IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports - Commission No. N05-03A

Stem cell transplantation in adults with acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML)[1]

Executive Summary

[1] Translation of the executive summary of the final report "Stammzelltransplantation bei den Indikationen Akute lymphatische Leukämie (ALL) und Akute myeloische Leukämie (AML) bei Erwachsenen" (Version 1.0; Status: 30.03.2007). Publication date of translation: 11.06.2007. 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Stem cell transplantation in adults with acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML)

Contracting agency:

Federal Joint Committee

Commission awarded on:

15.03.2005

Internal Commission No.:

N05-03A

Address of publisher:

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Executive summary

Research questions

The aims of this review were the

- evaluation of studies on certain types of stem cell transplantation versus conventional chemotherapy in adults with acute lymphoblastic leukaemia (ALL) or acute myeloid leukaemia (AML);
- evaluation of studies on certain types of stem cell transplantation compared with each other in adults with ALL or AML.

The focus of the evaluation was on patient-relevant therapy goals.

According to the commission awarded by the German Federal Joint Committee, the following types of stem cell transplantation were investigated in detail:

- Allogeneic stem cell transplantation with unrelated donors (ALL/AML)
- Autologous stem cell transplantation (ALL)
- Non-myeloablative allogeneic stem cell transplantation (ALL/AML)
- Stem cell transplantation with in-vitro manipulation of the graft (ALL/AML)

Methods

The evaluation referred to studies in adult patients with ALL or AML. Only studies were included in which the proportion of adult patients was over 80% or in which subgroup analyses for adult patients and/or the respective disease type had been performed.

All study types including a control group were considered. For retrospective studies, the restriction applied that these studies had to refer to data of the patient population of the same study group. For the group of patients with refractory disease who could not achieve remission with standard therapy, case series were also reviewed.

The endpoints selected were outcomes that enabled an assessment of patient-relevant therapy goals such as overall survival, disease-free survival, therapy-related complications, and health-related quality of life.

The literature search was performed in the bibliographic databases MEDLINE, EMBASE, and Cochrane Central in August 2005. The last update was performed in December 2006. Several other sources were screened to identify further published and unpublished studies. These included institutions that published evidence reports or were specifically involved in stem cell therapy or research, corresponding study groups, reference lists of relevant study publications and reviews, and relevant congress proceedings.

Results

This final report comprises the results of therapy studies in patients with AML or ALL in which different types of stem cell transplantation were compared with each other or with conventional chemotherapy. The systematic literature search in bibliographic databases identified 37 comparative studies, of which 11 were randomised and 26 were non-randomised. A total of 21 studies (thereof 9 randomised ones) were included in the evaluation; 6 of the 9 randomised studies referred to the research question “evaluation of autologous stem cell transplantation”. Overall, the studies included a total of 998 patients with ALL/AML (384 thereof in RCTs) in the test intervention arms, and 1656 patients (407 thereof in RCTs) in the control intervention arms. Moreover, for patients with refractory disease, 17 uncontrolled studies or studies including only one treatment arm relevant to the research questions were identified. These studies investigated 141 patients and were included in the evaluation.

If not already performed in the studies, additional subgroup analyses (e.g., for disease stages or prognostic factors) were not feasible due to the relatively small sample size in the single studies or the lack of data on relevant results.

For the types of stem cell transplantation investigated in this final report, no robust evidence showing a clear advantage of these interventions was available for any research question. Indications of a superiority of stem cell transplantation over chemotherapy can only be inferred for non-myeloablative therapy with a related donor in patients with AML. Likewise, the use of allogeneic stem cell transplantation with dose-reduced conditioning may show an advantage in patients with refractory ALL or AML. It could not be inferred from the data whether the type of donor is important in this context.

In particular, the relevance of stem cell transplantation with an unrelated donor could not be clarified so far. The analysis of other systematic reviews on stem cell transplantation confirm

the approach used in this final report, i.e. to primarily only consider direct comparative studies in the evaluation. An indirect comparison is inadequate both for methodological or medical reasons, as the essential prerequisites for such an approach, namely the investigation of comparable patient populations in studies with comparable designs and data analyses, are not fulfilled. Preliminary analyses of patients with AML from Germany (AMLCG 2000) provided for this final report and international abstract publications (UKALL XII/ECOG E2993) show that such direct comparisons are possible.

Conclusion

In this final report, the following patient-relevant outcomes were assessed for the relevant research questions: overall survival, disease-free survival, relapse rates, transplantation-related mortality, as well as further therapy-related complications (severe acute or chronic graft-versus-host disease [GVHD], infections, and impairment in health-related quality of life).

With regard to these outcomes, for the research questions investigated in direct comparisons, only non-myeloblative allogeneic stem cell transplantation with a related donor in patients with AML showed indications of a reduction in mortality compared with conventional chemotherapy. Furthermore, in patients with refractory AML or ALL, indirect indications were available for a prolonged overall survival after dose-reduced stem cell transplantation. However, particularly for patients with ALL, this result is of limited evidential value due to the lack of evaluable patients. The relevance of the type of donor remains unclear.

Evidence of an additional benefit was shown neither in ALL nor AML patients and their subgroups for the following subtypes or modifications of stem cell transplantation: allogeneic stem cell transplantation with non-myeloablative conditioning (compared with myeloablative conditioning) as well as in-vitro manipulation of the graft in allogeneic or autologous stem cell transplantation (compared with transplantation without manipulation of the graft). Likewise, in patients with ALL, no additional benefit of non-myeloablative therapy or autologous transplantation (both versus chemotherapy) could be inferred from the data. However, from the fact that no evidence of an additional benefit was shown for these types of stem cell transplantation, one cannot conclude an equivalence of these procedures to the control interventions investigated, as none of the studies identified were recognisably planned as equivalence or non-inferiority studies, and the data also cannot be interpreted this way.

In patients with ALL, AML, and their subgroups, no evidence of a benefit of allogeneic stem cell transplantation with an unrelated donor versus chemotherapy can be inferred from direct comparative studies. However, the evaluation of the literature available allows the possibility of a benefit, but also of a harm, from allogeneic stem cell transplantation with an unrelated donor versus chemotherapy in patients with ALL or AML.

With the best possible treatment of affected patients in mind, we therefore urgently recommend performing sound prospective controlled clinical trials on research questions where there is currently no evidence of a benefit of the intervention and potential harm may occur. Controlled clinical trials also refer to non-randomised studies, insofar as an appropriate setting is created to achieve as unbiased a comparison as possible.

Key words

Systematic review, acute lymphoblastic leukaemia, acute myeloid leukaemia, stem cell transplantation, allogeneic, autologous, dose-reduced conditioning, in-vitro manipulation, purging, unrelated donor