IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. N05-03E

Autologous stem cell transplantation for breast cancer[1]

Executive Summary

[1] Translation of the executive summary of the final report "Autologe Stammzelltransplantation bei der Indikation Mammakarzinom" (Version 1.0; Status: 15.10.2009). 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 breast cancer

Contracting agency:
Federal Joint Committee

Commission awarded on:
15.03.2005

Internal Commission No.:
N05-03E

Publisher's address:
Institute for Quality and Efficiency in Health Care
Dillenburger Str. 27
51105 Cologne
Germany

Tel.: +49 221 35685-0
Fax: +49 221 35685-1
berichte@iqwig.de
www.iqwig.de

Autologous stem cell transplantation for breast cancer

Executive summary

Background

The Institute for Quality and Efficiency in Health Care (IQWiG) was commissioned by the Federal Joint Committee (G-BA) to assess the benefit of autologous stem cell transplantation for breast cancer.

Research question

The aims of this investigation were to assess studies on certain types of autologous stem cell transplantation in breast cancer patients:

- compared to cytostatic therapy without stem cell support, and
- compared with each other.

The focus was on patient-relevant outcomes.

Methods

- The target population in the studies to be assessed comprised patients with breast cancer. Only studies that had a proportion of breast cancer patients greater than 80% were included, or in which subgroup analyses had been carried out for this patient group.
- The following patient-relevant outcomes were used in the investigation: survival (overall survival), disease-free survival or a comparable outcome, treatment-related complications, and health-related quality of life.
- The literature search for relevant published studies was conducted in the following bibliographic databases: BIOSIS Previews/MEDLINE/EMBASE (Ovid), and The Cochrane Library (Wiley); the last search was undertaken in October 2008. In addition, newly published literature in MEDLINE and EMBASE was retrieved up to August 2009 via Ovid's AutoAlert function. A series of additional sources were searched in order to identify further published and unpublished studies. This included literature indexes of relevant secondary publications (systematic reviews, current narrative reviews, HTA reports), abstracts from relevant conference proceedings, and international study registries accessible online.
- Only randomized trials were included in the benefit assessment. All results relevant to the benefit assessment were examined for their certainty of results, which consisted of risk of bias and the accuracy of the results. If questions arose during the assessment and no

answers could be found in the publications, authors of publications on studies were contacted. Provided that the trials were comparable as far as the research question was concerned, quantitative syntheses of the individual results were carried out using meta-analyses based on models with random effects.

Results

The results given below are presented separately for non-metastatic and metastatic breast cancer. With the exception of one male patient, only women were treated in the trials included in the benefit assessment.

Non-metastatic breast cancer

Included in the benefit assessment on non-metastatic breast cancer (which means that there are no distant metastases according to the TNM classification of malignant tumours) were 11 randomized trials on single autologous stem cell transplantation (single autologous SCT) and 2 trials on tandem autologous transplantation (tandem autologous SCT). All trials were designed as superiority trials versus conventional or dose-dense chemotherapy. In the trials on single autologous SCT, there were 2393 patients in the intervention arm and 2377 in the control arm, and in the trials on tandem autologous SCT there were 240 patients in the intervention arm and 241 in the control arm.

Those included in the trials were patients with operable breast cancer and at least 4 positive axillary lymph nodes. The intervention and control groups were balanced according to patient characteristics as far as possible.

The main criteria in evaluating study and publication quality were appropriate allocation concealment, traceability of patient flow, reporting independent of the results, and data consistency within the publications. When these aspects were considered, there was a high risk of bias in 8 out of 13 included trials (7 on single, 1 on tandem autologous SCT).

In all the trials that compared single autologous SCT with conventional or dose-dense chemotherapy, the outcome “overall survival” did not show a statistically significant difference between the treatment arms. This result was confirmed by a meta-analysis. However, in 1 trial comparing tandem autologous SCT with dose-dense chemotherapy, an indication of benefit of tandem autologous SCT could be derived for overall survival at 5 years. However, this indication of benefit is limited to the treatment regimen used in the trial.

A meta-analysis of disease-free survival or a comparable outcome at 5 years showed a statistically significant difference in favour of single autologous SCT compared to conventional chemotherapy, so that proof of a benefit of single autologous SCT could be derived at 5 years. In the comparison of tandem autologous SCT with dose-dense chemotherapy, there was also an indication of a benefit of tandem autologous SCT at 5 years.

This indication of benefit is limited to the treatment regimen used in the only trial that showed a statistically significant advantage of tandem autologous SCT.

Serious complications were classified into 3 categories and assessed: treatment-related mortality, additional severe or life-threatening or fatal treatment-related complications in toxicity grades 3 to 5,[2] and secondary neoplasia.

- There were no noticeable differences between single and tandem autologous SCT in treatment-related mortality. Only 4 trials on single autologous SCT could be included in a meta-analysis. They revealed high heterogeneity in the results. Overall, there was ambiguity in the data due to the large quantity of missing data in the remaining trials.

- Based on the results of individual trials, an indication of potential harm from single autologous SCT in a comparison with conventional-dose chemotherapy could be derived for the outcome "severe, life-threatening or fatal treatment-related complications". Meta-analyses could not be conducted for this (these) outcome(s), either. There was no benefit of or harm from tandem autologous SCT for either of the treatment arms in the trials.

- There were no relevant differences between the intervention and control groups for the outcome "secondary neoplasia". The meta-analyses conducted did not yield a statistically significant difference between the treatment arms, either. Moreover, there was no indication of harm or benefit in the comparison of tandem compared to single autologous SCT.

For health-related quality of life, 5 trials on single autologous SCT versus conventional chemotherapy could be included in the benefit assessment. A meta-analytical synthesis of the results was not possible due to the different survey tools used and the differing reporting of results. Overall, the results showed that there was a markedly greater reduction, in part statistically significant, in health-related quality of life for individual functions and symptoms in the group of transplant patients after treatment. Common to all results was the fact that these differences decreased with increasing time after treatment, so that in the long-term no disadvantage of single autologous SCT could be derived from these results. Due to a lack of data, the benefit of or harm from tandem autologous SCT could not be evaluated.

Subgroup analyses from 5 trials on single autologous SCT and from 1 trial on tandem autologous SCT could be included in the benefit assessment. Overall, based on the interaction test carried out, advantages from single autologous SCT could be derived for younger patients but it remained unclear whether the age limit should be 40 or 50 years of age. Moreover, based on 1 trial in each case, there was an advantage for pre-menopausal patients, for patients in a higher grading group, with higher nodal status or positive oestrogen receptor status or

[2] According to severity grade 3-5 of the National Cancer Institute Common Terminology Criteria for Adverse Events

negative HER2/neu status. Subgroup analyses on tandem autologous SCT were only carried out in 1 trial, but information on the interaction between subgroup characteristic and treatment was lacking. Based on these results, neither a benefit of nor a harm from autologous transplantation could be derived for individual subgroups.

Metastatic breast cancer

Included in the benefit assessment on metastatic breast cancer were 4 randomized trials on single and 2 trials on tandem autologous SCT. All trials were designed as superiority trials. Patients in the control group were treated either with conventional chemotherapy or, as in 1 trial, with single autologous SCT (intervention: tandem autologous SCT). In the trials on single autologous SCT there were 342 patients in the intervention arm and 321 in the control arm, and in the trials on tandem autologous SCT there were 142 patients in the intervention arm and 138 in the control arm.

Breast cancer patients with distant metastases were included in these trials. The trials were characterized by a high proportion of patients in partial remission (71% to 88%). Apart from a few exceptions, the trials were balanced in patient characteristics.

Evaluating the risk of bias across outcomes of all included trials yielded the grading “high” in 3 out of 6 trials (2 on single autologous SCT, 1 on tandem autologous SCT).

A statistically significant difference for the outcome “overall survival” in favour of single autologous SCT was observed only in 1 out of 4 trials comparing single autologous SCT with conventional chemotherapy. There was great heterogeneity in the meta-analysis of overall survival at 3 years, so that calculating a common estimate was dispensed with. In the only trial that showed a statistically significant difference in overall survival in favour of single autologous SCT, no indication of benefit could be derived as the remaining 3 trials included were consistent in not showing any superiority of single autologous SCT. In the 2 trials on tandem autologous SCT, there were no statistically significant differences between the treatment groups.

In 3 out of 4 trials on single autologous SCT, there was a statistically significant advantage for autologous SCT in “disease-free survival” or a comparable outcome. This effect was confirmed by a meta-analysis of disease-free survival at 3 years, so that proof of a benefit of single autologous SCT compared to conventional chemotherapy could be derived. With regard to tandem autologous SCT, no statistically significant difference between the treatment arms could be observed for this outcome in either of the 2 trials included in the benefit assessment.

As in the trials on non-metastatic breast cancer, serious complications were divided into 3 categories and assessed:

- Treatment-related mortality was only registered in the transplantation arms, whereby there were no noticeable differences between single autologous SCT and tandem autologous SCT. Due to insufficient or missing data on the control groups, it was not possible to carry out meta-analyses on this outcome. A potential harm could not be derived from the available data on autologous SCT.

- Severe toxicity was increased in the transplantation arm in all trials that compared single or tandem autologous SCT with conventional chemotherapy. Where it was possible to do our own calculations, statistically significant differences were revealed between the treatment groups. Thus, there is an indication of harm from single autologous SCT in the above-mentioned comparison. In the comparison of tandem with single autologous SCT, there was no indication of benefit or harm. Meta-analyses could not be carried out for this (these) outcome(s), either.

- Secondary neoplasia was reported in 2 trials only, of which only 1 trial had data available for the control group as well. The number of patients was low in both treatment arms. As a result of these factors, neither an advantage nor a disadvantage of autologous SCT could be derived for this outcome.

For the outcome “health-related quality of life”, no trial could be included in the benefit assessment.

Subgroup analyses were carried out in 2 trials on single autologous SCT. As no interaction tests were performed in any of the subgroup analyses included in the benefit assessment, it remained unclear whether certain patient groups benefited from autologous SCT.

Conclusions

In the case of non-metastatic breast cancer – i.e. there are no distant metastases - there is proof of a benefit of single autologous SCT compared to conventional chemotherapy at 5-years’ disease-free survival or a comparable outcome. However, there is also an indication of harm due to the occurrence of severe, life-threatening complications. This indication of harm can also be applied to the comparison with dose-dense chemotherapy. In the case of tandem autologous SCT when compared to conventional-dose chemotherapy, neither proof nor indications of benefit or harm can be derived for the outcomes assessed in this report. In contrast, if tandem autologous SCT is compared with dose-dense chemotherapy, there is an indication of benefit for the outcomes “overall survival” and “event-free survival”. However, this indication is limited to the therapy regimen in the WSG AM-01 trial, from which this benefit was derived. It must be noted that, with the exception of 1 trial, anthracycline-based chemotherapy was used in the control treatment of all trials included in the benefit assessment. Nowadays, a taxane-based chemotherapy protocol is generally recommended for patients with non-metastatic, nodal-positive breast cancer.

In the case of metastatic breast cancer, there is proof of a benefit of single autologous SCT compared to conventional-dose chemotherapy for "disease-free survival" or a comparable outcome. In contrast, there is an indication of harm due to the occurrence of severe, life-threatening complications. In the case of tandem autologous SCT when compared to conventional-dose chemotherapy, there is also an indication of harm due to the occurrence of severe, life-threatening complications. No proof or indication of benefit can be derived for tandem autologous SCT for any of the outcomes assessed in this report.

It cannot be excluded that individual subgroups of patients with breast cancer benefit from autologous SCT. However, subgroup analyses were only carried out in a few trials on selected patient collectives, and the statistical significance of the subgroup differences remains unclear. Consequently, no proof or indication of benefit can be derived.

For patients with metastatic breast cancer in particular, for whom there are still no curative treatment options, it is necessary to provide alternative treatment approaches while taking account of patient preferences and possibly in combination with autologous SCT. As the initial introduction of autologous SCT into health care was based on uncertain data, other therapy approaches should only be evaluated within controlled trials.

Keywords: autologous haematopoietic stem cell transplantation, high-dose chemotherapy, dose-dense chemotherapy, myeloablative, breast cancer, randomized trial, systematic review

The full report (in German) is available on www.iqwig.de/index.598.html