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IS THERE A “STANDARD” INDUCTION REGIMEN FOR PATIENTS WITH ACUTE MYELOID LEUKEMIA?

Farhad Ravandi, Jorge Cortes, and Hagop Kantarjian

University of Texas – MD Anderson Cancer Center

In this issue of the journal, Jin and colleagues report the results of a randomized study of 3 different regimens for induction treatment of patients younger than 60 years with acute myeloid leukemia (AML). They demonstrate that the addition of homoharringtonine (HHT) to a regimen of cytarabine (ara-C) and aclarubicin improved response rate and event-free survival. The addition of HHT to ara-C and daunorubicin was associated only with a trend of improvement in response rate and event-free survival leading to the suggestion by the authors that there may be a synergistic effect between HHT and aclarubicin but not with daunorubicin. Alternatively, the study may not have been statistically powered to show a lesser, but still important, benefit in the ara-C plus daunorubicin arm. This study is one of several recently reported studies examining the benefit of an additional agent to the ara-C and anthracycline induction regimens used to treat patients with AML. Homoharringtonine is a natural plant alkaloid derived from *Cephalotaxus fortune* that has been evaluated extensively by Chinese investigators in the treatment of myeloid neoplasms. A semisynthetic version, omacetaxinemepe succinate is a highly purified form that was recently approved by the Food and Drug Administration for the treatment of advanced chronic myeloid leukemia.

It is both remarkable and disheartening that after four decades and hundreds of clinical trials, what is referred to by the authors of this article as “the gold standard of induction therapy in AML” continues to be the same ara-C plus daunorubicin regimen introduced several decades ago. This is not due to the lack of efforts to improve upon this “standard”. Early studies explored the potential benefit of escalating the ara-C dose.^{1, 2} However, although a number of seminal studies have suggested that increasing the ara-C dose to an intermediate level may be associated with an improved outcome in the younger patients, this benefit has been recently challenged by a number of studies.³ The question ignored by most trials is whether an intermediate dose of ara-C (about 5–6 g/m²/course), which has been demonstrated by well-designed pharmacokinetic studies to lead to the saturation of intracellular ara-CTP levels⁴, is superior to both “standard” and high dose ara-C.⁵ Escalating the dose of daunorubicin from 45 mg/m²/day to 90 mg/m²/day has demonstrated a

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Correspondence: Farhad Ravandi, MD, Unit 428, Department of Leukemia, University of Texas – MD Anderson Cancer Center, 1515 Holcombe Boulevard, Houston, Texas 77030, Tel – 713-745-0394, fravandi@mdanderson.org.

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significant benefit in younger patients with more favorable disease biology.⁶ Similarly, idarubicin was shown to be superior or at least equivalent to daunorubicin.⁷

The role of additional agents in the backbone of ara-C and anthracycline has been explored in large randomized trials. Several trials did not demonstrate a benefit for the addition of growth factors in “priming” the leukemia cells for the action of chemotherapy.⁸ The Australian group showed an improvement in event-free survival with the addition of etoposide to ara-C and daunorubicin, but not a survival benefit.⁹ A recent study from Poland reported an advantage for adding cladribine (but not fludarabine) to an ara-C plus daunorubicin regimen.¹⁰ Studies by investigators from the Medical Research Council (MRC), France, and the South Western Oncology Group have shown that adding gemtuzumab ozogamycin to ara-C plus anthracycline improved survival in the more favorable risk patients.¹¹ A randomized trial by the MRC, UK showed that the combination of fludarabine, high-dose ara-C, idarubicin and granulocyte colony stimulating factor (GCSF), although intensive, can translate into a better outcome in patients who tolerate it.

Unfortunately, none of these studies have generated enough enthusiasm to challenge the status quo; the question then arises as to “why not?” Is the oncology community so averse to the risks associated with these strategies that it is willing to sacrifice the benefits? Many of the randomized studies failing to demonstrate any benefit for dose escalation or addition of new agents were conducted before the advent of optimal supportive care measures and effective antimicrobial therapies. Alternatively, we can be more selective in our approach in this era of personalized therapy, reserving such dose escalation or intensification to patients more likely to benefit from them, that is younger patients or those with a more favorable disease biology, who are able to withstand the toxic effects and reap the benefits? Clearly, be it simplistically, patients with AML can be considered to consist of two major subgroups: patients with chemosensitive disease who benefit from dose escalation of cytotoxic agents; and patients with chemoresistant disease in whom dose intensification is likely to lead only to increased toxicity. We need to better understand the biology of the disease in the latter group, and develop novel and targeted strategies to reverse the neoplastic phenotype. The addition to our armamentarium of new agents with novel mechanism of action, such as HHT, should be welcomed by physicians involved in treating patients with AML.

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