New fractionated dosing regimen for anticancer drug significantly improves outcomes for older leukemia patients

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Using fractionated doses of the targeted anticancer drug gemtuzumab ozogamicin allows for safer delivery of the drug into patients aged 50-70 years with acute myeloid leukaemia (AML) and substantially improves their outcomes. These are the conclusions of an Article published Online First by *The Lancet*, written by Professor Sylvie Castaigne, Centre Hospitalier de Versailles, France, and colleagues.

Previous studies have shown that treatment of AML with gemtuzumab ozogamicin can cause AML to go into remission, but the dosing schedule in these other studies was such that complications were frequently reported, including liver toxicity and veno-occlusive disease. In this new study, the authors investigated whether addition of low fractionated-dose gemtuzumab ozogamicin to standard front-line chemotherapy would improve the outcome of patients with this leukaemia without causing excessive toxicity.

This phase 3 randomised trial was undertaken in 26 haematology centres in France. patients aged 50-70 years with previously untreated de novo (primary) acute myeloid leukaemia were randomly assigned in a 1:1 ratio to standard treatment (control group) with or without five doses of intravenous gemtuzumab ozogamicin (3 mg/m^2 on days 1, 4, and 7 during induction and day 1 of each of the two consolidation chemotherapy courses). The primary endpoint was event-free survival (EFS). Secondary endpoints were relapse-free (RFS), overall survival

(OS), and safety.

A total of 280 patients were randomly assigned to the control (n=140) and gemtuzumab ozogamicin groups (n=140), and 139 patients were analysed in each group. Complete response with or without incomplete platelet recovery to induction was 104 (75%) in the control group and 113 (81%) in the gemtuzumab ozogamicin group. At 2 years, EFS was estimated as 17% in the control group versus 41% in the gemtuzumab ozogamicin group . OS was 42% versus 53% , respectively and RFS 23% versus 50% , respectively. Haematological toxicity, particularly persistent thrombocytopenia, was more common in the gemtuzumab ozogamicin group than in the control group (16% vs 3%), without an increase in the risk of death from toxicity.

The authors say: "The results of this study show that the addition of fractionated doses of gemtuzumab ozogamicin to standard chemotherapy improves the survival outcome in patients aged 50-70 years with de novo acute myeloid leukaemia. The regimen [used in this study] allows the delivery of a high cumulative dose of gemtuzumab ozogamicin without excess toxicity. We believe that our results support the reevaluation of the place of gemtuzumab ozogamicin in available front-line therapy for acute myeloid leukaemia."

They add: "The substantial benefit of adding gemtuzumab ozagamicin is noted not only in patients with acute myeloid leukaemia who have favourable cytogenetics, but also in the larger subpopulation of those with intermediate cytogenetics."

In a linked Comment, Dr Elihu Estey, University of Washington Medical Center, Seattle, WA, USA; and Fred Hutchinson Cancer Research Center, Seattle, WA, USA, says: "Should gemtuzumab ozogamicin be approved for treatment of acute myeloid leukaemia? The data suggest a nuanced response. Approval seems warranted for patients with acute

promyelocytic leukemia and, in combination with chemotherapy, for patients with favourable or intermediate risk cytogenetics, irrespective of age; in the best case scenario, cytogenetics might be used predictively. Indeed, experience with gemtuzumab ozogamicin suggests a need to move beyond focusing on an average result. Instead, emphasis needs to be placed on outcome in various subsets of this highly heterogeneous disease."

More information: Study online: www.thelancet.com/journals/lan … (12)60485-1/abstract

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