Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin's lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial.


BACKGROUND:
The role of bleomycin and dacarbazine in the ABVD regimen (ie, doxorubicin, bleomycin, vinblastine, and dacarbazine) has been questioned, especially for treatment of early-stage favourable Hodgkin's lymphoma, because of the drugs' toxicity. We aimed to investigate whether omission of either bleomycin or dacarbazine, or both, from ABVD reduced the efficacy of this regimen in treatment of Hodgkin's lymphoma.

METHODS:
In this open-label, randomised, multicentre trial (HD13) we compared two cycles of ABVD with two cycles of the reduced-intensity regimen variants ABV (doxorubicin, bleomycin, and vinblastine), AVD (doxorubicin, vinblastine, and dacarbazine), and AV (doxorubicin and vinblastine), in patients with newly diagnosed, histologically proven, classic or nodular, lymphocyte predominant Hodgkin's lymphoma. In each treatment group, 30 Gy involved-field radiotherapy (IFRT) was given after both cycles of chemotherapy were completed. From Jan 28, 2003, patients were centrally randomly assigned (1:1:1:1) with a minimisation method to the four groups. Because of high event rates, assignment to the AV and ABV groups stopped early, on Sept 30, 2005, and Feb 10, 2006; assignment to ABVD and AVD continued (1:1) until Sept 30, 2009. Our primary objective was to show non-inferiority of the experimental variants compared with ABVD in terms of freedom from treatment failure (FFTF), by excluding a difference of 6% after 5 years corresponding to a hazard ratio (HR) of 1·72, via a 95% CI. Analyses reported here include qualified patients only, and between-group comparisons include only patients recruited during the same period. The trial was registered, number ISRCTN63474366.

FINDINGS:
Of 1502 qualified patients, 566, 198, 571, and 167 were randomly assigned to receive ABVD, ABV, AVD, or AV, respectively. 5 year FFTF was 93·1%, 81·4%, 89·2%, and 77·1% with ABVD, ABV, AVD, and AV, respectively. Compared with ABVD, inferiority of the dacarbazine-deleted variants was detected with 5 year differences of -11·5% (95% CI -18·3 to -4·7; HR 2·06 [1·21 to 3·52]) for ABV and -15·2% (-23·0 to -7·4; HR 2·57 [1·51 to 4·40]) for AV. Non-inferiority of AVD compared with ABVD could also not be detected (5 year difference -3·9%, -7·7 to -0·1; HR 1·50, 1·00 to 2·26). 178 (33%) of 544 patients given ABVD had WHO grade III or IV toxicity, compared with 53 (28%) of 187 given ABV, 142 (26%) of 539 given AVD, and 40 (26%) of 151 given AV. Leucopenia was the most common event, and highest in the groups given bleomycin.

INTERPRETATION:
Dacarbazine cannot be omitted from ABVD without a substantial loss of efficacy. With respect to our predefined non-inferiority margin, bleomycin cannot be safely omitted either, and the standard of care for patients with early-stage favourable Hodgkin's lymphoma should remain ABVD followed by IFRT.

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