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Stem cell transplantation for multiple myeloma[1]

Executive Summary

[1] Translation of the executive summary of the final report "Stammzelltransplantation bei Multiplem Myelom" (Version 1.0; Status: 19.09.2011). Please note: 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.

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This report was prepared in collaboration with external experts. According to § 139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received." The Institute received the completed form "Disclosure of conflicts of interest" from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Appendix F of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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IQWiG thanks the external reviewer for his comments on the preliminary report. However, the external reviewer was not involved in the preparation of the final report. Individual sections and conclusions in the final report therefore do not necessarily reflect his opinion.

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Executive summary

Background

Multiple myeloma is a malignant tumour disease, which leads to the death of most symptomatic patients – even if treated. There are wide fluctuations in survival, depending on the time of diagnosis, the stage of the disease and specific prognostic factors. Spontaneous cure is unknown. For this reason, therapy should achieve long remission periods with the best possible quality of life for the individual patient.

Research question

The aim of the present investigation was to assess the benefit with respect to patient-relevant outcomes of a treatment strategy for multiple myeloma incorporating stem cell transplantation. Firstly, the added benefit was investigated of multiple autologous stem cell transplantation in comparison with the accepted standard therapy of simple autologous stem cell transplantation. Secondly, the added benefit of allogeneic stem cell transplantation was examined with respect to the donor type (related or unrelated), the intensity (reduced-intensity or non-reduced-intensity conditioning therapy), whether the treatment was administered alone or in combination (with autologous transplantation) and in comparison with a drug strategy (for example, with cytostatic chemotherapy or immunomodulatory therapy). Nine possible comparisons can be derived from this research question.

Methods

The target population consisted of patients with multiple myeloma. Studies were included in which the proportion of patients with multiple myeloma was at least 80% or in which a subgroup analysis was performed for these patients.

The patient-relevant outcomes considered were survival time (overall survival or survival in combination with patient-relevant events, such as disease progression), relevant therapy- and disease-related adverse events (such as therapy-related mortality, severe potentially fatal or fatal acute GVHD [graft-versus-host-disease], potentially fatal or fatal infections, secondary neoplasia, etc.) and health-related quality of life. If there were not enough studies of a high level of evidence and/or of adequate quality, lower level evidence studies including retrospective controlled studies were included in the assessment in addition to randomized controlled trials. The assessment could also include studies without a control group if indications emerged during work on the project that the test interventions were capable of causing *dramatic effects* with respect to the research questions.

A systematic literature search was performed in the following databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (Clinical Trials). The search for relevant secondary publications was performed in the databases MEDLINE and EMBASE in parallel to the search for relevant primary literature, as well as with a search in the databases Cochrane Database of Systematic Reviews (Cochrane Reviews), the Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment

Database (Technology Assessments). The last search was performed on 17.01.2011. In addition, trial registries as well as documents of the G-BA were searched for relevant studies, and, if necessary, study groups, professional societies and the authors of relevant studies were contacted.

Results

A total of 16 studies fulfilled the inclusion criteria and were included in the benefit assessment. These provided results on 5 of the 9 possible comparisons. None of the studies examined health-related quality of life.

1) Multiple autologous versus single autologous stem cell transplantation

Five studies were identified on this research question. However, the full texts of 3 of these have not yet been published, and they were therefore excluded from the benefit assessment. A total of 720 patients were included and evaluated in the 2 randomized multicentre studies that have been published as full texts. The median period of observation was between 68 and 139 months.

The risk of bias across outcomes in these 2 studies was assessed as being low. However, the risk of bias for the outcome "recurrence-free survival" in Attal was assessed as high. The 2 included studies did not give consistent results on overall survival. On the one hand, the older study (Attal 2003) gave a statistically non-significant advantage for the group with tandem autologous stem cell transplantation (7-year survival: 38% versus 28%, p = 0.08 in the log rank test). On the other hand, the more recent study (Cavo 2007) employed the currently recommended therapy protocol for the comparator group and found no numerical advantage: 7-year survival, 43% versus 46%, p = 0.90 in the log rank test. Cavo 2007 reported statistically significant advantages for the event-free survival (EFS) in favour of tandem autologous stem cell transplantation: 5-year rate of EFA 29% versus 17%, p = 0.001 in the log rank test.

In Attal 2003, this advantage was no longer statistically significant in the long-term evaluation: 10-year rate of EFS 13% versus 6%, p = 0.06 in the log rank test. For recurrence-free survival, both studies reported statistically significant advantages in favour of tandem autologous stem cell transplantation. However, one must assume that the results of Attal 2003 – for which there are no long-term data – incorporate relevant bias with respect to their long-term conclusion. In contrast to the main publication with the shorter follow-up period, the long-term follow-up no longer found statistically significant results with respect to either overall survival or event-free survival.

For all other outcomes (therapy-related mortality and therapy-related complications), there was neither an advantage nor a disadvantage for either of the treatment groups.

In addition to the 2 studies assessed in this report, 3 completed randomized trials were identified (DSMM-1, GMMG-HD2 and MAG95), 2 of which were under German

management. These studies were started in the 1990s and recruitment completed in 2002. The results have been presented at scientific meetings for several years, but have never been published as full texts. In spite of enquiries to the study investigators, no study reports or manuscripts were provided.

In the studies comparing tandem versus single stem cell transplantation (Attal 2003, Cavo 2007, DSMM-1, GMMG-HD2 and MAG95), a total of 1528 patients were included, 808 of whom (53%) were in the studies that have not been published as full texts. Thus, there are no adequate data for most of the relevant studies and most of the patients. What is more, the available information from the studies which have only been published as abstracts implies that the results of these studies were not positive, so that relevant publication bias cannot be excluded. Thus no proof, indication or hint of added benefit or harm of either of the 2 therapy options has been established.

2) Allogeneic stem cell transplantation with related donor versus drug therapy

Information on this comparison can be inferred from 2 of the 3-arm multicentre studies with 502 patients (thereof 492 evaluated). The median observation period in the treatment groups was between 3 and 92 months. In both studies, the results from the non-randomized arm with allogeneic stem cell transplantation were compared with the results from one of the randomized arms – comparison of autologous stem cell transplantation with non-myeloablative chemotherapy. The non-randomized allocation to the group with allogeneic stem cell transplantation was on the basis of donor availability, age and/or concomitant disease – which makes it more difficult to interpret the results. Neither of the studies undertook an analysis of the comparison of interest here. The risk of bias for both studies was classified as high. It should be borne in mind that for important aspects of the risk of bias, bias in favour of the interventional treatment could be assumed, as the inclusion criteria for age in both studies favour allogeneic stem cell transplantation. For both studies, the hazard ratios (HR) for overall survival gave a clear and statistically significant effect to the detriment of allogeneic stem cell transplantation: allogeneic stem cell transplantation versus non-myeloablative chemotherapy, HR = 2.52 [1.68; 3.83]; HR = 6.36, 95% CI [3.33; 12.14]). Because of the high risk of bias of the studies, the results of the individual studies only provide a hint that allogeneic stem cell transplantation is inferior to non-myeloablative chemotherapy to a relevant degree. For progression-free survival, there was no statistically significant difference between the treatment groups in the 2 studies.

For therapy-related mortality, there were higher rates in the group of patients receiving allogeneic stem cell transplantation (34% versus 4%; 39% versus 0.4%; $p < 0.001$ in both studies), as well as an increased rate of infection in the group of allogeneically transplanted patients. This was also interpreted as a hint of relevant inferiority with respect to these outcomes.

Because of their designs, no indications or proofs of added benefit or harm could be deduced for these studies. One exception is acute (grade III to IV) and chronic extensive GVHD,

which in 1 study had a frequency of 11% and 25% and was fatal in 2 cases (6%) in the second study. Bearing in mind that this adverse effect of treatment can only occur in the group of allogeneically transplanted patients, this was assessed as proof of harm.

3) Myeloablative allogeneic stem cell transplantation with related donor versus autologous stem cell transplantation

Seven non-randomized controlled trials were identified, in which 976 patients were evaluated. In 4 of these studies, it was unclear whether these were planned in a fully prospective fashion. The median observational period varied between 15.6 and 92 months. Both of the studies in the previous comparison – allogeneic stem cell transplantation with related donor versus drug therapy – also gave results for this comparison. For all 7 studies, the risk of bias was assessed as high. For example, none of the studies fulfilled the criteria of genetic randomization. Moreover, in 6 of the 7 studies, allocation to the treatment groups was dependent on the age of the patient. None of the studies showed that the groups were comparable or adjusted for incomparabilities. Finally, the differences in inclusion criteria made it difficult to interpret the results – aside from the risk of bias in all studies – and it was thus impossible to deduce proof or indications of benefit or harm.

All 7 studies provided results on overall mortality; in all cases, the direction of the effect was to the detriment of allogeneic stem cell transplantation. The hazard ratios were between 1.25 and 11.9 to the detriment of allogeneic stem cell transplantation. With one exception, all studies provided information on transplantation-related or therapy-related mortality. All estimates indicated clear numerical inferiority of allogeneic stem cell transplantation. The results on the outcomes overall survival and therapy-related or transplantation-related mortality in each case also provided hints of a relevant inferiority of allogeneic stem cell transplantation in comparison to autologous stem cell transplantation.

For other outcomes – event- or progression-free survival, secondary neoplasias, fatal infections – no effect could be deduced on added benefit or harm. One exception is the outcome GVHD, which occurred at a frequency of 29% (acute GVHD III-IV) or 52% (extensive chronic GVHD). Bearing in mind that this adverse effect can only occur in the group of allogeneically transplanted patients, this result was assessed as proof of harm.

4) Allogeneic stem cell transplantation with reduced-intensity conditioning versus allogeneic stem cell transplantation with myeloablative conditioning

For this research question, 2 retrospective registry analyses and a prospective study with a historical comparison were included. The median duration of observation varied between 6 and 36 months. In all studies, the risk of bias was classified as high – both at the study level and at the outcome level. A high risk of bias was inherent in the study design itself.

There was no consistent picture, for either the overall survival or for progression-free survival. In all 3 studies, there was a statistically significant reduction in the treatment group

with reduced-intensity conditioning with respect to the therapy-related or non-recurrence-related mortality. As a consequence of the high risk of bias and the somewhat heterogeneous results, no proof or indication of added benefit or harm from either treatment option could be deduced for any of the outcomes of interest.

5) Allogeneic stem cell transplantation with reduced-intensity conditioning versus autologous stem cell transplantation

For the research question of this comparison, 4 multicentre, prospective, non-randomized controlled trials were included. The median duration of observation varied between 56 and 85 months. The risk of bias across outcomes for 2 studies with genetic randomization was assessed as low and for the 2 other studies as high. However, in 1 of the 2 genetically randomized studies, the risk of bias at the level of the outcomes "overall survival" and "progression-free survival" was assessed as high. In addition, 3 studies were identified which have not yet been published as full texts and which were therefore excluded from the benefit assessment.

Two of the studies published in full text fulfilled the requirements of *genetic randomization*. In one of these studies, there was a statistically significant advantage with respect to overall survival in favour of a treatment strategy with reduced-intensity conditioning and allogeneic stem cell transplantation. In the other study with a high risk of bias for this outcome, there was a numerical advantage for a treatment strategy with autologous stem cell transplantation up to the time point of approx. 33 months. From an observation period of 36 months, a statistically significant advantage could be shown for a treatment strategy with reduced-intensity conditioning and allogeneic stem cell transplantation. Similar to overall survival, 1 genetically randomized study found a statistically significant advantage for the auto-allo-RIC group with respect to event-free survival. In the second genetically randomized study with a high risk of bias for this outcome, there was an advantage for the auto-allo-RIC group at longer follow-up times; there was a statistically significant result at the time point of 60 months. Up to approx. 23 months, there was a numerical advantage for the (auto-)auto group.

In all studies, the proportion of all therapy-related deaths tended to be higher in the auto-allo-RIC group than in the (auto-)auto group – being 10-16% versus 2-5%. The differences were statistically significant in only 1 study ($p<0.001$). Acute and chronic cases of GVHD were relatively frequent here too, with 24-43% acute GVHD and 36-66% chronic GVHD.

A total of 913 patients were included in these 4 studies, in comparison with 1131 patients in 3 studies (BMT-CTN 0102, DSMM-V and HOVON 50/54) that were not included in the benefit assessment, as they are not yet available in the full text. For 2 of these studies, final analyses were presented at a scientific meeting at the end of 2010. An interim analysis has been published for another study. As for this research question too, the assessment can only be made on the basis of a relevantly incomplete study pool, no proof, indication or hint can be established for added benefit or harm from either therapy option.

Conclusion

This report has examined 9 comparisons of the benefit of stem cell transplantation in multiple myeloma. All statements are primarily based on stem cell transplantation in patients who had not been previously treated; 2 comparisons also included mixed populations of patients with and without pretreatment; there was no study with patients refractory to therapy. The studies employed patient-relevant outcomes – overall survival, event-free survival or a comparable outcome, adverse events and health-related quality of life. There was no study for any comparison which permitted a statement about quality of life. An assessment of the relevance of autologous stem cell transplantation (in comparison to non-transplantation strategies) which is the first line therapy recommended in guidelines, was not an object of this report. Consequently, this report does not examine whether autologous stem cell transplantation might be of importance as a first-line therapy in combination with and in comparison to *newer* drugs (thalidomide, lenalidomide, bortezomib, etc.).

In addition to the 2 studies that were included in the benefit assessment and compared tandem and single autologous stem cell transplantation, another 3 studies were identified. These studies had been completed years previously, but had never been published as full text. These had about the same number of patients as the 2 studies included. In spite of enquiries to the authors, no study reports or previously unpublished manuscripts were made available. As moreover, the available information tends to suggest that the results of these studies were not positive, the presence of relevant publication bias cannot be excluded.

For the combination consisting of autologous and allogeneic stem cell transplantation with *reduced-intensity conditioning*, 4 studies were included in the benefit assessment. However, 3 additional studies were identified, with about the same number of patients, but which had not yet been published as full text. A final analysis has recently been presented for 2 of these studies; only an interim analysis is available for the third study. As the assessment for both of these research questions can only be made on the basis of a relevantly incomplete study pool, no proof, indication or hint of added benefit or harm can be established for either of the 2 therapy options.

Due to a lack of studies, no statement can be made about the use of *unrelated* donor sources in allogeneic stem cell transplantation.

If *related* donors are used as the source of stem cells, there are hints of relevant inferiority with respect to overall survival and adverse events for allogeneic stem cell transplantation with myeloablative conditioning. This inferiority was in comparison with both autologous stem cell transplantation and with non-myeloablative chemotherapy. Harm was considered to have been proven for GVHD (grade III-IV), which only occurs in allogeneic stem cell transplantation. This must be seen in the context of the lack of superiority of allogeneic stem cell transplantation with respect to the other outcomes analysed.

In the current state of knowledge, the use of allogeneic stem cell transplantation for the indication multiple myeloma can only be defended in the context of clinical studies. An essential requirement for future studies is that they should record quality of life and use randomized study designs. This applies all the more as this disease is still regarded as being incurable in most patients.

Keywords: multiple myeloma, stem cell transplantation, systematic review, benefit assessment

The full report (German version) is published under www.iqwig.de