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-fee 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 regimes. 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.

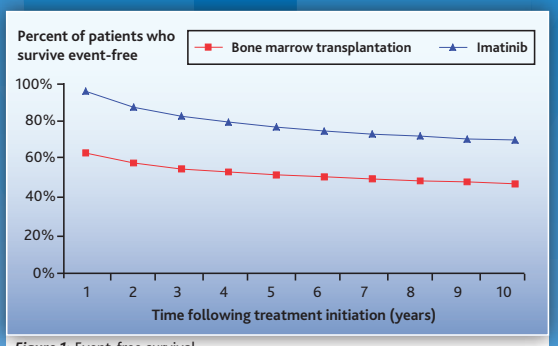

Figure 1: Event-free survival.

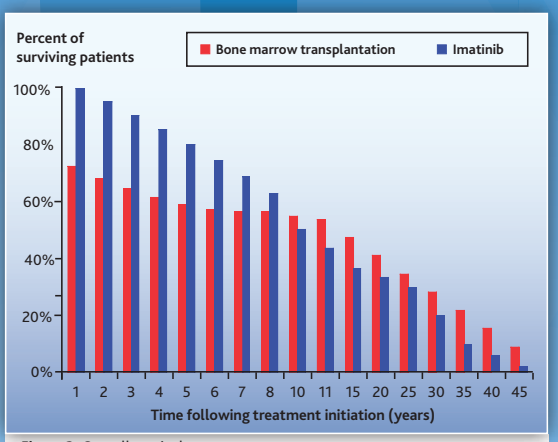

Figure 2: Overall survival.

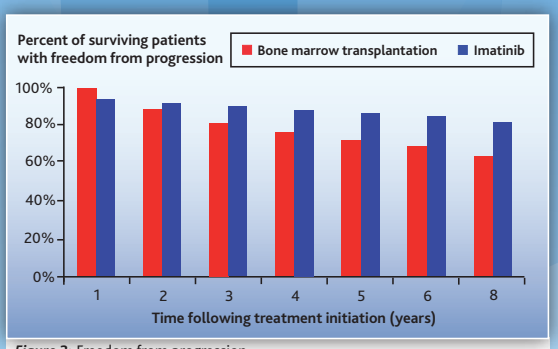

Figure 3: Freedom from progression.

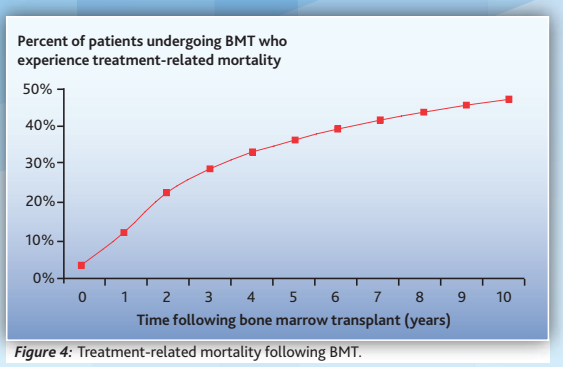

Figure 4: Treatment-related mortality following BMT.

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.

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