Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin’s disease: a randomised trial

Norbert Schmitz, Beate Pfistner, Michael Sextro, Markus Sieber, Angelo M Carella, Matthias Haenel, Friederike Boissevain, Reinhart Zschaber, Peter Müller, Hartmut Kirchner, Andreas Lohri, Susanne Decker, Bettina Koch, Dirk Hasenclever, Anthony H Goldstone, Volker Diehl, for the German Hodgkin’s Lymphoma Study Group (GHSG) and the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation (EBMT)

Summary

Background High-dose chemotherapy followed by transplantation of autologous haemopoietic stem cells (BEAM-HSCT) is frequently used to treat patients with relapsed Hodgkin’s disease. We aimed to compare this treatment with conventional aggressive chemotherapy without stem-cell transplantation (Dexa-BEAM).

Methods 161 patients between 16 and 60 years of age with relapsed Hodgkin’s disease were randomly assigned two cycles of Dexa-BEAM (dexamethasone and carbamustine, etoposide, cytarabine, and melphalan) and either two further courses of Dexa-BEAM or high-dose BEAM and transplantation of haemopoietic stem cells. Only patients with chemosensitive disease (complete or partial remission after two courses of Dexa-BEAM) proceeded to further treatment. The primary endpoint was freedom from treatment failure for patients with chemosensitive disease. Analysis was per protocol.

Findings 17 patients were excluded from the study after randomisation (ten given Dexa-BEAM and seven given BEAM-HSCT). Median follow-up was 39 months (IQR 3–78). Freedom from treatment failure at 3 years was significantly better for patients given BEAM-HSCT (55%) than for those on Dexa-BEAM (34%; difference –21%, 95% CI –39·87 to –2·13; p=0·019). Overall survival of patients given either treatment did not differ significantly.

Interpretation High-dose BEAM and transplantation of haemopoietic stem cells improves freedom from treatment failure in patients with chemosensitive first relapse of Hodgkin’s disease irrespective of length of initial remission.

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Introduction

Patients with advanced Hodgkin’s disease have an excellent outlook if treated with modern chemotherapy with or without radiotherapy. Patients who relapsed after first-line chemotherapy can achieve further remissions with salvage treatment; the chance of cure, however, is limited, and will depend on many prognostic factors, such as length of initial remission, age, type of treatment previously received, presence of B-symptoms (fever, night sweats, weight loss >10% of previous bodyweight), and stage. Disease status is the most important factor predicting outcome of patients scheduled to receive high-dose chemotherapy and autologous stem-cell transplantation.

What is the optimum type of salvage treatment, and does high-dose chemotherapy have any benefit compared with other forms of salvage treatment, not needing transplantation of haemopoietic stem cells? To address this latter question, we prospectively compared aggressive conventional chemotherapy (Dexa-BEAM) with high-dose chemotherapy and autologous stem-cell transplantation (BEAM-HSCT) in patients with relapsed Hodgkin’s disease responding to salvage chemotherapy.

Patients and methods

Patients

Patients 16–60 years of age were eligible for the study if they had received chemotherapy for advanced Hodgkin’s disease and had biopsy-proven relapse. We included patients with stage I or II disease at relapse if they presented with additional risk factors (bulky mediastinum, involvement of three or more lymph-node regions, extranodal disease, or erythrocyte sedimentation rate >30 mm), or if they had shown stage III or IV disease early in the course of disease before enrolment. Histological verification of relapse was not mandatory for patients with unequivocal progressive intrathoracic or abdominal disease. Other criteria for eligibility were Karnofsky performance score above 70% and adequate cardiac, pulmonary, renal, and liver function. We excluded patients if they were HIV positive, had infection unresponsive to treatment, or had previously been treated with Dexa-BEAM (dexamethasone and carbamustine, etoposide, cytarabine, and melphalan), mini-BEAM, or high-dose chemotherapy.

Department of Internal Medicine II, University of Kiel, Kiel, Germany (Prof N Schmitz MD); Medizinische Klinik I, University of Cologne, Cologne, Germany (B Pfistner MD, M Sextro MD, M Sieber MD, B Koch, Prof V Diehl MD); Ospedale San Martino, Genoa, Italy (Prof A M Carella MD); Klinikum Chemnitz, Chemnitz, Germany (Prof A M Carella MD); Klinikum Nürnberg, Nürnberg, Germany (Prof R Schmitz MD); Department of Oncology and Haematology, Hamburg-Eppendorf, Hamburg, Germany (Prof R Zschaber MD); Zentralklinikum Augsburg, Augsburg, Germany (P Müller MD); Krankenhaus Siloah, Hannover, Germany (H Kirchner MD); SAKK Bern, Bern, Switzerland (A Lohri MD); Department of Haematology and Oncology, University of Rostock, Rostock, Germany (S Decker MD); Institute of Medical Informatics, Statistics, and Epidemiology, University of Leipzig, Leipzig, Germany (D Hasenclever MD); and Department of Haematology, University College London Hospitals, London, UK (A H Goldstone MD).

Correspondence to: Prof Norbert Schmitz, Department of Haematology, AK St Georg, Lohmühlenstr 5, 20099 Hamburg, Germany (e-mail: Norbert.Schmitz@ak-stgeorg.itb.kh-hh.de)
Staging adhered to guidelines from the German Hodgkin’s Lymphoma Study Group (GHSG) and included computed tomography of the thorax and abdomen and bone-marrow biopsy. We defined bulky disease as one node or nodes 5 cm or greater, mediastinum 5 cm or greater, or mediastinal mass one-third or greater of maximum thoracic diameter. Response to treatment was defined as: complete remission (no evidence of Hodgkin’s disease); unconfirmed complete remission (patient fulfilled criteria for complete remission but had residual lymph-node mass >1·5 cm in diameter that regressed by more than 50% after chemotherapy); partial remission (substantial reduction of all lesions and reduction of large lymph nodes or measurable organ lesions by >50% at the largest diameter; in the case of mediastinal involvement, reduction of the tumour by >25% in the maximum thoracic diameter was needed); or less than partial remission if these criteria were not met.

The institutional review board of each participating centre approved the study protocol, and we obtained written informed consent from patients.

Randomisation and stratification

Data managers randomly assigned eligible patients at the GHSG trial office by computer before any therapeutic intervention. Early randomisation was done to allow time to treatment was defined as: complete remission (no evidence of Hodgkin’s disease); unconfirmed complete remission (patient fulfilled criteria for complete remission but had residual lymph-node mass >1·5 cm in diameter that regressed by more than 50% after chemotherapy); partial remission (substantial reduction of all lesions and reduction of large lymph nodes or measurable organ lesions by >50% at the largest diameter; in the case of mediastinal involvement, reduction of the tumour by >25% in the maximum thoracic diameter was needed); or less than partial remission if these criteria were not met. The institutional review board of each participating centre approved the study protocol, and we obtained written informed consent from patients.

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to find a hospital bed and also because we felt that this procedure would increase general acceptance of the study. We used the minimisation method of Pocock for randomisation, to account for type of relapse and participating institution. The types of relapse considered were early and late first relapse and multiple relapses. We substituted dropouts during the first two courses of Dexa-BEAM chemotherapy with the next randomly assigned patient who presented with the same type of relapse. The numbers of randomised patients therefore differ between treatment groups if all patients are considered, but are balanced for the strata of chemosensitive patients.

Patients with early first relapse had initial complete remission of at least 3 months but less than 12 months after first-line chemotherapy. Patients with late first relapse had first remission of more than 12 months; these patients could only be included in the study if their first-line treatment had consisted of seven or eight drugs. Patients with multiple (second or later) relapses were eligible for the study after failure of any first-line or salvage chemotherapy. We measured remission duration from the end of first-line treatment or from the end of salvage therapy for multiple relapses to the date when the most recent relapse was diagnosed.

Treatment
The treatment protocol is shown in figure 1. All patients received two courses of Dexa-BEAM, consisting of dexamethasone (8 mg every 8 h orally, days 1–10), carmustine (60 mg/m² intravenously, on day 2), etoposide (250 mg/m² intravenously, days 4–7), cytarabine (100 mg/m² intravenously every 12 h, days 4–7), and melphalan (20 mg/m² intravenously, on day 3). Etoposide was given at a total dose of 1000 mg/m² per cycle because preliminary information from a dose-escalation study suggested this dose would be feasible. The total dose of etoposide given with cycles one and two of Dexa-BEAM was reduced to 600 mg/m² after 111 patients had been randomly assigned because of toxic effects.

Granulocyte-colony-stimulating factor was given on day 8 of Dexa-BEAM, and was continued until leucocyte recovery or until the last day of stem-cell harvesting if blood-progenitor cells were gathered. Bone-marrow or progenitor cells were harvested after the second course of Dexa-BEAM. Because of difficulties in obtaining sufficient numbers of progenitor cells after two courses of Dexa-BEAM, harvesting of stem cells after the first course of Dexa-BEAM was allowed. Restaging was mandatory for all patients after the second course of Dexa-BEAM. We

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>BEAM-HSCT (n=21)</th>
<th>Dexa-BEAM (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s disease</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Early treatment-related toxic effect</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Septicaemia after salvage therapy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Overwhelming post-splenectomy infection</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Fibrosis of lung</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Pneumococcal meningitis and pneumonia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Secondary leukaemia</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 3: Causes of death in chemosensitive patients at last follow-up

Figure 3: Freedom from treatment failure for patients with relapsed chemosensitive Hodgkin’s disease

Figure 4: Freedom from treatment failure for patients with early relapse (upper), late relapse (middle), and multiple relapses (lower) of Hodgkin’s disease
excluded patients with bone-marrow biopsy findings positive for Hodgkin’s disease at restaging. Only patients who had complete or partial remission after two courses of Dexa-BEAM continued treatment as per study protocol. These patients are called chemosensitive hereafter. Chemosensitive patients randomly allocated Dexa-BEAM received the third cycle as soon as restaging showed at least partial remission and haemolologic recovery had happened. The fourth cycle of Dexa-BEAM was given after haemolologic recovery from cycle three. Patients randomly assigned BEAM-HSCT underwent high-dose chemotherapy followed by transplantation of either autologous bone marrow or peripheral-blood-progenitor cells. BEAM was started 4 weeks after white blood cell count returned to normal after Dexa-BEAM, and consisted of carmustine (300 mg/m² intravenously, on day –7), etoposide (150 mg/m² intravenously, every 12 h from day –7 to day –4), cytarabine (200 mg/m², every 12 h from day –7 to day –4), and melphalan (140 mg/m², on day –3). Cryopreserved bone-marrow or peripheral-blood-progenitor cells were infused on day 0 followed by granulocyte-colony-stimulating factor until leucocyte recovery. Involved-field radiotherapy was recommended for all patients with residual lesions judged to represent active Hodgkin’s disease. We did the first restaging 3 months after end of treatment, and overall survival. Freedom from remission for less than 3 months, three had relapsed with chemosensitive hereafter. The primary endpoint of our study was freedom from treatment failure in patients with chemosensitive disease. Patients with progressive disease or who did not achieve complete or partial remission. 27 patients (19%) did not proceed to achieve complete or partial remission (n=8), protocol violations or refusal of patients (6), death from treatment-related toxic effects (8), and development of serious infections precluding further treatment by protocol (5). Causes of death were sepsicaemia in five patients, pneumonia, lung abscess, and seizures probably due to cerebral bleeding in one each.

Table 4: Overall survival and freedom from treatment failure (FFTF) at 3 years

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment</th>
<th>Proportion of patients who survived or had FFTF*</th>
<th>Percentage difference (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients with chemosensitive relapse (n=117)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>Dexa-BEAM BEAM</td>
<td>65%</td>
<td>–6% (–23.88 to 11.88)</td>
<td>0.331</td>
</tr>
<tr>
<td>FFTF</td>
<td>Dexa-BEAM BEAM</td>
<td>71%</td>
<td>–21% (–39.87 to –2.13)</td>
<td>0.019</td>
</tr>
<tr>
<td>Patients with early relapse (n=38)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>Dexa-BEAM BEAM</td>
<td>40%</td>
<td>–3% (–36.85 to 30.85)</td>
<td>0.623</td>
</tr>
<tr>
<td>FFTF</td>
<td>Dexa-BEAM BEAM</td>
<td>43%</td>
<td>–29% (–53.37 to –4.83)</td>
<td>0.008</td>
</tr>
<tr>
<td>Patients with late relapse (n=55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>Dexa-BEAM BEAM</td>
<td>75%</td>
<td>–18% (–38.59 to –2.59)</td>
<td>0.088</td>
</tr>
<tr>
<td>FFTF</td>
<td>Dexa-BEAM BEAM</td>
<td>93%</td>
<td>–31% (–58.20 to –3.80)</td>
<td>0.025</td>
</tr>
<tr>
<td>Patients with multiple relapses (n=24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival</td>
<td>Dexa-BEAM BEAM</td>
<td>83%</td>
<td>13% (–21.83 to 47.83)</td>
<td>0.421</td>
</tr>
<tr>
<td>FFTF</td>
<td>Dexa-BEAM BEAM</td>
<td>70%</td>
<td>10% (–34.13 to 54.13)</td>
<td>0.365</td>
</tr>
</tbody>
</table>

*Estimated from curves, so exact numbers cannot be given.
Dexa-BEAM. 61 patients started BEAM high-dose chemotherapy followed by autologous transplantation of bone-marrow cells (n=6) or peripheral-blood progenitor cells (50) median 5·5 weeks (3–39) after the second course of Dexa-BEAM. 5 patients (8%) did not receive transplantation because of progressive disease (n=2) or if the treating physician made that choice (3). Involved-field radiotherapy was documented in 11 patients (five Dexa-BEAM and six BEAM-HSCT).

3 months after end of treatment, 91 (78%) of 117 patients with chemosensitive disease were in complete or unconfirmed complete remission (39 Dexa-BEAM and 52 BEAM-HSCT; p=0·067). Nine patients (8%) had achieved partial remission (six Dexa-BEAM and three BEAM-HSCT), and 11 (9%) had not responded (six Dexa-BEAM and five BEAM-HSCT). The higher rate of complete remission in patients on BEAM-HSCT than in those on Dexa-BEAM was not associated with better freedom from treatment failure at 3 years (p=0·064). Five patients given Dexa-BEAM died of infectious complications, and one given BEAM-HSCT died. Frequency of toxic effects did not differ significantly between groups (table 2).

At last follow-up (3–78 months after end of treatment), 38 (32%) of 117 patients with chemosensitive relapse of Hodgkin’s disease had died (table 3). 64 patients (55%) were alive in complete remission, one (1%) was in partial remission, and eight (7%) were alive with active disease. 32 patients had relapsed. Eight (47%) of 17 patients relapsing after Dexa-BEAM alone received high-dose chemotherapy later in the course of their disease.

At median follow-up of 39 months (3–78), 3-year survival of chemosensitive patients was 68% (95% CI 59–77); thus, median survival was not reached. Survival did not differ significantly between treatment groups (table 4).

Freedom from treatment failure for chemosensitive patients who received BEAM-HSCT was significantly better than for patients treated with Dexa-BEAM (figure 3). Median time to treatment failure was 12 months for Dexa-BEAM but was not reached for BEAM-HSCT patients.

Freedom from treatment failure was significantly better for patients with early or late first relapse if treated with BEAM-HSCT (figure 4). At 3 years, the estimated percentage of failure-free patients with early first relapse given BEAM-HSCT was about four times greater than with Dexa-BEAM (table 4). For patients with late first relapse the failure-free portion at 3 years was a third greater for those given BEAM-HSCT than those given Dexa-BEAM. For patients with multiple relapses, this percentage at 3 years was three-quarters greater for patients treated with Dexa-BEAM than with BEAM-HSCT. Survival differences within strata did not differ significantly (figure 5).

Comparison stratified for type of relapse confirmed the significant difference in favour of BEAM-HSCT for freedom from treatment failure and survival (p=0·010). Overall survival again did not differ significantly (p=0·405).

**Discussion**

We have shown that patients with first relapse of Hodgkin’s disease and tumour sensitive to salvage chemotherapy have significantly better freedom from treatment failure with BEAM-HSCT than after Dexa-BEAM. Overall survival did not differ significantly between treatments.

We noted some imbalances in patients’ characteristics, distribution of type of relapse, and rate of complete remission after two cycles of Dexa-BEAM between treatments. These differences were accounted for by stratified Kaplan-Meier analyses, which showed the effect of the type of relapse, but did not show an effect for rate of complete remission after two cycles of Dexa-BEAM.

These findings accord with the results of a small randomised trial by the British National Lymphoma Investigation.11 About half the patients who failed salvage chemotherapy received high-dose therapy later in the...
course of disease. To some extent, therefore, that study and ours also compare early with late high-dose treatment. This, together with the fact that patients with relapsed Hodgkin’s disease can achieve multiple remissions with conventional treatment, could explain why freedom from treatment failure, but not overall survival, was better after high-dose chemotherapy in both studies.

Early effects of the conventional treatment chosen by our group was higher than generally seen.\textsuperscript{23} Not only did the first two courses of Dexa-BEAM result in eight treatment-related deaths and five life-threatening infections but also cycles three and four given to patients on Dexa-BEAM led to five additional deaths in 56 patients (9%), whereas only one of 61 patients (2%) undergoing BEAM-HSCT died early. A high death rate from toxic effects of salvage chemotherapy was reported by Tourani et al.\textsuperscript{24} This high death rate was possibly the consequence of high-dose chemotherapy in both studies, in particular concomitant etoposide—the drug that presumably was the main cause of the frequent septic complications seen. We for the first time have shown that high-dose chemotherapy, which is very similar to conventional salvage therapy, gives significantly better results in patients with late compared with early relapse of Hodgkin’s disease.

Length of initial remission is an important prognostic factor, and disease characteristics could be more important than the combination of cytotoxic drugs, even if doses at the upper end of the dose range are used.\textsuperscript{3,17-19} Patients with multiple relapses did not show any obvious benefit from high-dose chemotherapy. These patients could represent a subtype of Hodgkin’s lymphoma, characterised by a chronically relapsing course, which repeatedly responds to various treatment modalities, the modality itself perhaps not being important. The numbers of such patients were small, however, and conclusions are difficult to draw.

We wanted to restrict high-dose chemotherapy and its accompanying risks to patients with chemosensitive disease, because results of many studies have shown that this group of patients has the most favourable prognosis after high-dose chemotherapy.\textsuperscript{11,12,20} Patients with disease refractory to salvage chemotherapy have a less favourable outcome after stem-cell transplantation than patients with chemosensitive disease,\textsuperscript{21} although a few might still benefit from high-dose chemotherapy.\textsuperscript{22} Further the outlook for patients with relapsed Hodgkin’s disease.

We conclude that all patients with Hodgkin’s disease at first relapse responding to conventional salvage chemotherapy should be offered high-dose treatment followed by autologous stem-cell transplantation. Close observation of the long-term effects of conventional treatment and high-dose chemotherapy, and continued investigation of new treatment modalities in well-designed prospective trials, will help to improve further the outlook for patients with relapsed Hodgkin’s disease.

**Contributors**

N Schmitz, D Hasenclever, and V Diehl had the original idea and designed the study. B Pfister did the statistical analyses and interpreted results. M Sextro, M Sieber, and B Koch were responsible for management and quality control of clinical data and patients’ follow-up. All authors analysed and interpreted data, wrote the draft report, and approved the final version.

**Participating centres**

University of Cologne, Cologne, Germany (M Sieber); Eematologiet Umrutroppantio di Midollo Osseo, Genoa, Italy (A M Carella); Klinikum Chemnitz, Chemnitz, Germany (M Hasel); Klinikum Nürnberg, Nürnberg, Germany (F Boissevan); Universitätskraentschranken Eppendorf, Hamburg, Germany (R Zschaber); Zentrumsklinikum Augsburg, Augsburg, Germany (P Mueller); Krankenhaus Sioah, Hannover, Germany (H Kirchner); SAKK, Bern, Switzerland (A Lohri); University of Rostock, Rostock, Germany (S Decker); University of Bonn, Bonn, Germany (R Kleinschmidt); University of Munich, Munich, Germany (M Sandher); Klinikum Kreiss Herford, Herford, Germany (M Jost); University of Ki, Kil, Germany (N Schmitz); University of Münster, Münster, Germany (P Koch); Heartland’s Hospital, Birmingham, UK (D Milligan, D H Peters); Radium Hospital, Oslo, Norway (H Holte); University of Dresden, Dresden, Germany (R Naumann); University of Jena, Jena, Germany (P Lange); Krankenhaus der Barmherzigen Bruder, Regensburg, Germany (K Harjung); Marienhospital Hagen, Hagen, Germany (H Eimermacher); St Bernward-Krankenhaus, Hildesheim, Germany (Th Heide); Ev Krankenhaus Hamm, Hamm, Germany (B Huelskamp); University of Saarland, Homburg, Germany (L Truemper); University of Magdeburg, Magdeburg, Germany (A Borstel); Katharinen-Hospital Stuttgart, Stuttgart, Germany (U Ruether); Städtische Kliniken Oldenburg, Oldenburg, Germany (A Klasen, B Metzner); University of Stetgitz, Berlin, Germany (S Schwartz); University of Prague, Prague, Czech Republic (L Markova); University of Halle, Halle, Germany (Ch Fibick); Karolinska Hospital, Stockholm, Sweden (A Osterberg); Klinikum Marburg, Marburg, Germany (B Reckzeh); University of Essen, Essen, Germany (L Menzheh); Krankenanstalt Mutterhaus der Borromäerinnen, Trier, Germany (H Gabriel); Bruderkrankenhaus Trier, Trier, Germany (W Weber); Evangelisches Krankenhaus Essen-Werden, Essen, Germany (Ch Tiirer); Städt Krankenhaus Lübeck-Süd, Lübeck, Germany (H Bartels); Städtisches Klinikum Magdeburg, Magdeburg, Germany (M Baer); Praxis Altona, Hamburg, Germany (J Kneifel); Gemeinschaftspraxis Oldenburg, Oldenburg, Germany (B Oterma); University of Ulm, Ulm, Germany (H Paschermeier); Krankenhaus Nordwest Frankfurt, Frankfurt, Germany (O Klein); Ev Diakonie-Krankenhaus gGmbH Bremen, Bremen, Germany (Ch Diedenmann); Klinikum Schwörer, Schwör, Germany (R Schubert); Kreiskrankenhaus Radebeul, Radebeul, Germany (C Schulte); Klinikum der Stadt Ludwigshaf, Ludwigshaf, Germany (M Baldu); St Vincentius Krankenhaus Limburg, Limburg, Germany (K P Schalk); Klinikum Ludwigshaf, Ludwigshaf, Germany (D Nothnagel); Krankenhaus Maria-Hilf, Krefeld, Germany (S Pesch); Kreiskrankenhaus Heidenheim, Heidenheim, Germany (M Mueller); Max-Debrueck Zentrum Berlin, Berlin, Germany (D Krahl); Tampere University Hospital, Tampere, Finland (A Maekiiphera); Klinik II Lemgo, Lemgo, Germany (U Weil); Diakonissenkrankenhaus Stuttgart, Stuttgart, Germany (R Mueck); Kreiskrankenhaus Guben, Guben, Germany (W Schren); Thorax-Klinik der LVA Baden, Heidelberg, Germany (H Bischof); Kreiskrankenhaus Offenburg, Offenburg, Germany (G Koehring).

**Conflict of interest statement**

None declared.

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References


ARTICLES

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