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# Current role of stem cell transplantation in chronic myeloid leukaemia

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Haematopoietic stem cell transplantation (HSCT) has seen considerable ups and downs in its role for patients with chronic myeloid leukaemia (CML). It has provided the first proof of the principle for cure and has confirmed the concept of successful immunotherapy of leukaemia. CML became the most frequent indication for an allogeneic HSCT worldwide. The frequency of HSCT declined rapidly when the specific BCR/ABL tyrosine kinase inhibitor (TKI) imatinib appeared. Today, a balanced view prevails. Risk assessment of both, disease risk and transplant risk, has become standard. Allogeneic HSCT remains the first-line approach for patients with CML in accelerated phase or blast crisis. It is the standard of care for patients with failed first-line therapy and a low-risk HSCT. It is the best option for all patients with failed second-line TKIs, with mutations T315I or with progressive disease. It can always be considered in situations with limited resources.

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## Introduction

Chronic myeloid leukaemia (CML) and haematopoietic stem cell transplantation (HSCT) have been closely linked together with success and failure over the past 50 years of clinical transplantation [1–5]. George Mathé described first the effects of graft-versus-leukaemia (GvL) when a patient with refractory acute leukaemia, pancytopenia and severe infection was given granulocyte transfusions from a donor with CML as an experimental approach [6]. The patient cleared his infection and, surprisingly,

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all his blasts. In addition, he showed a clinical syndrome with icterus, diarrhoea and skin rash, today well known as graft-versus-host disease (GvHD). This powerful GvL effect formed the basis for continued research in clinical HSCT, integrating the concepts of bone marrow ablation by high-dose chemo/radiotherapy and substitution by healthy donor bone marrow cells with immunological control of malignant disease [7]. The concept of GvL was further supported by the effects of donor lymphocyte infusions (DLIs), which were shown to be most effective in patients with CML [8,9]. Both bone marrow ablation and GvL combined gave the proof of the principle for the prospects of cure by allogeneic HSCT [7]. Revisiting the history of CML and HSCT, we realise today how much we learned. This includes not only the basic principles concerning the mechanisms of the disease, the potentials and risks of allogeneic HSCT but also the general principles of decision making in clinical medicine. Today, in the era of targeted therapy for CML it is especially worth looking at the role of HSCT in this disease.

## History and evolution of HSCT for CML

The disappearance of the Philadelphia chromosome in patients given intensive chemo/radiotherapy and bone marrow from their syngeneic twin donors more than 30 years ago marked the beginning of a new area in the treatment of CML [10]. It was the first therapy that was able to eradicate the Philadelphia+ clone. These few patients demonstrated that it could become possible to cure patients from their CML. The concept was rapidly adopted and followed by transplantations of bone marrow from human leucocyte antigen (HLA) identical sibling donors. The efficacy of allogeneic HSCT was proven in several large series in Europe and the USA [11–14]. Allogeneic HSCT became the treatment of choice for young patients with CML and a compatible donor. At the end of the last decade, CML was the most frequent indication for an allogeneic transplant worldwide, and more than 1000 HSCTs were reported to the European Group for Blood and Marrow Transplantation (EBMT) activity survey in 1999 (Fig. 1). The introduction of the specific tyrosine kinase inhibitor (TKI) imatinib [16] changed this trend completely. As early as in the year 2000, the numbers of HSCT for CML began to decline, years before the results of the first clinical trials with imatinib were published. In 2007 there were a total of 434 allogeneic HSCTs for CML, 228 in first chronic phase and 206 in advanced stages of the disease. It is of interest to note, as we discuss later in more detail, that the numbers of HSCTs for CML did not decline in all countries to the same extent and that the numbers of HSCTs in advanced stages of the disease remained relatively stable.

## Long-term results of HSCT and the factors associated with outcome

More than 2600 patients were transplanted in Europe between 1980 and 1990. Their outcome gives clear information on the long-term expectation with this form of treatment: about 40%, 20% and 10% of the patients transplanted in the first chronic phase, in the accelerated phase and in the blast crisis,

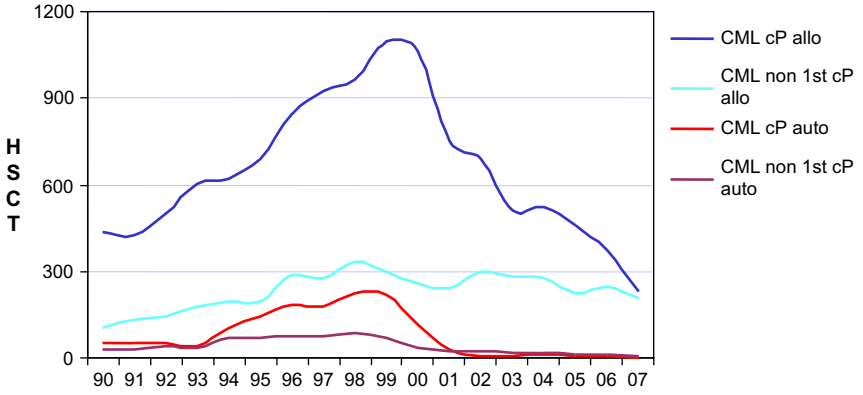


**Fig. 1.** Numbers of allogeneic and autologous HSCT for CML reported to the EBMT activity survey from 1990 to 2007.

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