資料 5-1

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JOURNAL OF THE AMERICAN SOCIETY OF HEMATOLOGY

Blood (ASH Annual Meeting Abstracts) 2006 108: Abstract 13

Oral Sessions

The Addition of Gemtuzumab Ozogamicin to Induction Chemotherapy for AML Improves Disease Free Survival without Extra Toxicity: Preliminary Analysis of 1115 Patients in the MRC AML15 Trial.

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Abstract

The MRC AML15 Trial is primarily for patients with any form of AML who are under 60 years. One of the questions addressed was whether the addition of the immunoconjugate, **Gemtuzumab Ozogamicin** (GO) to induction (course 1) and/or consolidation (course 3) is beneficial. In induction patients are randomised to receive either DA (Daunorubicin/Ara-C) or ADE (Ara-C/Daunorubicin/Etoposide) or FLAG-Ida (Fludarabine/Ara-C/Idarubicin/G-CSF) and in consolidation either MACE (Amsacrine/Etoposide) or HD Ara-C (3.0g/m^2 or 1.5g/m^2 per dose). Our prior pilot trial had shown that GO 3mgs/m^2 could be safely added to day 1 of each of these treatments (Kell et al Blood 102, 4277–4283). Here we report the preliminary results of the effect of combining GO with induction chemotherapy. This randomisation achieved its recruitment target and was closed on 30 June 2006. All other comparisons in the trial, including GO in consolidation, remain open.

Patients: A total of 1115 patients were randomised between July 2002 and June 2006. The median age was 49 (range 0–71) years: 53% of patients were male: 92% (n=1027) had de novo disease: 95% had WHO performance score of <2: 43% received DA, 43% FLAG-Ida, and 14% ADE. (Recruitment to ADE+GO opened in June 2005). Patients with WBC > 30 x 10^9/l and LFT's > normal were initially excluded but admitted from March 2004. APL patients were not eligible for entry. 15% of patients with data had favourable 71% intermediate, and 14% adverse cytogenetics. Over 83% were CD33 positive.

Results: The overall remission rate was 85% with no differences between the arms for GO vs no GO in CR (85% vs 85%) induction death (8% vs 7%) or resistant disease (7% vs 8%). There was a modest increase in mucositis on the GO arm in course 1 only (p=0.04) and increased AST and Alt toxicity in C1 (p=.002; p=.03) but no difference in bilirubin grades. GO patients used more platelets (19 vs 14; p<0.0001), but not red cells, and had more days on IV antibiotics (20.6 vs 18.6 p=0.001). The haemopoietic recovery and days in hospital were similar. With a median follow-up of 15 months (range 0–45), there is no significant difference in deaths in CR (GO vs no GO): 36 vs 45 (HR 0.75; C1.49–1.16 p=0.2), but relapse was reduced: 37% vs 52% at 3 years (HR 0.70 (0.52–0.92) p=0.01) resulting in an improved DFS: 51% vs 40% at 3 years (HR 0.72 (0.56–0.91) p=0.008). There is so far no significant difference in OS (53% vs 46% at 3 years; HR 0.91(0.73–1.14) p=0.4). Conclusion: This preliminary analysis of 1115 randomised patients indicates that the addition of GO to induction chemotherapy can reduce the relapse risk without adding significant extra toxicity and this has significantly improved the DFS in the GO arm. Longer follow up is required to determine the impact on survival.

Footnotes

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Disclosures: Investigational medicinal product evaluated in this trial was used outside its licenced indication.; European Advisory Board.; Trial received modest unrestricted research support.; European

Advisory Committee.