Best Practice & Research Clinical Haematology 29 (2016) 345–350

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

Should anyone with Philadelphia chromosome-positive ALL who is negative for minimal residual disease receive a hematopoietic stem cell transplant in first remission?

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Keywords:
Acute lymphoblastic leukemia
ALL
Allogeneic
Cytogenetics
Dasatinib
Imatinib
Minimal residual disease
MRD
Nilotinib
Philadelphia chromosome positive
Ph+
Ponatinib
Stem cell transplant
TKI
Tyrosine kinase inhibitor

A B S T R A C T

Outcomes for patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) in the pre-imatinib era were poor, particularly if patients did not receive an allogeneic hematopoietic stem cell transplant. This led to the recommendation that all patients with Ph+ ALL, if they were transplant candidates, should be transplanted. With the introduction of imatinib and subsequently other tyrosine kinase inhibitors, patient outcomes improved dramatically, raising the question of whether transplant in first complete molecular remission for these patients is really necessary. This review looks at evidence from clinical studies around the world in an attempt to answer this question.

Introduction

Prior to the introduction of the tyrosine kinase inhibitor (TKI), imatinib, approximately 15 years ago, patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) had poor

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http://dx.doi.org/10.1016/j.beha.2016.10.009
1521-6926/

outcomes. Data from the MRC UKALLXII/ECOG2993 ALL trial [1] indicated that patients who received chemotherapy alone had a 19% overall survival (OS) rate. Patients who received an allogeneic stem cell transplant with a matched unrelated donor had a 36% OS rate, and patients who received a sibling transplant fared the best, with a 44% (OS) rate. Because of results like these, the reigning standard of practice was to transplant all viable candidates with Ph+ ALL in first remission. The introduction of imatinib and subsequently other tyrosine kinase inhibitors in the 2000s has led to a gradual evolution in treatment philosophy.

Introduction of imatinib

When imatinib was introduced for Ph+ ALL, many groups in the United States, United Kingdom, Germany, and elsewhere studied how best to incorporate it into existing chemotherapy regimens. Investigators were concerned about possible adverse interactions with chemotherapy, and so in the Ph+ ALL arm of the UKALLXII/ECOG2993 study, they initially introduced imatinib after 2 cycles of induction, subsequently referred to as “late imatinib” [2]. Studies from other groups determined that imatinib could be combined with induction chemotherapy, and the UKALLXII/ECOG2993 trial later administered it during the second month of induction therapy, which was termed “early imatinib.” The data, published in 2014 by Fielding et al., reinforced the concept that the TKI should be introduced early in therapy. The probability of event-free survival (EFS) with early imatinib was 39%, while with late imatinib, EFS was 28% [2]. Additional studies have confirmed the benefit of early introduction of imatinib and other TKI with chemotherapy at diagnosis as is currently recommended in an evidence-based consensus document from Canada on the treatment of Ph+ ALL [3].

Imatinib has also been studied in a small cohort of pediatric Ph+ ALL patients on the Children's Oncology Group study AALL0031. Long-term follow-up has shown that patients who had imatinib combined with chemotherapy alone responded as well as patients who had an allogeneic transplant with a matched related or unrelated donor source [4]. This led the investigators to question whether transplant is really necessary in children who respond well to intensive chemotherapy and imatinib and raised the questions of whether some adults with Ph+ ALL may also do well without being transplanted.

Contemporary data

SWOG S0805

Phase 2 data from several different studies of a TKI and chemotherapy have examined where and how transplant fits in the treatment regimen. The Southwest Oncology Group (SWOG) trial S0805 was an intergroup trial of the second-generation TKI, dasatinib, combined with alternating cycles of the hyper-CVAD regimen [5]. Patients received dasatinib, 100 mg daily, for the first 2 weeks of cycle one and then continuously at 70 mg daily with all subsequent cycles. The 24-month maintenance phase consisted of 100 mg of dasatinib daily combined with alternating vincristine plus prednisone and methotrexate-cytarabine. Patients who were appropriate candidates for transplant could receive one.

The investigators treated 94 patients on this study. Eighty-six percent achieved a complete response (CR), and an additional 2% achieved a CR with incomplete recovery of blood counts (CRi). Three-year overall survival (OS) of the entire cohort was 71% (Fig. 1). This contrasts greatly with results from the ECOG/MRC study during the pre-imatinib era, discussed above, which had a 44% survival rate for patients who received a sibling transplant. Patients on SWOG S0805 who did not receive a transplant had a 3-year OS of 59%.

The investigators also compared patients on this study who received transplants with those who did not (Fig. 2). The survival curve for the non-transplanted patients was slightly inferior to that of transplanted patients, but the P value was not significant ($P = 0.088$). This suggests that patients who do not proceed to transplant can still fare quite well. Molecular data from this study are not yet available.