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PROCEEDINGS ARTICLE

Optimal induction and post-remission therapy for acute myeloid leukemia

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The approach to treatment of acute myeloid leukemia is substantially influenced by the age of the patient. Younger patients who are arbitrarily defined as those being <60 years, although comprising the minority of all patients with the disease, will always receive an intensive approach, whereas in older patients, an initial decision as to whether an intensive approach is appropriate or not has to be made. Standard chemotherapy for many years has been '3 + 7', followed by consolidation with high-dose Ara-C at a daily dose level of 3 g/m^2. It remains unclear as to what number of total treatment courses is optimal. Alternatives to this standard of care will be considered.

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INDUCTION

Daunorubicin dose

The question of whether daunorubicin (DA) should remain as a standard has been asked in randomized comparisons with idarubicin or mitoxantrone in several randomized trials without convincing evidence for substantial differences in survival being seen. There has always been an issue regarding dose equivalence of DA at doses of 45 mg/m^2 and 50 mg/m^2. Recent studies have raised the issue of dose intensification of DA either by dose escalation to a 90-mg dose or daily dosing for 5 days. The E1900 trial,[1] which has been undertaken by the Eastern Cooperative Oncology Group in 657 younger patients, compared a DA dose of 90 mg/m^2 versus 45 mg/m^2 in a 3 + 7 schedule for the first induction course. For those not in remission with course 1, an additional DA-containing course was recommended (with a 45 mg/m^2 dose). The higher doses achieved a higher overall remission rate (70% vs 56%, $P = <0.001$) with more in complete remission (CR) after course 1 (83% vs 72%), and a better overall survival (23.7 months vs 15.7 months; $P = 0.003$). A similar approach was taken by the HOVON-SAKK group[2] in older patients. In this study, the overall remission rate was similarly improved (64% vs 54%; $P = 0.002$), but overall survival did not improve, except in patients in the 60- to 65-year subgroup (38% vs 23%).

These data receive further support from a Korean trial[3] in 383 younger patients, in which the daunorubicin was intensified by giving DA (90 mg/m^2 vs 45 mg/m^2) by continuous infusion over 3 days which was also superior in the higher dose arm, CR 82% versus 72% ($P = 0.014$)and overall survival 47% versus 35% ($P = 0.03$).

There has been discussion for a long time about dose equivalence between DA and alternatives such as idarubicin. A study from the French ALFA group[4] compared the effect of DA at a dose of 80 mg/m^2 on days 1 to 3 with idarubicin at a dose of 12 mg/m^2 for either 3 or 4 consecutive days in patients aged 50–70 years. In 468 randomized patients, idarubicin treatment for 3 or 4 days produced more remissions than DA (83% vs 78% vs 70%; $P = 0.04$); however, this did not result in any difference in survival. A recent Japanese trial[5] in 1057 younger patients tested intensification, not by dose escalation but by administration of 50 mg/m^2 daily for 5 days compared with the traditional 3 days, that is, at a total exposure of 250 mg versus 150 mg during course 1, as compared with idarubicin for 3 days. The remission rates were similar (77.5% vs 78.2%) and survival was not different.

Whether these studies justify higher DA as the standard of care is not clear. All studies confirm that, at least with the follow-up available, cardiotoxicty is not a concern in adults. The benefits seen appear to differ in the cytogenetic risk subgroups, being less clear in the favorable and unfavorable subgroups. A 60 mg/m^2 dose is frequently used, and there has never been a comparison of doses of 90 mg versus 60 mg. Whether the overall survival is better than can be achieved with other regimens, which have not escalated, is doubtful. For example, in age-matched patients from the MRC database, the 90 mg data was not superior overall or in older patients in the 60- to 65-year subgroup.

Antibody-directed therapy

The immunoconjugate gemtuzumab ozogamicin (GO) (Mylotarg, Pfizer Inc., NY, USA) combines a humanized anti-CD33 antibody with the powerful DNA intercalator, calicheamicin. This provides the opportunity to more precisely direct chemotherapy with the aim of optimizing efficacy while limiting collateral toxicity. It remains unlicenced in Europe and has been withdrawn from the US market, but remains available in Japan. Its use as maintenance therapy has not been beneficial in three randomized trials, although the recruitment of participants into the trials was such that they were individually underpowered. When tested in addition to standard chemotherapy, at a dose of 6 mg/m^2 on day 4 of course 1, in 627 patients in the SWOG 106 trial,[6] the preliminary report showed no overall benefit on remission rate or survival. The larger MRC AML15 trial[7] ($n = 1113$), using 3 mg/m^2 on day 1 of course 1, also showed no overall effect on remission or survival; however, when evaluated in the pre-specified cytogenetic risk group, there was a substantial benefit in the favorable cytogenetic group, and a trend for benefit in those with intermediate risk. Using an internally validated risk score, 70% of

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individuals from the intermediate risk group were shown to have a 10% survival benefit at 5 years. Two recently presented trials add important new information to suggest that the addition of GO to induction can improve survival. In a study conducted by the French ALFA Group,[8] a fractionated dose (3 mg/m^2—or a maximum of 5 mg—on days 1, 4 and 7) in combination with Idarubicin/Ara-C induction in 278 patients aged 50 to 70 years was used. The event-free (18.7% vs 39.6%; $P = 0.0002$) and overall survival (43.5% vs 53.1%; $P = 0.047$) at 2 years was superior in the GO arm. The UK NCRI AML16 Trial[9] randomized 1115 older patients, predominantly over 60 years of age, to receive GO 3 mg/m^2 on day 1 of the first course of induction chemotherapy, using either DA/Ara-C or DA/clofarabine. The remission rate overall was 69% (60% CR; 9% CRp (complete marrow remission with incomplete platelet recovery)) and was not improved in the GO arm, but the relapse rate was significantly reduced (73% vs 78%; $P = 0.007$), which resulted in improved overall survival (20% vs 15%; $P = 0.05$). In both trials, the treatment was well tolerated, although there was more hematological toxicity with the fractionated dose.

Alternative nucleoside analogs

Escalation of cytarabine dose has been unconvincing, but there has been recent investigation into alternative nucleoside analogs such as cladrabine and fludarabine. The Polish Adult Leukaemia Group has compared cladrabine with cytarabine in two randomized trials.[10,11] In the first trial, the inclusion of cladrabine significantly increased the proportion of patients who achieved CR with one course, but an improved survival was not confirmed possibly because the number of patients was insufficient. In a recent study, the addition of cladrabine or fludarabine to cytarabine + DA was compared with cytarabine/DA alone in a three-arm study that recruited 652 patients under the age of 60 years. The inclusion of cladrabine improved the remission rate compared with DA, but the addition of fludarabine did not. This was also reflected in a survival benefit (44% vs 33%; $P = 0.02$) at 2 years for cladrabine, but not for fludarabine (35% vs 33%). In a subgroup analysis, the addition of either nucleoside appeared to be beneficial in patients with an adverse karyotype.

Post-induction treatment

The use of four courses of high-dose Ara-C at a daily dose of 3 g/m^2, followed by maintenance, was established two decades ago based on a CALGB Trial.[12] The maintenance component is now largely abandoned, and it is uncertain whether 3 g is the optimum dose and whether four courses are needed, and whether all risk subgroups derived similar benefit. The UK MRC15 trial[13] attempted to clarify some of these issues and found that there was no advantage in more than a total of four courses including induction, and that a dose of 1.5 g was equivalent to 3 g. Patients with adverse cytogenetics were randomized to high-dose Ara-C or a mitoxantrone/etopside/amsacrine approach, which was superior to either dose of Ara-C.

Immunotherapy as a strategy has been a failure, but optimism has been sustained by the efficacy of allogeneic transplant, which remains the most effective approach to prevent relapse. Trials of interleukin-2 have failed, partly owing to toxicity. The concept of rendering a smaller dose of interleukin-2 effective by combining it with histamine dichloride has been approved, as Ceplene (Epicept Inc., NY, USA)—this has been reported to significantly improve disease-free survival when applied as maintenance after consolidation, but overall survival was not the primary end point.[14] This requires a corroborative trial.

Summary

Remission can reliably be obtained in 75–85% of younger patients with any of several schedules. The potential benefit of more effective induction is therefore likely to be seen as a reduced risk of relapse. Three strategies of optimizing induction have been discussed and could be further refined and confirmed in future trials. Although discussion about conventional chemotherapy may appear unexciting in the molecular age, there is still a need to optimize the chemotherapy component of future treatments to which will be added molecular or other targeted treatments.

CONFLICT OF INTEREST

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REFERENCES

1 Fernandez HF, Sun Z, Yao X, Litzow MR, Luger SM, Paietta EM *et al.* Anthracycline dose intensification in acute myeloid leukemia. *N Engl J Med* 2009; **361**: 1249–1259.
2 Lowenberg B, Ossenkoppele GJ, van Putten W, Schouten HC, Graux C, Ferrant A *et al.* High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl.J Med* 2009; **361**: 1235–1248.
3 Lee JH, Joo YD, Kim H, Bae SH, Kim MK, Zang DY *et al.* A randomized trial comparing standard versus high-dose daunorubicin induction in patients with acute myeloid leukemia. *Blood* 2011; **118**: 3832–3841.
4 Pautas C, Merabet F, Thomas X, Raffoux E, Gardin C, Corm S *et al.* Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. *J Clin Oncol* 2010; **28**: 808–814.
5 Ohtake S, Miyawaki S, Fujita H, Kiyoi H, Shinagawa K, Usui N *et al.* Randomized study of induction therapy comparing standard-dose idarubicin with high-dose daunorubicin in adult patients with previously untreated acute myeloid leukemia: the JALSG AML201 Study. *Blood* 2011; **117**: 2358–2365.
6 Petersdorf S, Kopecky K, Stuart RK, Larson RA, Nevill TJ, Stenke L *et al.* Preliminary results of Southwest Oncology Group Study S0106: an international intergroup phase 3 randomized trial comparing the addition of gemtuzumab ozogamicin to standard induction therapy versus post-consolidation gemtuzumab ozogamicin versus no additional therapy for previously untreated acute myeloid leukemia. *Blood* 2009; **114**: 326–327.
7 Burnett AK, Hills RK, Milligan D, Kjeldsen L, Kell J, Russell NH *et al.* Identification of patients with acute myeloblastic leukemia who benefit from the addition of gemtuzumab ozogamicin: results of the MRC AML15 Trial. *J Clin Oncol* 2011; **29**: 369–377.
8 Castaigne S, Pautas C, Terre C, Raffoux E, Bordessoule D, Bastie J-N *et al.* Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet* 2012; **379**: 1508–1516.
9 Burnett AK, Russell N, Hills RK, Kell J, Freeman S, Kjeldsen L *et al.* The addition of gemtuzumab ozogamicin to induction chemotherapy improves survival in older patients with acute myeloid leukaemia. *J Clin Oncol* 2012 (in press).
10 Hołowiecki J, Grosicki S, Kyrcz-Krzemien S, Skotnicki AB, Piatkowska-Jakubas B, Warzocha K *et al.* Daunorubicin, cytarabine and fludarabine (DAF) for remission induction in relapsed or refractory acute myeloid leukemia. Evaluation of safety, tolerance and early outcome—Polish Adult Leukemia Group (PALG) pilot study. *Ann Hematol* 2008; **87**: 361–367.
11 Holowiecki J, Grosicki S, Giebel S, Robak T, Kyrcz-Krzemien S, Kuliczkowski K *et al.* Cladribine, but not fludarabine, added to daunorubicin and cytarabine during induction prolongs survival of patients with Acute Myeloid Leukemia. Multicenter, Randomized Phase III Study. *J Clin Oncol*; e-pub ahead of print 16 April 2012.
12 Mayer RJ, Davis RB, Schiffer CA, Berg DT, Powell BL, Schulman P *et al.* Intensive postremission chemotherapy in adults with acute myeloid-leukemia. *N Engl J Med* 1994; **331**: 896–903.
13 Burnett AK, Milligan D, Goldstone A, Prentice A, McMullin MF, Dennis M *et al.* The impact of dose escalation and resistance modulation in older patients with acute myeloid leukaemia and high risk myelodysplastic syndrome: the results of the LRF AML14 trial. *Br J Haematol* 2009; **145**: 318–332.
14 Brune M, Castaigne S, Catalano J, Gehlsen K, Ho AD, Hofmann WK *et al.* Hellstrand. Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. *Blood* 2006; **108**: 88–96.