

# A LITERATURE REVIEW on the CLINICAL and ECONOMIC OUTCOMES ATTRIBUTABLE to FIRST-LINE TREATMENT for CHRONIC MYELOID LEUKEMIA with IMATINIB MESYLATE and BONE MARROW TRANSPLANTATION

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## INTRODUCTION

- Chronic myeloid leukemia (CML) is diagnosed by the presence of a characteristic blood and bone marrow cellular pattern, using cytogenetic and molecular diagnostic techniques.
- It is a rare disease with an estimated incidence ranging from 7 per million to as much as 61 per million in the 20-44 years age group and >65 years age group, respectively [2]. The median age of diagnosis is 53 years [1].
- The natural course of the disease involves three sequential phases (chronic, accelerated, and blast crisis), each becoming progressively more resistant to therapy [1,2].
- The objective of this review was to summarise the available clinical and economic literature relating to the use of imatinib mesylate (IM) and bone marrow transplantation (BMT) as alternative first-line treatments for patients with chronic phase CML and to compare the clinical and economic outcomes of these treatments.

## METHODS

- A systematic literature search was performed using available computerised databases for papers on CML. Search terms were CML and one of the following: incidence, prevalence, epidemiology, mortality, imatinib mesylate, Glivec, bone marrow transplantation, stem cell transplantation, utilities, quality of life, cost-effectiveness, cost-utility, resource utilisation, economic and cost. The search strategy was not limited by year of publication, but only English language papers were included. A manual literature search was also undertaken, based on citations in the published papers.
- All available prospective and retrospective studies, randomised and non-randomised studies, multicentre trials and single centre reports, as well as clinical reviews evaluating clinical and economic outcomes associated with IM and BMT were included in the review.
- A meta-analysis was performed to estimate weighted (where possible) mean values from 29 publications that provided data on at least 4,931 IM-treated patients and 1,699 patients who received BMT (sample size was omitted in some instances).

## RESULTS

### Event-free Survival

- Ninety-six percent of IM-treated patients are expected to be event-free at year 1 compared to 64% of those who receive BMT. Moreover, event-free survival (defined for this study as time to relapse, death, or last follow-up) is maintained over a period of 10 years and is higher among IM-treated patients in year 10 by 46%, indicating a clear improvement in event-free survival among those treated with IM (Figure 1) [3-6,37].

### Overall Survival

- One hundred percent of patients who receive IM as a first-line treatment are expected to survive the first 12 months compared to 72% of those who receive a BMT. The survival advantage continues up to year 8, however by year 10 this advantage declines (Figure 2) [3,4, 6,8,9,21,22].

### Freedom from Progression

- Freedom from progression to advanced stages was estimated to be 100% among patients who survive a BMT compared to 94% of IM-treated patients in the first year. However, by the second year there is a 4% improvement among IM-treated patients compared to the BMT group. Moreover, this improvement continues and by year 8 disease-free progression is expected to be 28% higher in the IM group (Figure 3) [1,4,5,7,8,22,23].

### Remission

- The majority of patients receiving IM first-line treatment achieve remission, of which 97% achieve a complete haematological remission, and 40% achieve molecular remission by 1 year. Additionally, 92% achieve a major cytogenetic response and 87% a complete cytogenetic response by 5 years [20,24,25].
- Only 28% of patients are expected to achieve remission following BMT and of these, 25% achieve complete cytogenetic response, 5% haematological remission, and the remaining 70% a molecular remission [26], although this could be as high as 82% [8].
- The remission rates could not be stratified according to time to remission, although the median time of follow-up was an estimated 21 months and 48 months for patients treated with IM and BMT, respectively.

### Relapse

- Twenty one percent of patients who have a BMT were found to relapse after a median 34 months [5,6,9,13,16,26]. Of the patients who relapsed 19%, 23% and 58% experienced a cytogenetic, haematologic and molecular relapse respectively.

- Patients who relapse undergo further therapy with donor-leukocyte infusion, a second BMT and/or IM therapy.

### Adverse Events

- The incidence of adverse events especially haematological complications appears to be lower among IM-treated patients than BMT patients.
- Haematological adverse events associated with BMT include acute graft versus host disease (GVHD) (48% of patients), chronic GVHD (68% of patients) and febrile neutropenia (50% of patients) [1,5,6,8,9,11,13,26,27]. In contrast, serious haematological adverse events associated with IM therapy include neutropenia (17% of patients), thrombocytopenia (8% of patients) and anaemia (4% of patients) [4,25,28].
- Only 5% of patients were found to discontinue IM therapy due to adverse events. Also, most haematological adverse events tend to occur early in the treatment, decreasing in incidence after two years' continued IM therapy [7].

- Patients undergoing BMT have an 8% risk of life-time graft rejection, despite receiving prophylactic immunosuppression, and a time-dependant risk of treatment-related mortality [1,5,6,8,9,11,15,16,26,27,29,30] (Figure 4).

### Economic Outcomes

- A cost-effectiveness analysis considering only direct medical costs from the perspective of a third-party payer in the US estimated the incremental cost of using IM to be -\$5,000 (95% CI: -\$70,000; \$84,000) per surviving IM-treated patient. Moreover, IM was a dominant treatment in 84.69% of cases [2].
- One cost-analysis concluded that lifelong treatment with IM represents an excessive burden on resources especially in developing countries if the cost of BMT is viewed solely as a 'once only' procedure [8].
- Another cost-analysis estimated the total direct cost of BMT for all patients in the Czech Republic to be €1.6 million. The direct cost of IM treatment would have amounted to €2.0 million. Hence, the authors concluded that BMT is less expensive after approximately 2 years of follow-up. However, approximately 50% of the patients who received a BMT required further therapeutic interventions such as donor-leukocyte infusion and IM [26].

## DISCUSSION

- The availability of IM has revolutionised the treatment of CML, emerging as the current "gold standard" therapy for patients with chronic-phase disease without a potential bone marrow donor and those considered unsuitable for BMT.
- European and US treatment guidelines endorse IM as a first-line treatment option in chronic phase CML.
- When administered at the standard dose IM is generally well tolerated with major toxicities manageable by reducing the dose. Conversely, BMT is associated with greater toxicities, a risk of graft failure and transplant-related mortality. Nevertheless, the recent emergence of reduced intensity pre-conditioning regimens have been found to be associated with a lower incidence of haematological complications, lower treatment-related mortality, lower toxicity and improved remission and survival compared to standard BMT.
- This review found that IM-treated patients are more likely to achieve cytogenetic and haematological remission, whereas patients who survive a BMT are more likely to achieve molecular remission.
- The existing studies estimated that the incremental cost-effectiveness of IM relative to allogeneic BMT with a matched unrelated donor was -\$5,000 per surviving patient after approximately 2-4 years of follow-up.
- The evidence also shows that affordability and cost-considerations are important factors in decision-making and in some cases, BMT may be favoured over IM because it is perceived as a 'once only' procedure. This is especially true in the developing, low-income countries. However, the estimates of the 'once only' costs often do not account for the probability of repeat procedures or the costs of chronic medications to prevent rejection or manage adverse events.
- The present review has been drawn on information obtained from a limited number of studies with heterogeneous patient characteristics. There is also a lack of published data regarding the timing of adverse events and outcomes following BMT stratified according to (1) patients' risk-profile, (2) donor type and (3) pre-conditioning regimens. Consequently, the results should be viewed in the context of the above limitations and of emerging long-term clinical data.
- Moreover, even though published evidence supports the use of IM in patients eligible for transplant it has to be noted that BMT is currently the only potentially curative treatment.

## CONCLUSION

- Published evidence supports the use of IM in patients eligible for transplant. IM appears to be a cost-effective treatment compared to BMT in the management of CML in the short-term, but longer-term published data are lacking.

## REFERENCES

- Dalziel K, Round A, Stein K, et al. Effectiveness and cost-effectiveness of imatinib for first-line treatment of chronic myeloid leukaemia in chronic phase: a systematic review and economic analysis. *Health Technology Assessment* 2004;8(28).
- Skrpek GH, Ballard EE. Cost-efficacy of imatinib versus allogeneic bone marrow transplantation with a matched unrelated donor in the treatment of chronic myelogenous leukemia: a decision-analytic approach. *Pharmacotherapy* 2005;25(3):325-34.
- Bittencourt H, Funke V, Fogliatto L, et al. Imatinib mesylate versus allogeneic BMT for patients with chronic myeloid leukemia in first chronic phase. *Bone Marrow Transplant* 2008;42(9):597-600.
- Moën MD, McKeage K, Plosker GL, et al. Imatinib: a review of its use in chronic myeloid leukaemia. *Drugs* 2007;67(2):299-320.
- Van Rhee F, Szydlo RM, Hermans J, et al. Long-term results after allogeneic bone marrow transplantation for chronic myelogenous leukemia in chronic phase: a report from the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Bone Marrow Transplant* 1997;20:553-560.
- Blum W, Brown R, Lin HS, et al. Low-dose (550 cGy), single-exposure total body irradiation and cyclophosphamide: consistent, durable engraftment of related-donor peripheral blood stem cells with low treatment-related mortality and fatal organ toxicity. *Biol Blood Marrow Transplant* 2002;8(11):608-18.
- Hochhaus A, O'Brien SG, Guilhot F, et al. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia* 2009;23(6):1054-61.
- Ruiz-Arquelles CJ, Tarin-Ariza LC, Gonzalez-Carrillo ML. Therapeutic choices in patients with Ph-positive CML living in Mexico in the tyrosine kinase inhibitor era: SCT or TKIs? *Bone Marrow Transplant* 2008;42(1):23-8.
- Khoury H, Adkins D, Brown R, et al. Low incidence of transplantation-related acute complications in patients with chronic myeloid leukemia undergoing allogeneic stem cell transplantation with a low-dose (550 cGy) total body irradiation conditioning regimen. *Biol Blood Marrow Transplant* 2007;13(6):352-8.
- Mochly M, Jacot W, Faucher C, et al. Infectious complications following allogeneic HLA-identical sibling transplantation with antithymocyte globulin-based reduced intensity preparative regimen. *Leukemia* 2003;17(11):2168-77.
- Das M, Saikia TK, Advani SH, et al. Use of a reduced-intensity conditioning regimen for allogeneic transplantation in patients with chronic myeloid leukaemia. *Bone Marrow Transplant* 2003;32(2):125-9.
- Kerbauf FR, Storb R, Hegenbart U, et al. Hematopoietic cell transplantation from HLA-identical sibling donors after low-dose radiation-based conditioning for treatment of CML. *Leukemia* 2005;19(6):990-7.
- Gaziev D, Galimberti M, Polchi P. Fate of chronic myeloid leukemia patients treated with allogeneic bone marrow transplantation or chemotherapy and/or interferon at a single center: long-term results. *Bone Marrow Transplant* 2002;29(1):1-8.
- Ohnishi K, Minami S, Ueda T, et al. Multicenter prospective study of interferon-alpha and conventional chemotherapy versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia. *Int J Hematol* 2000;72:229-36.
- Ohnishi K, Ino T, Kishimoto Y, et al. Multicenter prospective study of interferon-alpha and conventional chemotherapy versus bone marrow transplantation for newly diagnosed patients with chronic myelogenous leukemia: a preliminary analysis. *Cancer Chemother Pharmacol* 2001;48:559-64.
- Italian Cooperative group no authors listed. Monitoring treatment and survival in chronic myeloid leukemia. Italian Cooperative Study Group on Chronic Myeloid Leukemia and Italian Group for Bone Marrow Transplantation. *J Clin Oncol* 1999;17(6):1858-68.
- Gale RP, Hehlmann R, Zhang MJ, et al. Survival with bone marrow transplantation versus hydroxyurea or interferon for chronic myelogenous leukemia. The German CML Study Group. *Blood* 1998;91(5):1810-9.
- Reed SD, Anstrom KJ, Li Y. Estimates of survival and cost effectiveness for imatinib versus interferon-alpha plus low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukaemia. *Pharmacoeconomics* 2008;26(5).
- Dalziel K, Round A, Garside R, et al. Cost effectiveness of imatinib compared with interferon-alpha or hydroxycarbamide for first-line treatment of chronic myeloid leukaemia. *Pharmacoeconomics* 2005;23(5):515-26.
- Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukaemia. *N Engl J Med* 2006;355(23):2408-17.
- Hensley ML, Van Hoornissen IC, Krahnik T, et al. Imatinib in chronic myeloid leukemia (CML): outcomes in >7000 patients treated on expanded access program (EAP). *Proc Am Soc Clin Oncol* 2003;(22):Abstract 2328.
- Roy L, Guilhot J, Krahnik T. Survival advantage from imatinib compared with the combination interferon-alpha plus cytarabine in chronic-phase chronic myelogenous leukemia: historical comparison between two phase 3 trials. *Blood* 2006;108(5):1478-84.
- Silver RT, Talpaz M, Sawyers CL, et al. Four years of follow-up of 1027 patients with late chronic phase (L-CP), accelerated phase (AP), or blast crisis (BC) chronic myeloid leukemia (CML) treated with imatinib in three large phase 2 trials. *Blood* 2006;108(11):130-1.
- Fausel C. Targeted chronic myeloid leukemia therapy: seeking a cure. *Supplement of Journal of Managed Care Pharmacy* 2007;13(8):S8-S12.
- Denninger MW. Management of early stage disease. *Hematology Am Soc Hematol Educ Program* 2005;174-82.
- Krejci M, Mayer J, Doubek M, et al. Clinical outcomes and direct hospital costs of reduced-intensity allogeneic transplantation in chronic myeloid leukaemia. *Bone Marrow Transplant* 2006;38:483-491.
- Zaretsky Y, Rifkind J, Lockwood G, et al. Long-term follow-up of allogeneic bone marrow transplantation for patients with chronic phase chronic myeloid leukemia prepared with a regimen consisting of cyclophosphamide, cytarabine and single-dose total body irradiation conditioning. *Bone Marrow Transplant* 2007;40:423-430.
- Peggs K. Imatinib mesylate - gold standards and silver linings. *Clin Exp Med* 2004;4:1-9.
- Talpaz M, Silver RT, Druker BJ, et al. Imatinib induces durable hematologic and cytogenetic responses in patients with accelerated phase chronic myeloid leukemia: results of a phase 2 study. *Blood* 2002;99(6):1928-37.
- Hehlmann R, Berger U, Pfirrmann M, et al. Randomised comparison of primary allogeneic stem cell transplantation and best available drug treatment in CML. *Blood (ASH Annual Meeting Abstracts)* 2006;108:Abstract 2154.

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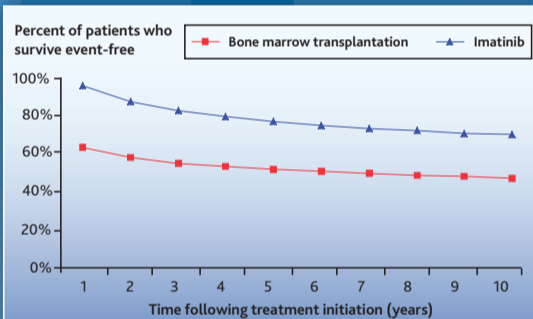


Figure 1: Event-free survival.

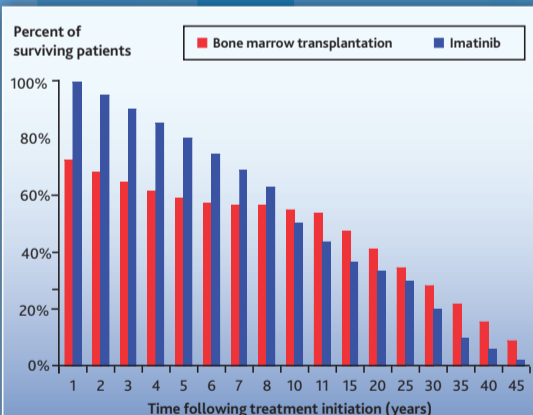


Figure 2: Overall survival.

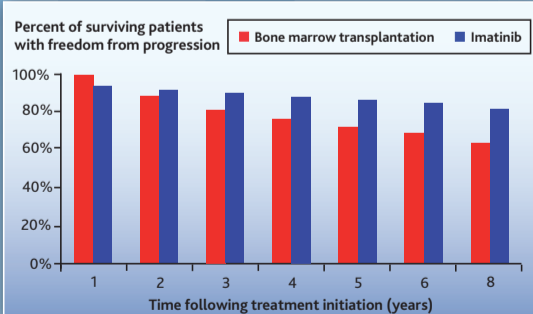


Figure 3: Freedom from progression.

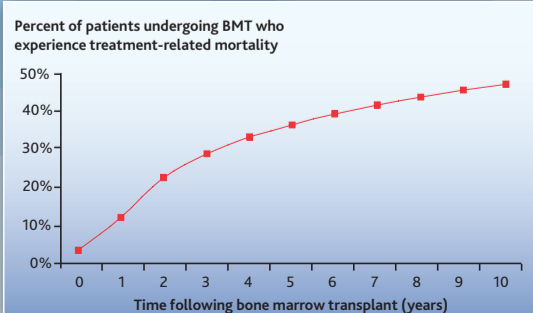


Figure 4: Treatment-related mortality following BMT.