Best Practice & Research Clinical Haematology 30 (2017) 193–200

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

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

Which tyrosine kinase inhibitor should we use to treat Philadelphia chromosome-positive acute lymphoblastic leukemia?

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ARTICLE INFO

Article history:
Received 3 April 2017
Received in revised form 9 May 2017
Accepted 29 May 2017

Keywords:
Acute lymphoblastic leukemia
Philadelphia chromosome
Tyrosine kinase inhibitor
Imatinib
Dasatinib
Ponatinib

ABSTRACT

The incorporation of tyrosine kinase inhibitors (TKIs) into chemotherapy regimens has significantly improved the long-term survival of patients with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL). Successive generations of TKIs with increased potency against *BCR-ABL* and broader spectrum of activity against *ABL* kinase domain mutations have led to incremental improvements in the outcomes of patients with this disease. In particular, ponatinib, a potent pan-BCR-ABL TKI capable of overcoming the *T315I* mutation, holds significant promise in the treatment of Ph+ ALL, although the potential cardiovascular toxicity of this agent remains a concern. With the development of more potent TKIs that are capable of inducing deep and sustained remissions, future studies re-evaluating the need for intensive chemotherapy as well as the role for stem cell transplantation in first remission for patients with Ph+ ALL are warranted.

1. Outcomes in the pre-tyrosine kinase inhibitor era

Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) is an aggressive subtype of ALL characterized by the presence of the *BCR-ABL* gene fusion [1]. Prior to the development of inhibitors targeting the *BCR-ABL* tyrosine kinase, the outcomes of patients with Ph+ ALL were dismal [2]. This was driven, in part, by lower response rates with combination chemotherapy compared to those achieved in Ph-negative disease [3]. However, the outcomes remained poor even for patients who achieved a complete remission (CR) mainly due to high rates of relapse. For example, using the hyper-CVAD regimen, a CR rate of 91% could be achieved in patients with Ph+ ALL, but relapse was nearly universal, leading to a 5-year overall survival (OS) rate of only 7% [4]. In the largest study assessing the prognostic impact of karyotype in adults with ALL, the presence of t(9; 22) was associated with significantly worse event-free survival (EFS) and OS compared to Ph-negative patients, even after adjusting for other pretreatment characteristics (5-year EFS: 16% versus 36%; 5-year OS: 22% versus 41%, respectively) [5].

Prior to the introduction of tyrosine kinase inhibitors (TKIs), the best chance of cure for patients with Ph+ ALL was to receive an allogeneic stem cell transplantation (AlloSCT) in first remission. This approach was supported by the UKALLXII/ECOG 2993 study, which showed significantly longer relapse-free survival (RFS) among patients who underwent AlloSCT

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http://dx.doi.org/10.1016/j.beha.2017.05.001
1521-6926/

compared to those who received chemotherapy only [6]. OS was also superior in patients who underwent AlloSCT, although this did not reach statistical significance, likely due to the high rate of treatment-related mortality seen in the AlloSCT cohort.

2. Efficacy of TKIs in Ph+ ALL

With the incorporation of TKIs into chemotherapy regimens for patients with Ph+ ALL, long-term survival rates of 30–80% have been achieved, with improved outcomes seen in patients receiving later-generation TKIs [7–12]. Frontline studies of TKIs in Ph+ ALL are summarized in Table 1.

2.1. First-generation TKI: Imatinib

Imatinib was the first TKI evaluated in Ph+ ALL [13]. In the initial studies of single-agent imatinib in patients with relapsed blast phase chronic myeloid leukemia (CML) or Ph+ ALL, CR rates of 20–29% were achieved, although resistance rapidly developed and responses were short-lived [13,14]. However, given the clinical activity observed in these early studies, imatinib was next evaluated in combination with chemotherapy in the frontline setting [7–9,15–19]. In all of these reports, the addition of imatinib to intensive chemotherapy led to CR rates >90%. More importantly, most of these studies reported significant survival benefit for the imatinib-containing regimen compared to historical cohorts treated with the same chemotherapy backbone alone [15–20]. In updated analyses, long-term survival rates of approximately 30–50% have been achieved with imatinib-based regimens (Table 1). It should be noted that, in most of these studies, the majority of patients underwent AlloSCT in first remission, with the notable exception of the report from MD Anderson in which only 30% underwent AlloSCT [8]. Despite this lower rate, 5-year RFS and OS rates were 43% and 43%, which is comparable to other studies with higher AlloSCT rates and generally younger cohorts. This raises the possibility that a significant proportion of patients with Ph+ ALL treated with a TKI-based chemotherapy regimen may be able to forgo AlloSCT in first remission. CALGB Study 10001 suggested that autologous SCT may be a reasonable alternative to alloSCT in some patients who receive imatinib-based chemotherapy [21]. However, at most institutions, including our own, autologous SCT is not performed in patients with Ph+ ALL, given the limited data available supporting this approach and the potential for collection of contaminated residual lymphoblasts.

Given the clear benefit of imatinib-based therapy in Ph+ ALL in multiple single-arm studies, a randomized trial of chemotherapy with or without a TKI is unlikely to be performed. The UKALLXII/ECOG299 study however did prospectively evaluate the impact of adding imatinib to standard combination chemotherapy [7]. The addition of imatinib was associated

Table 1
Frontline studies in adults using TKIs for Ph+ ALL.

Study	N	Age, median [range]	Combination regimen	CMR rate	AlloSCT rate	RFS rate	OS rate
Imatinib							
Lee *et al.* 2005 [16]	87	41 [16–71]	Intensive chemotherapy	66% (at remission)	68%	39% (5-year)	33% (5-year)
Yanada et *al.* 2006 [17]	80	48 [15–63]	Intensive chemotherapy	50% (day 63)	49%	–	76% (1-year)
Vignetti et *al.* 2007 [23]	29	69 [61–83]	Corticosteroids	4%	–	48% (1-year)	74% (1-year)
Bassan et *al.* 2010 [18]	59	45 [20–66]	Intensive chemotherapy	–	72%	39% (5-year)	38% (5-year)
Tanguy-Schmidt et *al.* 2013 [19]	45	45 [16–59]	Intensive chemotherapy	29% (induction)	76%	44% (4-year)	52% (4-year)
Fielding et *al.* 2014 [7]	169	42 [16–64]	Intensive chemotherapy	–	72%	50% (4-year)	38% (4-year)
Daver et *al.* 2015 [8]	54	51 [17–84]	Intensive chemotherapy	45% (overall)	30%	43% (5-year)	43% (5-year)
Chalandon et *al.* 2015 [9]	133	45 [21–59]	Intensive chemotherapy	23% (2 cycles)	65%	–	46% (5-year)[a]
Chalandon et *al.* 2015 [9]	135	49 [18–59]	Low-intensity chemotherapy	29% (2 cycles)	62%	–	46% (5-year)[a]
Dasatinib							
Foa et *al.* 2011 [35]	53	54 [24–77]	Corticosteroids	15% (day 85)	42%	22% (20 months)	31% (20 months)
Ravandi et *al.* 2015 [10]	72	55 [21–80]	Intensive chemotherapy	65% (overall)	17%	44% (5-year)	46% (5-year)
Chiaretti et *al.* 2015 [36]	60	42 [19–59]	Corticosteroids ± chemotherapy	19% (day 85)	–	49% (30 months)	58% (3-year)
Ravandi et *al.* 2016 [34]	97	44 [20–60]	Intensive chemotherapy	–	42%	62% (3-year)	69% (3-year)
Rousselot et *al.* 2016 [37]	71	69 [55–83]	Low-intensity chemotherapy	24% (consolidation)	10%	28% (5-year)	36% (5-year)
Nilotinib							
Ottmann et *al.* 2014 [39]	47	66 [55–85]	Low-intensity chemotherapy	42% (consolidation)	15%	–	–
Kim et *al.* 2015 [11]	90	47 [17–71]	Intensive chemotherapy	77% (3 months)	63%	72% (2-year)	72% (2-year)
Ponatinib							
Jabbour et *al.* 2015 [12]	37	51 [27–75]	Intensive chemotherapy	78% (overall)	24%	–	80% (2-year)

CMR, complete molecular remission; AlloSCT, allogeneic stem cell transplantation; RFS, relapse-free survival; OS, overall survival.

[a] 5-year OS was 46% for the pooled cohort of patients who received intensive or low-intensity chemotherapy. OS was not significantly different between these 2 arms in this randomized trial ($P = 0.37$).