

High-dose chemotherapy followed by autologous stem cell transplantation for patients with relapsed or refractory Hodgkin lymphoma: A systematic review with meta-analysis

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Contents

1. Introduction	2
2. Methods	2
2.1. Criteria for the trial selection	2
2.2. Search methods	2
2.3. Data collection and analysis	3
2.4. Assessment of risk of bias in included trials	3
3. Results	3
3.1. Search results and inclusion of studies	3
3.2. Risk of bias analysis	7
3.3. High-dose chemotherapy followed by autologous stem cell transplantation versus conventional chemotherapy	7
3.3.1. Effect on overall survival	7
3.3.2. Effect on progression-free survival	7
3.3.3. Response rates	7
3.3.4. Treatment-related mortality	7
3.3.5. Adverse events	8
3.4. Additional sequential high-dose chemotherapy versus high-dose chemotherapy before autologous stem cell transplantation	8
4. Discussion	8
Conflicts of interest	9
Reviewers	9
Acknowledgement	9
References	9

Abstract

Treatment for Hodgkin lymphoma is effective for about 85% of the patients. A gold-standard for the 15% of relapsing patients is still missing. High-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) has shown efficacy and safety for patients, but up to date no survival benefit revealed. After systematic literature search we identified three randomised controlled trials from 1663 total hits. Meta-analysis of two trials (157 patients) showed a statistically significant increase in progression-free survival (hazard ratio 0.55, 95% confidence interval 0.35–0.86) for patients treated with HDCT and ASCT compared to conventional chemotherapy, but no difference in overall

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survival nor increased adverse events. The third trial (241 patients) showed an statistically significant increase in infections and 5% more treatment-related mortalities following sequential HDCT plus HDCT and ASCT compared to HDCT plus ASCT, without differences in the efficacy endpoints overall survival or progression-free survival.

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1. Introduction

Hodgkin lymphoma (HL) is a malignancy of the lymphatic system with possible involvement of one or more organs. It is a relatively rare disease, with a yearly incidence of 2–3 patients per 100,000 inhabitants and a prevalence of 4600 patients in the year 2008 in Germany [1]. Even with these small rates, HL is counted as one of the most common malignancies in young adults between the age of 20 and 30 years. Therefore, the impact of mortality and the lost number of years from productivity play a major role for those patients. A second disease peak usually affects patients beyond the age of 60.

Several treatment approaches for patients with HL have been developed and are used nowadays: conventional chemotherapy, escalated chemotherapy (main treatment option in advanced stages), radiotherapy, a combination of chemo- and radiotherapy (which has evolved to be standard for early and intermediate stages) [2,3]. With highly efficacious treatment modalities 5-year survival rates nowadays exceed 95% for Hodgkin lymphoma patients, even in advanced stages [3]. However, there still is a considerable proportion of 15% of the patients who do not respond to treatment and have a refractory disease or who respond but then eventually relapse after first-line therapy [3–5]. For those patients high-dose chemotherapy (HDCT) followed by autologous stem cell transplantation (ASCT) has become the treatment of choice [6–8]. But also other treatment modalities are available for relapsed patients: allogeneic stem cell transplantation, reduced-intensity allogeneic stem cell transplantation, different salvage modalities before HDCT, and other non-curative treatment schemes [2,3]. The prognosis of the patients is additionally influenced by the presence of negative prognostic risk factors: early relapse 3–12 months after treatment, stage III or IV disease and anaemia at the time of relapse. A retrospective analysis of the German Hodgkin Study Group (GHSG) showed that patients presenting all three risk factors had a lower 4-year freedom from second treatment failure (FF2F) of 17% and a low OS of 27%, than patients without risk factors (FF2F: 48% and OS 83%) [9]. The positive influence of salvage treatment is additionally influencing patients' outcomes.

The role of HDCT plus ASCT has been assessed in randomised and non-randomised trials, but so far no statistically significant effect regarding overall survival has been demonstrated. This systematic review with meta-analysis was conducted to evaluate the effect of HDCT plus ASCT on

overall survival compared to chemotherapy without stem cell transplantation.

2. Methods

2.1. Criteria for the trial selection

Trials were eligible for inclusion, if they were prospective randomised controlled trials (RCTs). Both, full-text and abstract publications were of relevance for this systematic review. The patient population of interest were adult patients with a relapsed Hodgkin lymphoma or a primary refractory disease after first-line treatment for HL. Restriction on gender, ethnicity and for languages was not applied in order to minimise biases. The main intervention was HDCT followed by ASCT. For the control groups, any HDCT without ASCT, conventional chemotherapy without ASCT, and different HDCT regimens followed by ASCT would have been possible. Other treatment approaches, such as radiotherapy or combined-modality treatments compared to HDCT plus ASCT would also have been considered relevant, but no RCTs were found regarding these topics. The primary outcome measure was OS, defined as the time interval from random treatment assignment or entry into the study to death from any cause or to last follow-up. Secondary outcomes included progression-free survival (PFS), response rates (overall response rate, complete response rate (CRR), and partial response rate), treatment-related mortality (TRM), adverse events and quality of life.

2.2. Search methods

Search methods for this systematic review with meta-analysis were conducted according to the quality standards of the Cochrane Collaboration addressed in the Cochrane Handbook for Systematic Reviews of Interventions [10]. The medical databases MEDLINE (from 1946 until January 2013) and the Cochrane Central Register of Controlled Trials (from 1990 to January 2013) were searched electronically. Additionally, hand searching of the following international conferences for published data between 1990 and January 2013 was conducted: the conference of the American Society of Hematology, the conference of the American Society of Clinical Oncology, the conference of the European Hematology Association, the International Conference on Malignant Lymphoma, and the International Symposium on Hodgkin

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