IQWiG Reports – Commission No. N14-03

Stem cell transplantation for multiple myeloma – update[1]

Executive Summary

[1] Translation of the executive summary of the rapid report *Stammzelltransplantation bei Multiplem Myelom – Update* (Version 1.0; Status: 30 March 2015). 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.

The responsibility for the contents of the report lies solely with IQWiG.

According to §139 b (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 for disclosure of potential 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 E 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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Executive summary

On 16 October 2014 the Federal Joint Committee (G-BA) wrote to the Institute for Quality and Efficiency in Health Care (IQWiG) to commission the update of the benefit assessment of stem cell transplantation in multiple myeloma.

Research question

The aim of the present investigation was to answer the question whether and, if any, which changes of the conclusion of the final report N05-03C and of the working paper GA11-01 resulted from the literature on the topic of commission N05-03C published in the meantime.

Methods

In principle, the same methods were used for the present rapid report as in commission N05-03C.

Randomized controlled trials (RCTs), controlled clinical trials (CCTs) or comparative studies below the level of evidence of a CCT (so-called non-CCTs) could be included as relevant scientific literature for 9 possible different comparisons. Studies with lower level of evidence were only included in the assessment when studies with higher level of evidence were not available for comparison in sufficient numbers and/or quality.

A systematic (update) literature search was performed in the following databases: MEDLINE, Embase, Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant (systematic) reviews took place in the databases MEDLINE and Embase in parallel with the search for relevant primary studies. Searches were also conducted in the databases Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (Other Reviews), and the Health Technology Assessment Database (Technology Assessments). The update of the search was conducted on 17 October 2014. Furthermore, (systematic) reviews and the publicly accessible trial registries ClinicalTrials.gov and ICTRP Search Portal were screened. The G-BA additionally made enquiries to authors regarding study results of studies for which no full publication was available and which were already identified in the final report N05-03C.

The selection of relevant studies was performed by 2 reviewers independently of each other for the result from the bibliographic literature search and the search in publicly accessible trial registries as well as for potentially relevant studies from (systematic) reviews.

To evaluate the certainty of results, the risk of bias at study and outcome level was assessed and rated as low or high respectively. The results of the individual studies were described, organized by outcomes. The assessment of the evidence was conducted according to the currently valid methods paper.

Results

There were no data on 3 of 9 research questions at the time point of the final report N05-03C or when the working paper GA11-01 or this rapid report were produced. This concerned the following research questions: allogeneic stem cell transplantation with unrelated donor versus drug therapy, myeloablative allogeneic stem cell transplantation with unrelated donor versus autologous stem cell transplantation, and allogeneic stem cell transplantation with reduced-intensity conditioning versus drug therapy.

In the final report N05-03C, studies could be identified for 3 further research questions and used for the benefit assessment (multiple versus single autologous stem cell transplantation, allogeneic stem cell transplantation with related donor versus drug therapy, and myeloablative allogeneic stem cell transplantation with related donor versus autologous stem cell transplantation). No further studies on this were found in the update search. Hence the overall conclusions of the final report N05-03C did not change.

Further studies could be identified in the update search on the 3 remaining research questions. The results are described below.

Allogeneic stem cell transplantation with related donor versus allogeneic stem cell transplantation with unrelated donor

In the update search, one small retrospective study (non-CCT) (El-Cheikh 2012) could be identified on the research question of allogeneic stem cell transplantation with related donor versus allogeneic stem cell transplantation with unrelated donor. There was no statistically significant difference in the study for any of the reported outcomes such as overall survival, therapy- or transplantation-related mortality or graft-versus-host disease (GVHD). No hint of benefit or harm could be derived for any outcome.

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

In addition to the 3 studies already included in the final report N05-03C (Badros 2002, Crawley 2007, Shaw 2003), one further publication could be identified (Bensinger 2012) for the research question of allogeneic stem cell transplantation with reduced-intensity conditioning versus allogeneic stem cell transplantation with myeloablative conditioning. Like the other 3 studies, this study was also a non-CCT. It pointed in the same direction as the 3 studies included before regarding the outcomes “overall survival”, “therapy-related mortality” and “GVHD”. In addition, the newly included Bensinger 2012 study was the only study to report data on serious adverse events within this research question. All serious adverse events such as fatal infection (26% versus 4%), multi-organ failure (11% versus 0%), idiopathic pneumonia syndrome (6% versus 0%) and fatal acute GVHD (13% versus 0%) occurred statistically significantly more often in the group with allogeneic stem cell transplantation and myeloablative conditioning than in the group with allogeneic stem cell transplantation with reduced-intensity conditioning. Only fatal chronic GVHD (1% versus

9%) was statistically significantly more common in the latter group than in the group with allogeneic stem cell transplantation and myeloablative conditioning. Due to the overall low quality of the certainty of results, the overall assessment of the final report N05-03C did not change: No hint of benefit or harm could be derived for any of the outcomes in this research question. The studies included provided no information on health-related quality of life or psychosocial aspects.

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

Most studies were available on the last one of the 9 research questions. Allogeneic stem cell transplantation with reduced-intensity conditioning was compared with autologous stem cell transplantation in a total of 6 studies. Four of these studies already formed part of the final report N05-03C (Björkstrand 2011, Bruno 2007, Garban 2006, Rosinol 2008). Another study was evaluated in the working paper GA11-01 (BMT CTN 0102). Besides a study update on the Björkstrand 2011 study, a 6th study was identified in the update search for this rapid report (HOVON 50/54). All studies were CCTs, 2 of which fulfilled the criteria of a so-called genetically randomized trial.

Regarding overall survival, there was overall a heterogeneous picture with a statistically significant result (Bruno 2007: hazard ratio = 0.5, 95% confidence interval [0.3; 0.8], p-value < 0.001) in favour of a treatment strategy with hybrid transplantation (auto-allo-RIC) in comparison with tandem autologous stem cell transplantation (auto-auto). In the Björkstrand 2011 study, in which the patients in the control arm had the option to undergo simple or tandem autologous stem cell transplantation, a numerical advantage of the (auto-)auto group was observed up to a follow-up period of approximately 33 months (see final report N05-03C). After this time point, there was a numerical advantage of the auto-allo-RIC group, which was statistically significant at the time point of 8 years after the first transplantation (p-value = 0.03). There were no statistically significant differences between the treatment groups in the 4 other studies (BMT CTN 0102, Garban 2006, HOVON 50/54, Rosinol 2008). The information from the HOVON-50/54 study and from the study update on the Björkstrand 2011 study newly included in this rapid report did not change the derivation of the overview of the evidence in comparison with the working paper GA11-01: The studies provided an indication that the treatment strategy with reduced-intensity conditioning and allogeneic stem cell transplantation in comparison with (tandem) autologous stem cell transplantation has an added benefit in overall survival.

The proportion of therapy-related deaths tended to be higher in the auto-allo-RIC group than in the (auto-)auto group in all studies that reported the results on this patient-relevant outcome. In 3 studies (BMT CTN 0102, Björkstrand 2011, HOVON 50/54), statistically significant disadvantages were reported for the auto-allo-RIC group ($p < 0.001$); in the BMT CTN 0102 study however, this disadvantage only referred to some of the patients. In Björkstrand 2011, statistical analyses were only reported for the 2-, 3- and 5-year rates, but not for the 8-year rates. The information from the HOVON-50/54 study and from the study

update on the Björkstrand 2011 study newly included in this rapid report did not change the derivation of the overview of the evidence of the working paper GA11-01: As before, the available evidence allows the indication that allogeneic stem cell transplantation and reduced-intensity conditioning (following autologous stem cell transplantation) has increased therapy-related mortality and hence harm in comparison with (tandem) autologous stem cell transplantation.

Secondary neoplasia was not reported in any of the studies. There was no new information regarding serious infection and other grade 3 to grade 5 toxicities in this rapid report, and the assessment of the working paper GA11-01 therefore remained unchanged: The available data was insufficient, and therefore no hint of benefit or harm was found.

The proportion of acute GVHD (grade II–IV) and chronic GVHD (extensive) in the auto-allo-RIC group ranged from 11 to 48% and from 23 to 66%. The information from the HOVON-50/54 study and from the study update on the Björkstrand 2011 study newly included in this rapid report did not change the derivation of the overview of the evidence of the working paper GA11-01: This aspect of adverse events specific for allogeneic stem cell transplantation does not occur under the comparator treatment and was therefore assessed as proof of harm of the allogeneic stem cell transplantation and reduced-intensity conditioning following autologous stem cell transplantation.

The studies included provided no information on health-related quality of life or psychosocial aspects.

Conclusions

Under consideration of the studies published in the meantime and newly included in this rapid report, the derivation of the overview of the evidence or the conclusions did not change for any of the 9 research questions in comparison with previous reports.

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

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/nichtmedikamentoese-verfahren/n14-03-stammzelltransplantation-bei-multiplem-myelom-folgeauftrag-zu-auftrag-n05-03c.6361.html#overview.