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Is there a role for intensifying induction therapy in acute myeloid leukaemia (AML)?

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Intensifying induction is not a new concept, but some recent and emerging information suggests that intensifying induction may be a relevant strategy for both young and older patients with acute myeloid leukaemia (AML). There are several potential strategies for intensifying induction therapy, including modulation of anthracyclines; modulation of ara-C; addition of other agents, including high-dose ara-C (HiDAC); addition of targeted or immunomodulatory agents, including gemtuzumab ozogamicin; or using timed-sequential therapy or very early intensification. It is clear that daunorubicin at a 45 mg m^{-2} dose is no longer acceptable as the standard for induction therapy in AML, but the optimal dose is unknown. No anthracycline dose attenuation should be made for older, fit adults, and modulation of induction can lead to significant survival benefit even without improving the initial response rate.

Standard induction therapy in acute myeloid leukaemia (AML) began in the late 1960s, when both cytarabine (ara-C) and anthracyclines were shown to have significant single-agent activity. Complete remission (CR) rates were between 30% and 40% [1–3]. The combination of ara-C and anthracyclines induced CR rates of over 50% [4,5]. The Cancer and Leukemia Group B (CALGB) conducted a series of carefully controlled randomised studies in the 1980s that established a standard of care that stood for more than 2 decades [6,7]. Results showed that continuous infusion ara-C was the most effective regimen, and 200 mg m^{-2} of ara-C had no advantage over 100 mg m^{-2}. Daunorubicin was found to be less toxic than adriamycin, and anything less than 45 mg m^{-2} of daunorubicin produced inferior results. A regimen of 3 days of daunorubicin and 7 days of ara-C by continuous infusion (3 + 7) proved

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to be more effective than a regimen of 2 days of daunorubicin and 5 days of ara-C (2 + 5). Finally, the addition of thioguanine to daunorubicin and ara-C did not improve the overall results of induction.

Today, new regimens are still tested against the standard 3 + 7 induction regimen with 45 mg m^{-2} of daunorubicin and 100 mg m^{-2} of ara-C. However, data for more than 20 years call into question the superiority of the 'standard' 3 + 7 regimen. In the early 1990s, newer anthracyclines or anthraquinones, such as idarubicin [8–11], mitoxantrone [12], aclarubicin[13] and amsacrine [14], were compared with the standard 45 mg m^{-2} or 50 mg m^{-2} of daunorubicin (Table 1). In each study, the alternative anthracycline was superior to daunorubicin in either CR rate, disease-free survival, overall survival or in the number of courses needed to induce a CR. Furthermore, sequential studies of induction by the same groups of investigators showed a significant disadvantage to 45 mg m^{-2} of daunorubicin (Table 2) [15–20]. The Southwest Oncology Group reported a CR rate of 70% with 70 mg m^{-2} of daunorubicin[15] and a CR rate of 58% with 45 mg m^{-2} of daunorubicin [16]. The Eastern Cooperative Oncology Group (ECOG) had similar results; in older patients, the CR rate was 60% when 60 mg m^{-2} of daunorubicin was used[17] and only 42% when the dose was decreased to 45 mg m^{-2} [18]. In another series of sequential studies by ECOG, 12 mg m^{-2} of idarubicin, which had already been shown to be better than 45 mg of daunorubicin in previous studies (see above), did not produce superior results to those previously reported by ECOG when using 60 mg m^{-2} of daunorubicin [19,20].

Despite all these data, 45 mg m^{-2} of daunorubicin has remained the standard dose in 3 + 7 in most studies until recently, is the only dose approved by the Food and Drug Administration (FDA) and is still commonly used in the community.

Intensifying induction therapy

A discussion of induction intensification needs to take into account the impact on efficacy. Efficacy can consist of improving initial response rate or improving the long-term overall survival without effect on the initial response. In addition, the impact on toxicity must be considered; toxicity may be increased, depending on the regimen, or decreased, if fewer patients require more than one cycle to achieve remission.

There are several potential strategies for intensifying induction therapy, including modulation of anthracyclines; modulation of ara-C; addition of other agents, including high-dose ara-C (HiDAC); addition of targeted or immunomodulatory agents, including gemtuzumab ozogamicin; or using timed-sequential therapy or very early intensification. However, none of these strategies has convincingly altered the standard of care until very recently [21].

Modulating anthracyclines

Although data show that many agents appear to induce better results than 45 mg m^{-2} of daunorubicin, there has never been a prospective study that has compared standard-dose daunorubicin with

Table 1
Randomized studies of daunorubicin (45 mg/m^2 or 50 mg/m^2) and ara-C vs other combinations in adults <50–60 years with AML [27]. Rowe JM, Tallman MS. Therapy for acute myeloid leukemia. In: Hoffman R, Furie B, McGlave P, Silberstein LE, Shattil SJ, Benz EJJr, Heslop H, editors. Hematology: Basic principles and practice. Philadelphia: Churcill Livingstone, 2009:965-989, with kind permission.

Study	DNR (mg/m^2)	Other (mg/m^2)	CR (%)	*P*	DFS better*	OS better*	More in CR after 1 course*
Vogler 1992 [8]	45	Idarubicin (12)	58 vs 71	.03			
Wiernik 1992 [9]	45	Idarubicin (13)	70 vs 88	.03		+	
Berman 1991 [10]	50	Idarubicin (12)	58 vs 80	.005		+	+
Mandelli 1991 [11]	45	Idarubicin (12)	same	–			+
Arlin 1990 [12]	45	Mitoxantrone (12)	53 vs 63	.1			+
Hansen 1991 [13]	45	Aclarubicin (75)	50 vs 64	.04	+		
Berman 1989 [14]	50	Amsacrine (190)	54 vs 70	.03	+		

*$P < 0.05$.
Abbreviations: CR, complete response; DFS, disease-free survival; DNR, daunorubicin; OS, overall survival.