IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. N05-03D

Autologous stem cell transplantation for soft tissue sarcoma[1]

Executive Summary

[1] Translation of the executive summary of the final report "Autologe Stammzelltransplantation bei Weichteilsarkomen" (Version 1.0; Status: 17.09.2009). Please note that this translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Autologous stem cell transplantation for soft tissue sarcoma

Contracting agency:
Federal Joint Committee

Commission awarded on:
15.03.2005

Internal Commission No.:
N05-03D

Publisher's address:
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Executive summary

Research question

The aim of this investigation was to assess the benefit of autologous hematopoietic stem cell transplantation (HSCT) on patient-relevant outcomes in patients with soft tissue sarcomas compared to a procedure without HSCT.

Methods

Population

The *World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of Soft Tissue and Bone*, published in 2002, was used as the basis for inclusion and exclusion of diagnoses in this report. The osseous and non-osseous types in the Ewing family of tumours are still treated separately in the WHO classification. Since close genetic links between the tumours in this family have been identified, they are now considered as one group. This was also assumed in this report, and all Ewing family of tumours diagnoses were excluded, as described in the report plan and notwithstanding the WHO classification.

Outcomes

The following outcomes were used in the investigation enabling patient-relevant outcomes to be evaluated: overall survival, event-free survival or a comparable outcome, serious adverse events (for example, treatment-related death, secondary neoplasia), and health-related quality of life.

Study types and study characteristics

All the evidence from clinical descriptions, including case reports as well, was evaluated, as it could be seen from the preliminary search that the number of studies with clinical data on autologous HSCT in soft tissue sarcomas was low. Studies with aggregated data were included if at least 80% of the analysed study participants had soft tissue sarcomas or a separate analysis for patients with soft tissue sarcomas had been carried out. Aggregated data often could not be included because they were based on a mix of included soft tissue sarcomas and other solid tumours. Providing the results of individual patients (individual data) were given, these were included in the benefit assessment.

Information procurement and identification of relevant studies

Sources for information procurement were bibliographic databases (MEDLINE/Ovid, EMBASE/Ovid, Cochrane Library/Wiley), study registries accessible online, literature

indexes, documents from the Federal Joint Committee (G-BA), and contacts with various institutes, professional associations, and study groups. The last bibliographic search was conducted on 29 May 2009 with a broader search strategy than the previous searches.

Assessment of study quality

The quality of the studies with control group and the estimation of bias potential were described and assessed by means of the following:

- comparability of patient and treatment characteristics in both groups
- method of allocating patients to the groups
- scope and accuracy of the data

The assessment of the remaining studies without control group was limited to the description of study characteristics. In the studies with individual data, those conditions were examined that were prerequisites for considering whether to conduct a pooled survival analysis.

Information synthesis

The results on rhabdomyosarcoma could be presented separately for this individual diagnosis. The scope of data for each of the other diagnoses was insufficient for diagnosis-specific reporting. As a result, the data of the remaining diagnoses were synthesized under the term “miscellaneous soft tissue sarcomas”.

The following conditions had to be met for the results to be included in the benefit assessment:

1. With aggregated data, an estimate had to be given for the overall survival or for the event-free survival or a comparable outcome (progression-free survival, disease-free survival). In some studies, patients with other entities were also included. In these cases, either the proportion of patients with the diagnoses included in the report had to be at least 80%, or the therapy results had to be clearly allocated to the patient group with soft tissue sarcomas.

2. With individual data, an estimate was calculated for the overall survival by means of a pooled survival analysis. The condition for including the data was that information was provided on survival or non-survival of individual patients as well as the point in time of each observation. In addition, the start of follow-up for all patients had to be clearly assigned to the time of transplantation or of high-dose chemotherapy.

Results

Search result and study design

A total of 105 studies were included in the assessment. Only 5 studies had a comparative, yet not randomized study design. The remaining 100 studies were case series or individual case descriptions.

Rhabdomyosarcoma

The results on the diagnosis of rhabdomyosarcoma were based on 63 studies with 652 patients (465 transplant patients), of which 4 were comparator studies; the remaining 59 studies consisted of case series or case descriptions. The majority examined were children and young adults.

A comparator study, in which high-risk patients were examined, had a prospective study design [Klingebiel T. Pediatr Blood Cancer 2008; 50(4): 739-745]. The difference in overall survival between the treatment groups was statistically significant and was estimated at 22% vs. 55% after 3 years and 15% vs. 52% after 5 years for transplant patients vs. non-transplant patients. Another comparator study, in which high-risk patients were examined as well, had a retrospective study design and was based on the results of a questionnaire [Hosoi H. Int J Clin Oncol 2007; 12(2): 137-145]. The difference in overall survival between the treatment groups was also statistically significant and was estimated at 53% vs. 18% after 3 years for transplant patients vs. non-transplant patients. Estimates for after 5 years could not be extracted. Both studies have a high bias potential, which is essentially due to a non-random allocation of patients to the treatment arms. Due to this, the results certainty in both studies in general must be open to question. The different treatment results are not immediately explicable. The different therapy regimens should be particularly noted in the two studies. In 2 further comparator studies, also with high bias potential, the differences between the results of the treatment groups were statistically not significant.

The estimates from the studies without control group were comparable with the above-mentioned results, although a wide range was observed. Our own calculation based on the individual data yielded 35% after 3 years (95% confidence interval 23 to 47) and 27% after 5 years (95% confidence interval 15 to 41). Only 42% of the patients included in the report (79 out of 187 patients) were suitable for evaluation in a pooled survival analysis.

Treatment-related deaths were noted for 15 transplant patients in 16 studies, secondary neoplasia for 3 transplant patients in 4 studies. There was a lack of data on toxicity in a large proportion of the included studies. Due to the low quantity of analysable data, it was not possible to evaluate toxicity. A study on health-related quality of life could not be included in the benefit assessment.

Miscellaneous soft tissue sarcomas

The results from the diagnosis group of miscellaneous soft tissue sarcomas are based on 54 studies with 288 patients (219 transplant patients). One study was designed as a comparative investigation [Ivanova NM. Vestn Ross Akad Med Nauk 2007; (10): 26-32]; the remaining 53 studies were either case series or case descriptions. In the studies on miscellaneous soft tissue sarcomas, the majority of those investigated were adults.

In the only comparator study, there was a statistically significant difference between the treatment groups for overall survival. The overall survival was estimated at 62% ±9.5% vs. 23% ±5.1% after 2 years for transplant vs. non-transplant patients. When assessing these results, it must be taken into account that this comparator study reveals a high bias potential due to an incomplete presentation of methods and results.

In the studies without control group (aggregated data), the corresponding estimates on overall survival of transplant patients after 2 years was 20%, 52% and 64%. Our own calculation based on individual data of transplant patients yielded 47% (95% confidence interval 31 to 61) after 2 years. Only 42% of the patients included in the report (52 out of 124 patients) were suitable for evaluation in a pooled survival analysis.

Treatment-related deaths were noted for 11 patients in 8 studies, secondary neoplasia for 1 patient in 1 study. For miscellaneous soft tissue sarcomas as well, there was a lack of data on toxicity in a large proportion of the included studies. Due to the low quantity of analysable data, an evaluation was not possible. Analysable results on health-related quality of life could not be identified.

Overall assessment

The bias potential of all studies must be classified as high on account of the design or study quality. The results from a prospective and a retrospective comparator study on rhabdomyosarcoma contradict each other. No robust results can be deduced from the comparator studies, and the significance of autologous HSCT in patients with soft tissue sarcomas cannot be determined.

Conclusions

The evidence available at the time of publication of this report is not sufficient to deduce a possible additional benefit or a harm of autologous HSCT in soft tissue sarcomas. Thus, at present, there is neither proof nor indication of (additional) benefit or of harm from autologous HSCT in soft tissue sarcomas.

At present, therefore, it does not appear justifiable to use autologous HSCT in patients with soft tissue sarcomas except in controlled clinical trials. The term “controlled clinical trials” includes non-randomized in addition to randomized controlled trials. However, adequate

conditions are required to minimize bias in comparisons, for example, by reducing selection bias. In the interests of the patient, a major improvement is urgently needed in the quality of the data, including making publication of the results compulsory. If transplantation is to be used, the patient must be properly informed over the uncertain quality of the data.

Keywords: autologous haematopoietic stem cell transplantation, high-dose chemotherapy, soft tissue sarcoma, rhabdomyosarcoma, systematic review

The full report (in German) is available on www.iqwig.de/index.597.html