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Lymphoma

PET-guided omission of radiotherapy in early-stage unfavourable Hodgkin lymphoma (GHSG HD17): a multicentre, open-label, randomised, phase III trial

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BACKGROUND

Combined-modality treatment consisting of chemotherapy and consolidation radiotherapy is standard of care for patients with early-stage unfavourable Hodgkin lymphoma. However, the use of radiotherapy can have long-term sequelae, which is of particular concern, as Hodgkin lymphoma is frequently diagnosed in young adults with a median age of approximately 30 years. In the German Hodgkin Study Group HD17 trial, we investigated whether radiotherapy can be omitted without loss of efficacy in patients who have a complete metabolic response after receiving two cycles of escalated doses of etoposide, cyclophosphamide, and doxorubicin, and regular doses of bleomycin, vincristine, procarbazine, and prednisone (eBEACOPP) plus two cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD) chemotherapy (2.0 + 2.0).

METHODS

In this multicentre, open-label, randomised, phase III trial, patients (aged 18–60 years) with newly diagnosed early-stage unfavourable Hodgkin lymphoma (all histologies) and an Eastern Cooperative Oncology Group performance status of 2.0 or less were enrolled at 224 hospitals and private practices in Germany, Switzerland, Austria, and the Netherlands. Patients were randomly assigned (1:1) to receive either standard combined-modality treatment, consisting of the 2.0 + 2.0 regimen (eBEACOPP consisted of 1250 mg/m two intravenous cyclophosphamide on day one, 35 mg/m two intravenous doxorubicin on day one, 200 mg/m two intravenous etoposide on days 1.0–3.0, 100 mg/m two oral procarbazine on days 1.0–7.0, 40 mg/m two oral prednisone on days 1.0–14, 1·4 mg/m two intravenous vincristine on day eight [maximum dose of two mg per cycle], and 10 mg/m two intravenous bleomycin on day eight; ABVD consisted of 25 mg/m two intravenous doxorubicin, 10 mg/m two intravenous bleomycin, six mg/m two intravenous vinblastine, and 375 mg/m two intravenous dacarbazine, all given on days one and 15) followed by 30 Gy involved-field radiotherapy (standard combined-modality treatment group) or PET4-guided treatment, consisting of the 2.0 + 2.0 regimen followed by 30 Gy of involved-node radiotherapy only in patients with positive PET at the end of four cycles of chemotherapy (PET4; PET4-guided treatment group). Randomisation was done centrally and used the minimisation method and seven stratification factors (centre, age, sex, clinical symptoms, disease localisation, albumin concentration, and bulky disease), and patients and investigators were masked to treatment allocation until central review of the PET4 examination had been completed. With the final analysis presented here, the primary objective was to show non-inferiority of the PET4-guided strategy in a per-protocol analysis of the primary endpoint of progression-free survival. We defined non-inferiority as an absolute difference of 8% in the five-year progression-free survival estimates between the two groups. Safety analyses were done in the intention-to-treat population. This trial is registered with ClinicalTrials.gov, NCT01356680.

FINDINGS

Between 13 Jan 2012, and 21 March 2017, we enrolled and randomly assigned 1100 patients to the standard combined-modality treatment group (n=548) or to the PET4-guided treatment group (n=552); two patients in each group were found ineligible after randomisation. At a median follow-up of 46·2 months (IQR 32·7–61·2), five-year progression-free survival was 97·3% (95% CI 94·5–98·7) in the standard combined-modality treatment group and 95·1% (92·0–97·0) in the PET4-guided treatment group (hazard ratio 0·523 [95% CI 0·226–1·211]). The between-group difference was 2·2% (95% CI −0·9 to 5·3) and excluded the non-inferiority margin of 8.0%. The most common grade three or four acute haematological adverse events were leucopenia (436 [83%] of 528 patients in the standard combined-modality treatment group vs 443 [84%] of 529 patients in the PET4-guided treatment group) and thrombocytopenia (139 [26%] vs 176 [33%]), and the most frequent acute non-haematological toxic effects were infection (32 [6.0%] vs 40 [8%]) and nausea or vomiting (38 [7.0%] vs 29 [6.0%]). The most common acute radiotherapy-associated adverse events were dysphagia (26 [6%] in the standard combined-modality treatment group vs three [2.0%] in the PET4-guided treatment group) and mucositis (nine [2.0%] vs none). 229 serious adverse events were reported by 161 (29%) of 546 patients in the combined-modality treatment group, and 235 serious adverse events were reported by 164 (30%) of 550 patients in the PET4-guided treatment group. One suspected unexpected serious adverse reaction (infection) leading to death was reported in the PET4-guided treatment group.

INTERPRETATION

PET4-negativity after treatment with 2.0 + 2.0 chemotherapy in patients with newly diagnosed early-stage unfavourable Hodgkin lymphoma allows omission of consolidation radiotherapy without a clinically relevant loss of efficacy. PET4-guided therapy could thereby reduce the proportion of patients at risk of the late effects of radiotherapy.