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Stem cell transplantation in Europe: Trends and prospects

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ABSTRACT

The aim of the present study was to identify trends in numbers of European patients treated with autologous and allogeneic haematopoietic stem cell transplantation (HSCT) as well as to provide anticipated transplant rates for the upcoming years. The following indications were considered: haematological malignancies (acute leukaemias, myeloproliferative disorders, lymphoproliferative disorders and multiple myeloma), solid tumours and non-malignant diseases. Numbers of patients treated from 1990 to 2004 were extracted from the European Group for Blood and Marrow Transplantation database, extrapolated to 2012 using mathematic models and adjusted to the literature study and expert opinion. In Europe, a 13% raise in HSCT utilisation is to be expected from 2005 to 2010, mostly due to the growing application of reduced-intensity conditioning regimens followed by allogeneic HSCT. Growing transplant rates are likely to exert health expenditure budgets and put pressure on health care providers and health insurers in Europe. Therefore, the rapid expansion would ideally imply a simultaneous increase in HSCT budgets.

1. Introduction

During the last century, autologous haematopoietic stem cell transplantation (auto-HSCT) and allogeneic haematopoietic stem cell transplantation (allo-HSCT) have developed into effective therapies for patients with a variety of haematological and genetic diseases. Increases in transplant rates were caused by the shift towards more HSCT derived from peripheral blood, improved possibilities to prevent and treat graft versus host disease (GVHD), the clear trend towards more unrelated donor HSCT and a wider range of indications for which HSCT is applicable.[1,2] Currently, HSCT is most commonly performed in patients with haematological malignancies.[2]

In 1990, the European Group for Blood and Marrow Transplantation (EBMT) started an initiative to prospectively make an inventory of HSCT performed in Europe according to indication, treatment modality, donor type and stem cell source.[3] Results are presented through annual surveys, in which applications of HSCT are assessed and trends are recognised. Similar reviews have been conducted by others.[1,4,5] However, these analyses were all restricted to past and current practice and imply no prognosis for future developments. Anticipation on transplant rates is a useful tool for the identification of budgetary capability and future use of medical resources, such as transplant centres and medical staffing. Therefore, the aim of the present study was to identify trends in numbers of European patients treated with auto-HSCT and allo-HSCT as well as to provide anticipated transplant rates for the upcoming years.

2. Materials and methods

MEDLINE, controlled by the United States National Library of Medicine, was searched by using the individual search terms

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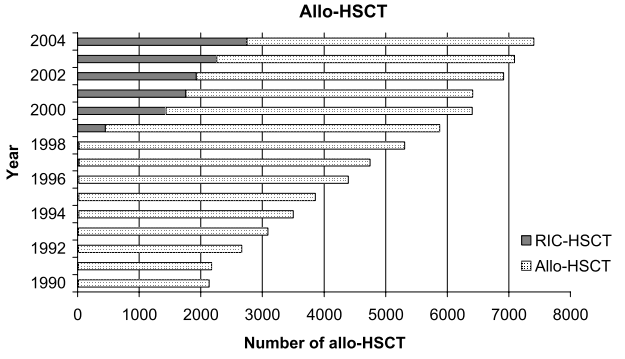
'leukaemia', 'Hodgkin', 'non-Hodgkin', 'myeloma', 'neuroblastoma', 'germ cell cancer', 'Ewing', 'breast cancer', 'soft tissue sarcoma', 'renal cell carcinoma', 'severe aplastic anaemia', 'thalassaemia', 'severe combined immunodeficiency', 'metabolism', 'auto immune disease', in combination with 'stem cell', 'stem cell therapy', 'transplantation', 'bone marrow', 'blood' and 'progenitor' in order to get insight in the indications for which HSCT are currently performed, as well as in the standard therapies for these indications. The search was restricted to publication after 1999 and to the English language. In addition, specific criteria were used for searching the published literature and for grading the quality and strength of the evidence and the strength of the treatment recommendations. The selection of articles took place in August 2006.

Websites of the Dutch haemato-oncology association (HOVON) and the International Trial Registers were explored to get insight in the clinical trials that are currently in progress. Data on numbers of patients treated with *first* HSCT were extracted from the EBMT database. This database also includes centres not reporting primary data to the EBMT, reaching more than 95% of activity in the field.[2] HSCT utilisation in Europe was specified per year (1990–2004), per indication (acute leukaemias, myeloproliferative disorders (MPD), lymphoproliferative disorders (LPD), multiple myeloma (MM), solid tumours and non-malignant diseases) and per treatment modality (auto-HSCT and allo-HSCT). Unfortunately, data of 2005 were not yet available at the time of this survey.

As a starting point for the forecasting of increase or decrease in transplant rates, the numbers of HSCT performed from 1990 to 2004 were extrapolated using linear regression models. A moving average forecast with exponential smooth was applied, which comprised updating the forecast each period by some fraction of the error in the prior period. Statistical analyses were conducted with the statistical software programme SPSS for Windows version 13.0.

Subsequently, extrapolated data were adjusted to the literature study and expert opinion. To confirm credibility, expert opinions of four haemato-oncologists, two oncologists specialised in solid tumours and one neuro-oncologist were asked to verify our findings. All experts were active in the current practice of HSCT and in clinical trials concerning HSCT and were engaged in university medical centres in the Netherlands.



Allo-HSCT = allogeneic haematopoietic stem cell transplantation
RIC-HSCT = reduced-intensity conditioning regimens followed by allo-HSCT

Fig. 1 – Share of RIC-HSCT in allo-HSCT utilisation in Europe from 1990 to 2004.

3. Results

Actual numbers of HSCT performed in Europe from 1990 to 2004 specified per indication and treatment modality are presented. The figures also show anticipated HSCT activity from 2005 to 2012. Fig. 1 shows the number of reduced-intensity conditioning regimens followed by allo-HSCT (RIC-HSCT) as a percentage of allo-HSCT. Specifications of HSCT utilisation specified per donor type and stem cell source have been reported elsewhere.[2]

4. Indications

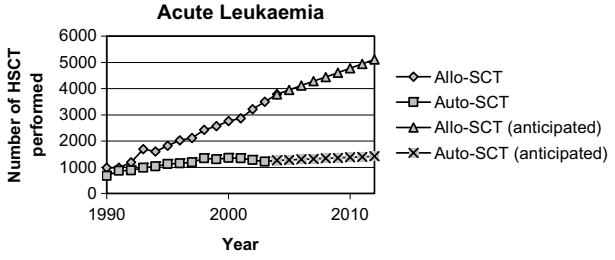
4.1. *Haematological malignancies*

4.1.1. *Acute leukaemia*

With conventional chemotherapy in acute lymphoblastic leukaemia (ALL), the event-free survival in children is over 70%, whereas only 20–38% of adults are eventually cured. The addition of both auto-HSCT and allo-HSCT to chemotherapy has proven to be effective in the treatment of more selected patient categories.[6,7] Newer chemotherapy regimens are continuously being proposed for adult patients with ALL and some recent studies suggest that intensifying the early phases of therapy may have an impact on survival.[6]

For the treatment of acute myeloid leukaemia (AML), induction chemotherapy in combination with a type of consolidation treatment is recommended. The optimal consolidation therapy should be based on the availability of a donor and risk factors.[8] An auto-HSCT can serve as an alternative when no human leucocyte antigen (HLA)-identical donor is available.[8] In case of an unfavourable risk profile, an allo-HSCT is preferred over chemotherapy.[9] RIC-HSCT has recently become a more popular treatment option for AML, especially in patients over 40 years of age, but its precise role within an overall treatment strategy has not yet been well defined.[1,10] The use of HSCT as a consolidation treatment and as a treatment option for patients between 60 and 75 years of age is subject to several ongoing studies of amongst others HOVON and the Medical Research Council (MRC).

Actual numbers of HSCT performed in Europe from 1990 to 2004 and anticipated numbers of HSCT from 2005 to 2012 are shown in Fig. 2. After a steady, persisting rise in auto-HSCT procedures for acute leukaemia from 672 in 1990 to 1190 in



Auto-HSCT = autologous haematopoietic stem cell transplantation
Allo-HSCT = allogeneic haematopoietic stem cell transplantation

Fig. 2 – Acute leukaemia: actual numbers of HSCT performed in Europe from 1990 to 2004 and anticipated numbers of HSCT from 2005 to 2012.

1997, the number levelled off at around 1300 per year since 1998. Most patients fulfilling entry criteria are already being treated with auto-HSCT. Therefore continuation of the plateau is probable in the years to come.

Acute leukaemia has been the most frequent indication for allo-HSCT in Europe. Allo-HSCT procedures have seen rapid expansion in the last decade and numbers are expected to carry on rising. Increased use of RIC-HSCT in elderly AML patients and increasing worldwide donor availability will contribute to this sustained growth.

4.1.2. *Myeloproliferative disorders*

The treatment of myelodysplastic syndrome (MDS) is predominantly aimed at reducing symptoms, because the disease is incurable for most patients. Younger patients with a high risk profile could benefit from intensive chemotherapy in combination with allo-HSCT, aiming at prolonged disease free survivals. Although RIC-HSCT provides possibilities to perform allo-HSCT in older patients, its place remains unclear.[11] Studies of HOVON and the MRC are in progress to evaluate the efficacy of chemotherapy in various combinations and cycles.

In more than 50% of eligible patients with chronic myeloid leukaemia (CML), allo-HSCT has been the only curative treatment for 20 years, reaching overall and disease free survivals of over 80%.[12] For ineligible patients, interferon with or without chemotherapy has been offered as a rather simple and widely applicable alternative treatment. However, the introduction of imatinib in 2001 has initiated a new era in the management of CML. Imatinib provides cytogenetic responses in up to 90% and molecular responses in most of the patients with minimal toxicity.[13] Allo-HSCT today is almost exclusively offered to patients who do not successfully respond to imatinib or develop imatinib resistance.[14] Many studies are ongoing to investigate the durability of imatinib induced response and the efficacy of salvage strategies using allo-HSCT or interferon after failure of imatinib.

The practice of auto-HSCT seems to be consistently low for MDS and has almost completely come to a halt for CML (Fig. 3).

Allo-HSCT activity shows a straightforward trend upwards for MDS and currently appears to have stabilised at around 800 per year for CML. Only 5 patients in 1990 were treated with RIC-HSCT, whereas about 17% of patients were given RIC-HSCT in most recent years. New developments in drug treatment for imatinib resistant CML, such as newer tyrosine kinase inhibitors and vaccination strategies, are forecasting a slight decrease in use of allo-HSCT. Nevertheless, HSCT will likely remain an important treatment option for patients with resistant CML.

4.1.3. *Lymphoproliferative disorders*

Treatment options for LPD are numerous and varied. Chemotherapy, often combined with immunotherapy, is the preferred treatment for most types of LPD,[15,16] reaching disease free survival rates of around 70%. Although a variety of regimens induces high levels of complete remission and prolongs long term survival rates,[16] this strategy still requires long term confirmation from ongoing randomised studies.

Lymphocyte predominant Hodgkin's lymphoma (HL) stage I may be treated with involved field irradiation only and for chronic lymphoblastic leukaemia (CLL) in an early stage an expectative regimen with regular controls could be the treatment of choice before proceeding to chemotherapy.[17]

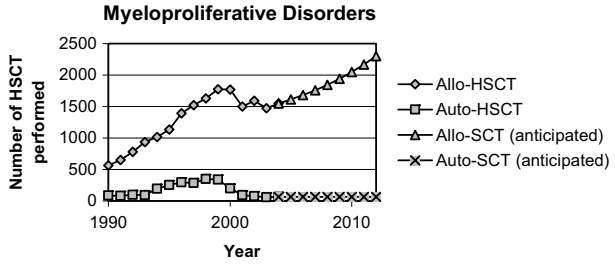
Currently, almost all relapsed and refractory aggressive B-cell LPD patients are offered auto-HSCT, allo-HSCT or RIC-HSCT.[17–20] Although allo-HSCT is increasingly offered to indolent B-cell non-Hodgkin's lymphoma (NHL) patients who progress after first or second line (immuno)chemotherapy, its clinical significance is not yet clear.

From 1990 to 2004, auto-HSCT utilisation in HL multiplied by 5% per year (Fig. 4). For NHL this percentage amounted to 10% per year since the early 1990s. The addition of immunotherapy to conventional chemotherapy in patients with NHL and CLL might cause a slight decrease in the years to come.

The number of allo-HSCT performed in LPD showed a continuous increase of 20% per year up till 2000. Afterwards, a plateau in transplant rates is observed at a level of around 750 per year. Increasing likelihood of finding a compatible donor and the development of RIC-HSCT will likely result in a modest increase in the immediate future.

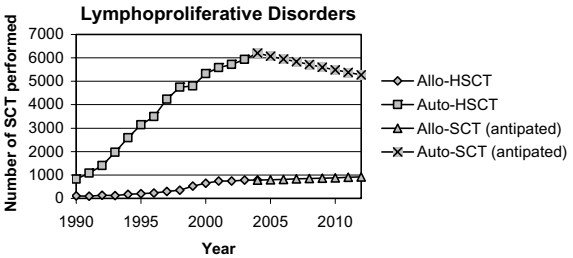
4.1.4. *Multiple myeloma*

The treatment of MM has changed drastically in the past 10 years. Intensive chemotherapy with auto-HSCT has improved the prognosis for younger patients, RIC-HSCT has decreased the high transplant related mortality of allo-HSCT and new anti-myeloma agents have become available.[4,17,18] Because



Auto-HSCT = autologous haematopoietic stem cell transplantation
Allo-HSCT = allogeneic haematopoietic stem cell transplantation

Fig. 3 – Myeloproliferative disorders: actual numbers of HSCT performed in Europe from 1990 to 2004 and anticipated numbers of HSCT from 2005 to 2012.



Auto-HSCT = autologous haematopoietic stem cell transplantation
Allo-HSCT = allogeneic haematopoietic stem cell transplantation

Fig. 4 – Lymphoproliferative disorders: actual numbers of HSCT performed in Europe from 1990 to 2004 and anticipated numbers of HSCT from 2005 to 2012.

patients in stage I of MM could remain stable for years without therapy, an expectative regime with regular follow-up is believed to be sufficient. In contrast, patients in stages II and III should be treated upfront.[4,21] The treatment of choice for patients up to 65 years of age consists of induction chemotherapy, autografting of peripheral blood stem cells, high dose chemotherapy and auto-HSCT.[4] With this treatment, 50% of the newly diagnosed patients achieve complete remission. Oral combination of melphalan and prednisone combined with newer drugs, e.g. thalidomide, remains the standard treatment for patients ineligible for intensive chemotherapy with stem cell support.[21] The role of RIC-HSCT after preceding auto-HSCT is being studied in an ongoing study of HOVON.

Fig. 5 shows actual and anticipated numbers of HSCT performed in patients with MM from 1990 to 2012. Transplantation in MM increased with an annual rate of almost 10% and nowadays almost all patients up to 65 years of age will get an auto-HSCT. A substantial increase came when auto-HSCT was reported to be beneficial.

Stable low numbers of allo-HSCT over the years reflect the experimental status of the procedure, although recently allo-HSCT after auto-HSCT is administered more often. Although a slight reduction is observed since 2002, allo-HSCT activity is expected to increase in the years to come, mostly due to the introduction of RIC-HSCT. However, MM numbers may drop (if any change is to be expected) in the future due to the availability of alternative treatments such as bortezomib and lenalinomide.

4.2. *Solid tumours*

Solid tumours comprise a diversity of diseases, of which most HSCT in Europe is applied in neuroblastoma, germ cell cancer, Ewing sarcoma, breast cancer, soft tissue sarcoma and renal cell carcinoma. Surgery in combination with chemotherapy and radiotherapy is the first choice treatment in most solid tumours. Nevertheless, the preferred treatment for neuroblastoma is myeloablative chemotherapy in combination with auto-HSCT.[22] The latter therapy is also performed in refractory and relapsed germ cell cancer, Ewing sarcoma, the *HER2/neu*-negative type of breast cancer and soft tissue sarcoma, although benefit is not yet demonstrated.[23–25] RIC-HSCT might represent a new approach in solid tumours, especially in renal cell carcinoma, but clinical results are not yet available.

Auto-HSCT activity in solid tumours largely followed the trend of breast cancer utilisation in the previous 15 years, because 50% of the auto-HSCT was applied in breast cancer (Fig. 6). Transplant rates have increased massively in the early 1990s, which was essentially caused by positive results of phase II trials in breast cancer. However, phase III trials were unable to show for clinical benefit, which brought about a firm decline in HSCT use. In contrast, there is a constant variable but steady increase for neuroblastoma and Ewing sarcoma. For soft tissue sarcoma and germ cell tumours, stable situations are seen generally over the observation period. On the whole, the introduction of alternative strategies, such as oxaliplatin, gemcitabine, paclitaxel and disappointing results of auto-HSCT, is predicted to challenge the role of auto-HSCT in the treatment of solid tumours.

Allo-HSCT was performed in less than 20 patients a year up to 1997, but has increased to 159 in 2002, mainly due to its application in renal cell carcinoma.

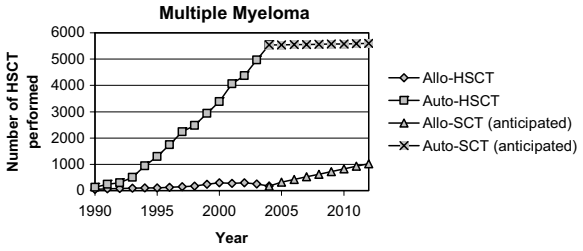
4.3. *Non-malignant diseases*

Non-malignant diseases in which HSCT is applied cover a wide variety of disorders. In 2004, most HSCT were performed in severe aplastic anaemia, thalassaemia, severe combined immunodeficiency (SCID), inborn errors of metabolism and auto immune diseases.

Immunosuppression is the preferred treatment for most types of non-malignant diseases. However, allo-HSCT is the preferred treatment in children and young adults with aplastic anaemia, beta-thalassaemia major patients with an HLA-identical donor and SCID.[26,27] RIC-HSCT renders the procedure more attractive for patients previously not eligible for allo-HSCT.

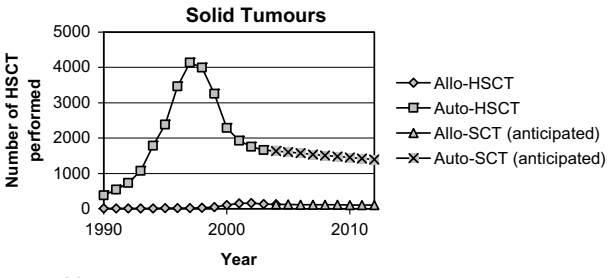
After a rise in auto-HSCT procedures from 16 in 1990 to 197 in 1999, the number dropped to level off at around 100 per year since 2002 (Fig. 7). Auto-HSCT is performed mostly in auto immune diseases, amongst which are multiple sclerosis, systemic lupus erythematosus and rheumatoid arthritis.[28,29] Few controlled studies are available and different opinions prevail, which makes it hard to predict future use.

Allo-HSCT procedures have been extending at an annual rate of 5–10% since the beginning of the registration. Increased use of RIC-HSCT in older patients and patients with co-morbidities will likely result in some growth.



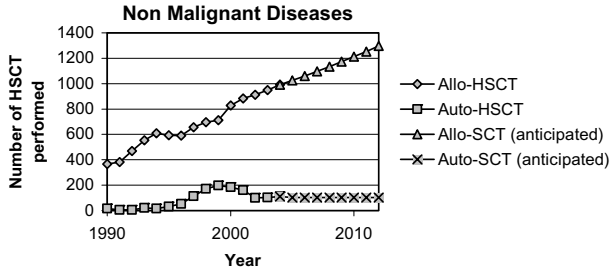
Auto-HSCT = autologous haematopoietic stem cell transplantation
Allo-HSCT = allogeneic haematopoietic stem cell transplantation

Fig. 5 – Multiple myeloma: actual numbers of HSCT performed in Europe from 1990 to 2004 and anticipated numbers of HSCT from 2005 to 2012.



Auto-HSCT = autologous haematopoietic stem cell transplantation
Allo-HSCT = allogeneic haematopoietic stem cell transplantation

Fig. 6 – Solid tumours: actual numbers of HSCT performed in Europe from 1990 to 2004 and anticipated numbers of HSCT from 2005 to 2012.



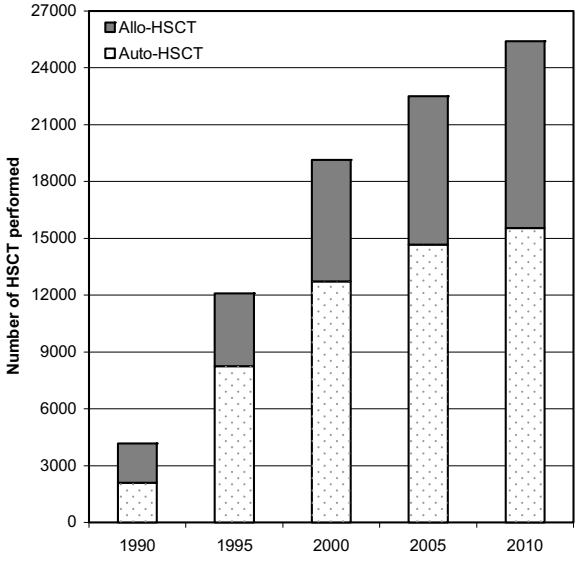
Auto-HSCT = autologous haematopoietic stem cell transplantation
Allo-HSCT = allogeneic haematopoietic stem cell transplantation

Fig. 7 – Non-malignant diseases actual numbers of HSCT performed in Europe from 1990 to 2004 and anticipated numbers of HSCT from 2005 to 2012.

5. Treatment modalities

5.1. *Auto-HSCT*

Actual numbers of HSCT performed in Europe in 1990, 1995 and 2000 and anticipated numbers of HSCT in 2005 and 2010 are shown in Fig. 8. Overall, an increase in auto-HSCT utilisation of 6% from around 15,000 in 2005 to almost 16,000 in 2010 is predicted. Even though the introduction of alternative strategies might cause a slight decrease in activity for LPD, MM and solid tumours, transplant rates are likely to remain continuously high. Increase in auto-HSCT utilisation is mainly expected in acute leukaemias and in auto immune diseases, where auto-HSCT is believed to provide clinical benefit over chemotherapy.



Auto-HSCT = autologous haematopoietic stem cell transplantation
Allo-HSCT = allogeneic haematopoietic stem cell transplantation

Fig. 8 – Actual numbers of HSCT performed in Europe in 1990, 1995 and 2000 and anticipated numbers of HSCT in 2005 and 2010.

5.2. *Allo-HSCT*

A more convincing increase of 20% from around 7500 in 2005 to around 10,000 in 2010 is predicted for allo-HSCT utilisation. Transplant rates for allo-HSCT are expected to rise for all indications except CML, mostly due to the growing application of RIC-HSCT especially in older patients and in patients with comorbidities. Nevertheless, RIC-HSCT regimens vary widely in intensity of myeloablation and immunoablation and thus the optimal regimen for each disease entity is still to be determined.

6. Discussion

Our analyses show an overall anticipated increase in HSCT utilisation of 13% from 2005 to 2010 in Europe. Growing transplant rates are likely to exert health expenditure budgets and put pressure on health care providers and health insurers in Europe. Therefore, the rapid expansion would ideally imply a simultaneous increase in HSCT budgets. In an earlier study, budgetary implications were assessed for the Netherlands in a scenario analysis taking the average price indexation of 2% into account and no changes in transplant indications.[30] An increase in HSCT use of 20% would require the budget to expand from €20 million in 2003 to about €75 million in 2010. A remarkable outcome of the scenario analysis was that even a hypothetical decline of 20% in transplant rates would necessitate a substantial raise in budget to €54 million in 2010. Applying this methodology to data from the present study, total anticipated auto-HSCT and allo-HSCT costs in Europe would add up to €1478 million and €1717 million in 2005 and 2010, respectively.

Certain reservations have to be made as to the analyses presented. Firstly, our analyses did not capture second or later transplants. We do not expect that the inclusion of only first transplants would have a major impact on our results, since numbers of second transplant are believed to have declined for auto-HSCT and increased for allo-HSCT, e.g. in MM. Nevertheless, although the number of retreatments by transplantation is low, there are some indications where double transplantation is customary.

Secondly, shifts in HSCT use due to newer therapies in established indications and for new indications cannot be anticipated with much confidence in our analyses and would remain speculating. However such shifts could obviously have an immediate impact on HSCT activity. Assessment for best strategy of established indications is complicated by the fact that opinions can undergo rapid change. This is well illustrated by the increase and subsequent decrease in HSCT for indications such as breast cancer and CML. New indications are continuously being explored. Performance of allo-HSCT for solid tumours and HSCT for auto immune disorders appeared without much prior notice. Accordingly, HSCT utilisation could emerge as a treatment option for patients with metabolic diseases, neurodegenerative disorders, cardiac diseases and diseases of the bone structure. Ongoing trials will show whether or not these indications become established.

Thirdly, our analyses did not consider the important variability of these transplant rates in the various European coun-

tries and the current difference in utilisation of HSCT in Western as opposed to Eastern Europe where major shifts are to be expected.

In conclusion, a 13% raise in HSCT utilisation and corresponding costs is expected from 2005 to 2010. The most likely increase is caused by RIC-HSCT transplants, although no study so far has documented the superiority of RIC-HSCT over standard HSCT in the long term. Even though increasing transplant rates are associated with rising health care expenditures, they also bring about improved long-term survivals in patients for which HSCT are performed currently and in the future.

Conflict of interest statement

No financial or personal relationships with other people or organisations that could inappropriately influence this work to declare.

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