR, followed by 1–4 courses of ATO for consolidation, was promising, with an 86% CR rate, 67% DFS and 64% OS at 5 years. At the recent 2012 annual meeting of the American Society of Hematology, Lo-Coco and colleagues presented remarkable results of a phase III trial that randomized newly-diagnosed patients with low- and intermediate-risk APL to ATRA + ATO vs. ATRA + idarubicin (IDA). In this non-inferiority trial, the ATRA + ATO combination not only proved “not inferior” but it also was superior to ATRA + idarubicin with respect to 2-year EFS (97% vs. 86.7% for ATRA + ATO vs. ATRA + IDA respectively; P = 0.03) and OS (98.7% vs. 91.1%; P = 0.03), with fewer episodes of fever and less prolonged cytopenia in the ATRA + ATO arm. ATO has been combined with chemotherapy, ATRA, and/or gemtuzumab ozogamicin (GO) in newly diagnosed APL and is currently being tested in combination with GO, ATRA, and chemotherapy for newly-diagnosed high-risk APL in an intergroup trial.

**AML salvage therapy**

Despite major advances in the upfront management of AML, relapse remains the leading cause of death for most patients. Among the total number of AML patients who relapse, about 10% survive long term. While there is no standard salvage regimen...
for relapsed AML, what is well accepted is that relapsed AML patients should be considered for inclusion onto clinical trials of salvage therapy and that for those who achieve a subsequent remission, allogeneic transplantation can be curative. Several groups have attempted to define prognostic factors for success/failure to facilitate treatment decisions for relapsed AML.\textsuperscript{108–111} Despite the promise of cure with high-dose therapy and allogeneic transplantation, this approach carries significant treatment-related morbidity and mortality, and until recently there was no reproducible way to predict who is most likely to benefit from this approach.

Chevallier et al published a prognostic scoring system based on an analysis of 138 adult patients with relapsed/refractory AML undergoing treatment with an intensive salvage regimen of chemotherapy + GO.\textsuperscript{112} 3 poor prognostic markers were identified: early relapse (<1 year after complete remission), unfavorable cytogenetics, and the presence of FLT3-ITD. Age was not found to be a significant prognostic factor. The prognostic scoring system was validated on an independent cohort of 111 patients and a clear-cut difference existed between relapsed AML patients with 0–1 factors (2-year OS 23%–35%), and those with 2–3 adverse factors (2-year OS 0%) in the validation group.\textsuperscript{112} In addition, a study by the Center for International Blood and Marrow Transplant Research (CIBMTR) focused on AML patients not in CR at the time of transplantation (with myeloablative conditioning) and identified 5 adverse factors: first CR < 6 months, circulating blasts, donor other than matched sibling, Karnofsky performance status < 90%, and adverse risk cytogenetics, with 3-year survival of 42% for those with none of those factors, 28% for those with 1 adverse factor, 15% for 2 factors and 6% if ≥3 adverse factors were present.\textsuperscript{113} These are important studies to keep in mind when tailoring intensive therapy for relapsed AML patients.

Clofarabine is a novel purine nucleoside analogue that is structurally similar to fludarabine and cladribine. Clofarabine has shown activity against AML in phase I/II studies.\textsuperscript{114,115} Recent trials have shown efficacy of clofarabine (CLO) in combination with high-dose cytarabine and granulocyte colony-stimulating factor (G-CSF) priming (GCLAC), in the treatment of patients with relapsed or refractory acute myeloid leukaemia, where 46% of patients achieved CR (61% CR + CRi) and their median survival was 9 months.\textsuperscript{114} In addition, the CLASSIC I trial, a phase III trial comparing ara-C alone to CLO+ ara-C in patients with relapsed/refractory AML age ≥ 55 showed a superior CR rate for the combination (35% vs. 22.9% respectively; \(P < 0.01\)), but no difference in OS was seen.\textsuperscript{116} An interesting combination included temsirolimus, a mammalian target of rapamycin (mTOR) inhibitor, in combination with lower-dose clofarabine as salvage therapy for older patients with AML. In this phase II trial reported by the Gruppo Italiano Malattie Ematologiche dell’Adulto (GIMEMA) cooperative group, CLO was administered at 20 mg/m\(^2\) on days 1–5 with temsirolimus at 25 mg on days 1, 8, and 15, followed by monthly maintenance with temsirolimus for those who achieved CR. The overall response rate (ORR) was 21% (8% CR and 13% CRi), with a median DFS and OS of 3.5 months and 4 months, respectively, and 30-day induction mortality of 13%. Perhaps the most interesting finding was that >50% in vivo inhibition of S6 ribosomal protein phosphorylation was highly correlated with responses (75% response with inhibition and 0% without inhibition).\textsuperscript{117} The role of CLO alone and in combination for AML continues to be investigated (see Tables 5 and 6).

### Table 5. Selected clinical trials in older AML ≥ 60.

<table>
<thead>
<tr>
<th>Population</th>
<th>Treatment</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML &gt; 60</td>
<td>Cladribine + LDAC</td>
<td>II</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Temozolomide + vorinostat</td>
<td>II</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Entinostat, AZA</td>
<td>I</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Len, AZA or combo</td>
<td>II</td>
</tr>
<tr>
<td>AML &gt; 65</td>
<td>Tipifarnib</td>
<td>II</td>
</tr>
<tr>
<td>AML &gt; 70</td>
<td>Sapacitabine + decitabine</td>
<td>III</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Plerixafor + clofarabine</td>
<td>I</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Midostaurin + decitabine</td>
<td>I</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Everolimus, mito, VP16, AR-A-C, Ida</td>
<td></td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>TKI AC220, plerixafor w SI</td>
<td>I</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Clofarabine + Ara-C</td>
<td>I</td>
</tr>
<tr>
<td>AML &gt; 65</td>
<td>Panobinostat</td>
<td>I</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Clofarabine or DA followed by decitabine</td>
<td>III</td>
</tr>
<tr>
<td>AML &gt; 65</td>
<td>Panobinostat</td>
<td>I</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>LDAC + AZD1152</td>
<td>II</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Sorafenib</td>
<td>II</td>
</tr>
<tr>
<td>AML &gt; 60</td>
<td>Clofarabine + Ara-C + decitabine</td>
<td>II</td>
</tr>
</tbody>
</table>
Mitoxantrone and etoposide (ME)-based salvage regimens alone (ME) or with intermediate dose cytarabine (MEC) have been successfully used for the treatment of primary induction failure or relapsed AML, but the activity of ME vs. MEC has not been directly compared. Recently, Trifilio et al reported outcomes of 65 patients with relapsed/refractory AML who received either MEC or ME as salvage. They found a CR rate of 59% for MEC treated patients and 34% for ME treated patients (P = NS) with a similarly poor median OS at 5.2 months of follow-up. The MEC regimen is commonly used as the comparator arm in randomized trials of salvage therapy.

Fludarabine-based combinations provided an important advance in the management of AML. Fludarabine plus cytarabine (FA) was active in newly-diagnosed AML and MDS, with 53% CRs. The addition of G-CSF (FLAG) did not add to the activity of the regimen, although it accelerated the time to neutrophil recovery (34 days for FA vs. 21 days for FLAG; P < 0.001). In a prospective multi-center phase II trial, FLAG achieved CRs in 17/21 (81%) of patients with late relapse AML and 13/44 (30%) in those with early relapse/refractory AML, with the main toxicity being severe myelosuppression. The addition of Idarubicin (FLAG-Ida) did not add to the response rate. Adding GO to FLAG-Ida in the salvage setting does not appear to improve response rates. In a randomized setting, a large study by the MRC (MRC-HR) found that fludarabine and high-dose cytarabine (FLA) may be inferior to their standard cytarabine, daunorubicin, and etoposide (ADE) combination for high-risk (relapsed, refractory, or adverse cytogenetic) AML, with no differences in CR and DFS, but worse survival with FLA vs. ADE (16% vs. 27% at 4 years respectively; P = 0.05). In addition, the trial found no benefit to the addition of G-CSF or ATRA to either regimen. This study highlighted the difficulty in defining a standard treatment for AML salvage and clarifies some of the questions raised in small, single-center studies, which comprise the majority of data on relapsed/refractory AML.

Newer approaches for AML salvage include the addition of targeted agents to chemotherapy combinations. Due to the poor prognosis associated with FLT3 ITD and point mutations in both newly diagnosed and relapsed AML, targeting FLT-3 became the subject of intense study. Several FLT3 inhibitors in the form of monoclonal antibodies and tyrosine kinase inhibitors have been developed. Among those, lestaurtinib (CEP 701) has been evaluated in Phase III, in a randomized multi-center trial of 224 adult patients with FLT3-mutant AML in first relapse. Patients were randomized prior to the start of salvage chemotherapy to either receive or not receive lestaurtinib starting 2 days after completion of salvage chemotherapy (day 7). Salvage chemotherapy was selected based on duration of 1st CR (CR1), with either MEC (CR1 of 1–6 months) or high-dose cytarabine (HiDAC; CR1 of 6–24 months). This large, randomized trial failed to demonstrate improvement in CR rate or survival, with 29/112 (26%) patients on the lestaurtinib arm achieving CR + CRp compared to 23/112 (21%) for the control arm (P = 0.35). There was, however, a difference in the level of toxicity, with discontinuation due to toxicity in 24% of patients on the lestaurtinib arm compared to 7% of control arm. In addition, there was a lack of correlation between high lestaurtinib drug levels and

<table>
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<th>Population</th>
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<th>Phase</th>
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<td>AML</td>
<td>Plerixafor, mitoxantrone, VP16, ARA-C</td>
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<tr>
<td>AML</td>
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<td>[119]</td>
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<td>Decitabine + bexarotene</td>
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<td>Temsirolimus</td>
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<td>AML</td>
<td>Plerixafor, mitoxantrone, VP16, ARA-C</td>
<td>I</td>
<td>[118]</td>
</tr>
<tr>
<td>AML</td>
<td>Tosedostat + ARA-C or decitabine</td>
<td>II</td>
<td>[118]</td>
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<tr>
<td>AML</td>
<td>Alvocidib + mitoxantrone + DA</td>
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<tr>
<td>FLT3 AML</td>
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<tr>
<td>AML</td>
<td>Clofarabine vs. fludarabine with IA</td>
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<td>Fludarabine + IA + GCSF</td>
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<tr>
<td>AML</td>
<td>GO, mitoxantrone, VP16</td>
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<td>[118]</td>
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</table>
in vivo FLT3 inhibition. Although there was a hint that FLT3 inhibition may correlate with activity, this conclusion could not be drawn due to the small number of responders. Results of a Phase II trial of quizartinib (AC220), an effective FLT3 inhibitor, were presented to the 2012 ASH meeting. This drug showed single-agent activity against both FLT3-ITD+ (CRc [CR + CRp + CRi] = 44/99 or 44%) and FLT3-ITD-(CRc = 13/38 or 34%) relapsed/refractory AML. Approximately 1/3 of the patients in this trial were bridged to allogeneic transplantation. This level of single-agent activity in relapsed/refractory AML is unprecedented and warrants further development of quizartinib for AML.

Other available agents registered on trial are seen in Tables 5 and 6. The absence of a standard for relapsed/refractory AML makes patients with relapsed/refractory AML potential candidates for clinical trials. For those who achieve subsequent remissions, allogeneic transplantation may be curative.

Summary
Advances in diagnostic technology leading to better classification and risk stratification in AML have led to improved outcomes for younger patients. However, more efforts are being focused on the older AML population. Treatment decisions should take into account patient and disease-related factors in order to improve responses and limit treatment-related toxicity (see Fig. 1 for a proposed algorithm for older AML patients). Inclusion of patients into clinical trials remains critical if we hope to improve AML outcomes in the future. Among APL patients, efforts continue to focus on improving the incorporation of targeted therapy into multi-agent regimens.

Author Contributions
Conceived and designed the experiments: FER, MA. Analyzed the data: FER, MA. Wrote the first draft of the manuscript: FER, MA. Agree with manuscript results and conclusions: FER, MA. Jointly developed the structure and arguments for the paper: FER, MA. All authors reviewed and approved of the final manuscript.

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Competing Interests
Author(s) disclose no potential conflicts of interest.

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ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

References


