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Time to Reconsider Haematopoietic Cell Transplants in Chronic Myeloid Leukaemia?

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Summary

The article concerns whether we need to reconsider whether haematopoietic cell transplants are an appropriate therapy in some persons with chronic phase chronic myeloid leukaemia. The answer may be yes in some persons failing tyrosine kinase-inhibitor therapy or unlikely to achieve therap-free remission.

Keywords

Chronic myeloid leukemia, imatinib, hematopoietic stem cell transplantation, treatment strategy.

Introduction

The question I want to address is whether we abandoned haematopoietic cells transplants too soon in people with chronic phase chronic myeloid leukaemia (CML)? I think so. The idea of re-addressing transplants was suggested by the late CML expert Prof. Michele Baccarani to whom I dedicate this typescript [1].

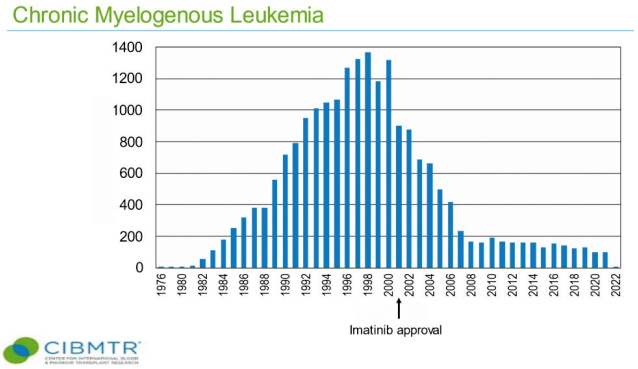


Figure 1. Numbers of hematopoietic cell transplants in CML reported to the CIBMTR (1976-2022) [2]

Figure 1 displays numbers of transplants for CML 1976-2022 reported to the Centre for Blood and Marrow Research (CIBMTR). These data indicate that whilst CML was once the most common transplant indication, the introduction of imatinib, a tyrosine kinase-inhibitor (TKI), in 2001 markedly reduced numbers of transplants done. The reason, of course, is the remarkable improvement in survival of persons with chronic-phase CML receiving TKIs reaching an adjusted 10-year survival of about 90 percent.

To define the efficacy of a therapy, we first need to define the goal. Is it *cure* defined as normal sex- and age-adjusted survival with a normal *quality-of-life* **off** therapy, or is it *operational* cure defined as *near-normal* sex- and age-adjusted survival **off** or **on** therapy with a *near normal quality of life*. When operational cure is achieved **off** therapy, it is termed therapy-free remission (TFR). Therapy goals in CML are displayed in Fig. 2.

Unfortunately, very few persons with chronic-phase CML achieve *operational cure* and even few, if any, are cured with TKI therapy. Figure 3 is a cartoon of endpoints starting with 100 people with chronic-phase CML starting TKI-therapy. Only about 15 percent achieve therapy-free remission (TFR). Also controversial is the issue whether TKI, if any, is *best* to achieve TFR.

Results of transplants for chronic-phase CML from diverse donor types are indicated in Fig. 4 and 5. Quite similar survival curves are observed when using different types of donor grafts including those from haploidentical donors.

Overall substantial decrease in early deaths after allo-HSCT was registered in 2013-2017 compared to early 2000's (Fig. 5A). Moreover, the 15-year probability of survival of transplant recipients alive at 5 years as displayed in Fig. 5B.

There are several issues which impact the metric for considering transplants in persons with chronic-phase CML. The 1st is median age of CML diagnosis is 60 years in the West and 50 years in Asia making > one-half potential transplant recipients. Second, the reduced-intensity conditioning (RIC) transplants are being done in older persons, albeit with a higher relapse rate compared with conventional conditioning. Third, usage of HLA-haplotype-matched relatives as donors with posttransplant cyclophosphamide means almost everyone has a suitable donor. Lastly, as indicated, early transplant-related deaths have decreased substantially. However, an early death rate of up to 20 percent must be acknowledged in this population. We also need to consider we can predict relatively early and accurately people unlikely to achieve TFR on TKI-therapy.

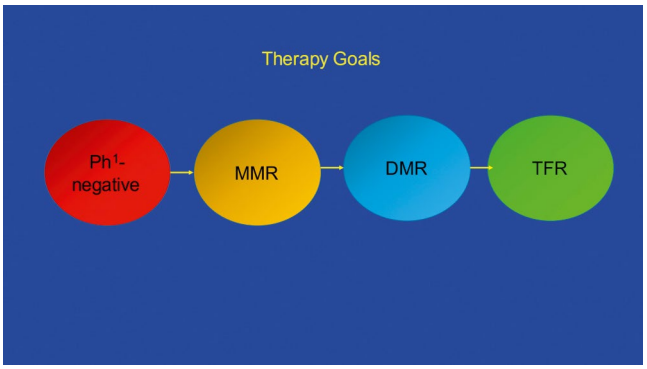


Figure 2. Stages of response to TKI-therapy in chronic phase CML

Abbreviations: Ph1-negative, Ph1-chromosome-negative; MMR, major molecular response; DMR, deep molecular response; TFR, therapy-free remission.

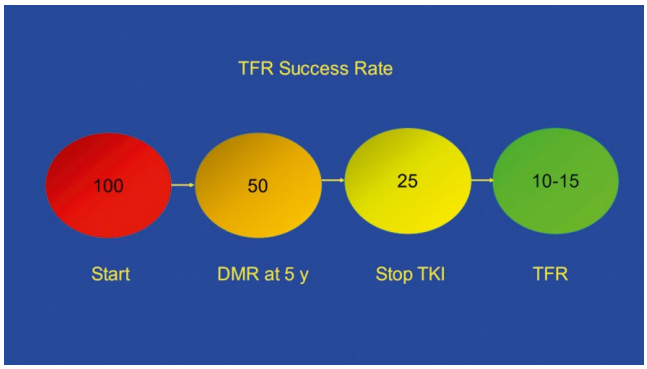
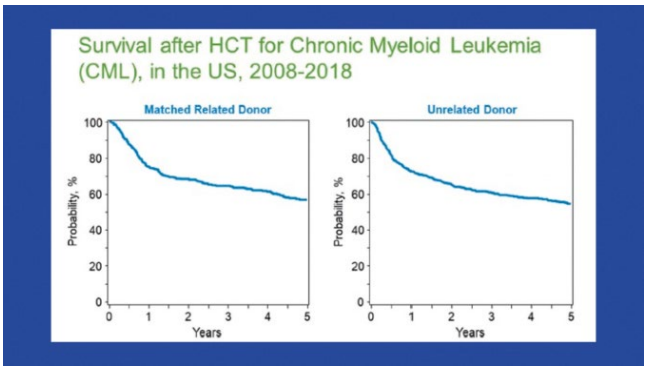


Figure 3. Approximate per cent frequencies of achieving different therapy goals starting with 100 people

Abbreviations are the same as in Fig. 2.



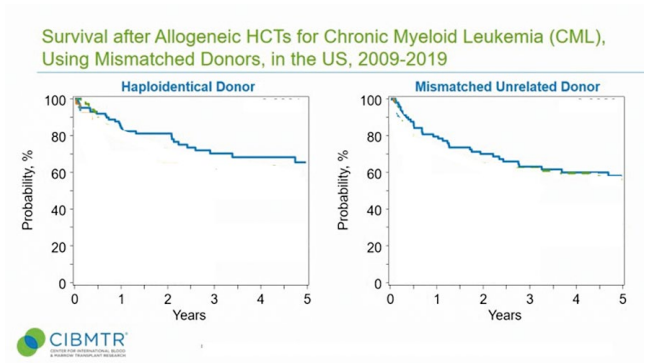
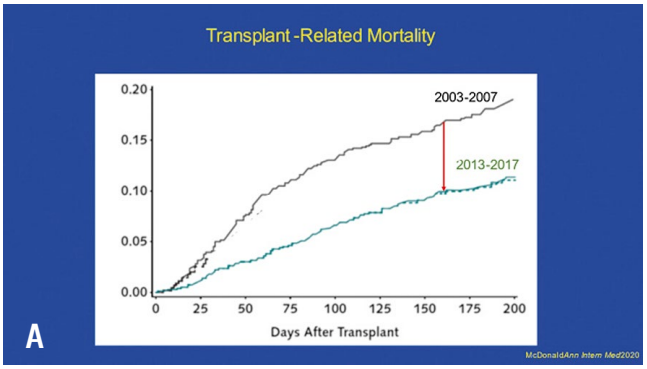


Figure 4. Survival after transplants from HLA-matched relatives and HLA-matched unrelated donors (A), as well as HLA-haplotype- matched relatives and HLA-mismatched unrelated donors (B) reported to the CIBMTR [2]



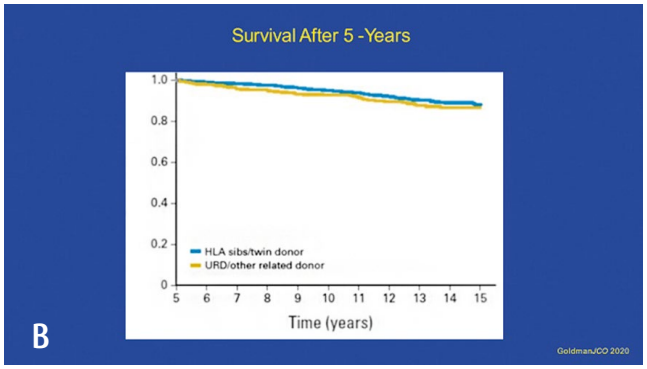
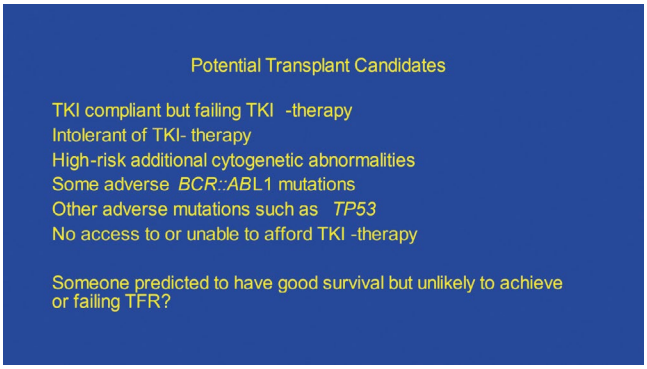


Figure 5. Reduction in early transplant-related death (A) [3], 15-year probability of survival of transplant recipients alive at 5 years (B) [4]

These considerations raise the question who is a reasonable candidate to receive a transplant in chronic phase. I suggest the following answers in Table 1.

Table 1. Persons and conditions where a transplant in chronic phase might be considered



Returning to the question, whether we have abandoned transplants in chronic phase CML too soon I suggest why this question deserves reconsidered as shown below. I also consider some concerns of using transplants in an era of TKI-therapy, as follows:

- Few people receiving TKI therapy achieve therapy-free remission, and even fewer are cured.
- Most people likely to fail TKI-therapy can be identified relatively early
- However, there are few recent transplants limiting our prediction models.
- Subject selection biases arise for transplants.
- 20% 1-year deaths and risk of chronic GvHD.
- Randomized trial will never be done.

There is not and cannot be a universal answer to who should receive a transplant. For example, the metric of an otherwise healthy 30-year-old person facing potentially 50 years of TKI-therapy is rather different than that of a 70 year-old with other health problems more likely to kill him than CML. Helping people decide is our responsibility as physicians, a difficult challenge. As Sir William Osler, the great Canadian, British, American physician said: *Medicine is a science of uncertainty and an art of probability*.

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Conflict of interest

Consultant to NexImmune Inc. and Ananexa Pharma Ascentage Pharm Group, Antengene Biotech LLC, Medical Director, FFF Enterprises Inc.; partner, AZAC Inc.; Board of Directors, Russian Foundation for Cancer Research Support; and Scientific Advisory Board: StemRad Ltd.

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К вопросу о роли трансплантации гемопоэтических клеток при хроническом миелоидном лейкозе

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Резюме

В статье затрагивается вопрос: нужно ли нам пересматривать применение трансплантации гемопоэтических клеток в качестве адекватной терапии у некоторых пациентов с хроническим миелоидным лейкозом в хронической фазе? Ответ может быть положительным для некоторых больных, которые не отвечают на лечение ингибиторами тирозинкиназы или вряд ли достигнут ремиссии без дальнейшей терапии.

Ключевые слова

Хронический миелоидный лейкоз, иматиниб, трансплантация гемопоэтических стволовых клеток, стратегия лечения.