Women with breast cancer may benefit from autologous stem cell transplantation

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Compared to conventional chemotherapy, autologous stem cell transplantation can extend "event-free survival" for breast cancer patients. Clinical trials provide proof of this for breast cancer with and without distant metastases. However, there are indications that this type of stem cell transplantation can more frequently give rise to severe complications affecting almost all organ systems. This is the conclusion of the final report of the Institute for Quality and Efficiency in Health Care (IQWiG) published on 16 December 2009.

In autologous stem cell transplantation (autologous SCT), the patient's own (autologous) haematopoietic stem cells are removed at a suitable time during treatment and re-implanted after high-dose chemotherapy. Initially, this treatment was hailed with great excitement and widely used in the 1980s, but its benefit for patients with advanced breast cancer has been hotly debated by scientists for some years. The Federal Joint Committee (G-BA) therefore commissioned IQWiG to examine the available literature to find out whether autologous SCT could have advantages for breast cancer patients compared to conventional chemotherapy.

Many different treatments exist

Comprising over 25% of new cases of cancer, breast cancer is the most common type of cancer for women. Men are also affected in a rare number of cases. The choice of treatment depends on the stage at which

the tumour is diagnosed. Two factors that play an important role are its size and spread. Also of relevance is whether distant metastases, i.e. secondary tumours, are present in other parts of the body.

Usually, the tumour is surgically removed. Depending on the therapy regimen, this is supplemented by radiotherapy, hormonal therapy or chemotherapy. In particular, hormonal therapy and chemotherapy are frequently combined in this treatment.

Doctors will introduce high-dose chemotherapy in certain patients at the locally advanced or metastasized stage. The increased dose is intended to overcome the resistance of the remaining tumour cells.

Autologous transplantation: patient donates own stem cells

High-dose chemotherapy usually damages vital haematopoietic stem cells in addition to tumour cells. Consequently, haematopoietic stem cells are removed from the patient before the treatment and then re-implanted afterwards. These stem cells mostly colonize the bone marrow and stimulate haematopoiesis. If the transferred stem cells originate from the patient, this is known as autologous stem cell transplantation (autologous SCT). Autologous tandem transplantation (tandem autologous SCT) represents extremely intensified therapy: following a recovery phase, the patient receives a second transplant.

Quality of data relatively good

In accordance with the G-BA's commission, IQWiG conducted a search for trials that compared autologous SCT versus chemotherapy without stem cell transplantation or compared different types of autologous SCT with each other. A total of 19 randomized controlled trials (RCTs) could

be included in the benefit assessment. 13 trials investigated patients with breast cancer without distant metastases, 6 trials investigated patients with metastatic breast cancer. Overall, the quality of data was noticeably better than that of all previous IQWiG reports on stem cell transplantation (acute leukaemia N05-03A; severe aplastic anaemia N05-03B; soft tissue sarcoma N05-03D).

Trials reveal both advantages and disadvantages

IQWiG and its external experts have come to the conclusion that autologous stem cell transplantation has an advantage over conventional chemotherapy for patients with breast cancer in that it extends "event-free survival". This refers to the period of time from allocation of patients to one of the treatment groups until recurrence of the disease, progression of the disease or death. They found proof of this in patients with breast cancer both with and without distant metastases.

However, this proof of benefit is countered by an indication of potential harm: severe complications affecting almost all organ systems, in particular the haematopoietic system and gastrointestinal tract, occurred more frequently under autologous SCT than under the control therapies. However, the difference could not be precisely quantified, because there was insufficient reporting of complications in the trials. Indications of relevant differences were found in both metastatic and non-metastatic tumours.

Longer overall survival found in only one trial

The comparison of tandem autologous SCT with intensified chemotherapy was the only one where patients with non-metastatic breast cancer not only survived longer without recurrence of breast cancer ("event-free survival"), but also lived longer ("overall survival").

However, these indications are only found in one trial and only apply to a specific therapy regimen (WSG AM-01Trial), so that they cannot be generalized.

In general, IQWiG is concerned that some of the available trials are quite old. Nowadays, other chemotherapy regimens are normally used, particularly for patients with advanced non-metastatic breast cancer.

Further testing must only take place within clinical trials

High-dose chemotherapy in combination with autologous SCT appeared in the 1980s as a promising treatment and was introduced into medical care without adequate clinical trialling (in IQWiG's view an ethically questionable act). When the results of the first reproducible RCTs became available at the end of the 1990s, disillusionment set in and the number of transplants in breast cancer fell dramatically: in 2002 only 316 patients in Europe received transplants whereas in 1997 this figure was 2626.

For patients with metastatic breast cancer in particular, for whom there is still no curative treatment, alternatives must be tested. This also applies to therapies combined with autologous SCT. In view of the risks associated with autologous SCT, the authors of the final report believe that this testing should only take place within controlled trials. In order to better assess the benefits and harms, it would be particularly useful to investigate in further clinical trials whether treatment, optionally with autologous SCT, can extend the life of patients with metastatic breast cancer. This would be a trial looking at the primary outcome of overall survival.

Commenting procedure

IQWiG published the preliminary results in the form of the preliminary report in the middle of June 2008 and interested parties were invited to submit comments. When the comments stage ended, the preliminary report was revised and sent as a final report to the contracting agency, the Federal Joint Committee, at the end of April 2009. As the only written comment submitted did not raise any questions that had to be discussed, no oral debate took place. Appraisal of this written comment was incorporated into the discussion part of the final report. The written comment itself was recorded separately and published simultaneously with the final report. The report was produced in collaboration with external experts.

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