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Original Research

Rituximab maintenance improves overall survival of patients with follicular lymphoma—Individual patient data meta-analysis

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KEYWORDS
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Abstract ***Background:*** Randomised trials of rituximab maintenance (MR) for patients with follicular lymphoma support improved progression-free survival (PFS), but the effect on overall survival has been inconclusive. To evaluate the effect of MR on overall survival according to patient and disease characteristics, and to explore certain adverse events, we performed an individual patient data (IPD) meta-analysis.
Methods: All investigators of randomised controlled trials that compared MR therapy with observation or treatment only at relapse (no MR) for patients with follicular lymphoma were invited to participate in an IPD meta-analysis. We obtained baseline patient and disease characteristics and time to progression and death for each patient. All analyses took into account the trial and original randomised treatment group. We analysed data in two ways: a two-stage analysis and a multivariate model including patient and disease characteristics.
Findings: Seven trials including 2315 patients were analysed. Overall survival of patients improved with MR compared with no MR (hazard ratio [HR] 0.79, 95% CI 0.66–0.96). We could not detect any patient or disease characteristics that were associated with a survival benefit with MR. In all of the models, MR had a beneficial effect on overall survival compared with observation for all types of patients, which was not shown in a particular subgroup in which the patient had already received rituximab in the induction phase and received first-line therapy. MR improved PFS compared with observation (HR 0.57, 95% CI 0.51–0.64). The risk of adverse events was higher with MR, specifically infection of any grade and grade 3–4 infections.
Interpretation: Based on IPD from randomised controlled trials, MR improves overall survival consistently in all patients, regardless of patient and disease characteristics when compared with observation, and should be prescribed after a successful induction with R-CVP or R-CHOP for patients with follicular lymphoma. It is still uncertain if that holds when the patient has already received rituximab in his/hers first induction. The effect of MR after bendamustine-rituximab induction compared with rituximab at progression should be further explored.

1. Introduction

Randomised controlled trials support the benefit of rituximab maintenance treatment (MR) for patients with follicular lymphoma. Their results have consistently shown improved progression-free survival (PFS), but evidence of improved overall survival has been inconclusive. A summary data meta-analysis of studies addressing patients with follicular lymphoma demonstrated an improved overall survival with MR among patients with relapsed or refractory lymphoma (hazard ratio [HR] for death 0.72 95% CI 0.57–0.91, 909 patients) [1]. It remains unclear whether MR has a similar effect in other specific subgroups of patients.

To evaluate the effect of rituximab maintenance on overall survival according to patient, disease and treatment characteristics, and to explore specific adverse events, we performed an individual patient data (IPD) meta-analysis.

IPD meta-analysis, considered the gold-standard of meta-analysis, allows analyses that are not feasible using summary data such as subgroup analysis of overall survival or analysis of specific adverse events that are not uniformly reported in the literature.

2. Methods

2.1. Inclusion criteria

We included all randomised controlled trials that compared rituximab maintenance therapy given after induction with observation or treatment only at relapse in patients with histologically confirmed B-cell follicular lymphoma. In all the trials that contributed data for this study, patients in the control group were observed and none used treatment with rituximab at progression. We included trials regardless of publication status, date of publication and language.

2.2. Search for trials

The process of systematic review including search and study selection was previously described [1]. The search was updated in June 2014. Eleven eligible trials performed between 1998 and 2009 were found [2–13] and the investigators of these trials were invited to cooperate. A collaborative group consisting of investigators from seven study groups that contributed IPD was formed.