

Online Research @ Cardiff

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository: <http://orca.cf.ac.uk/118286/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Ottmann, Oliver 2018. Tyrosine kinase inhibitor therapy or transplant in children with Philadelphia chromosome-positive acute lymphoblastic leukaemia: striking the balance. *Lancet Haematology* 5 (12) , e606-e607. 10.1016/S2352-3026(18)30181-9 file

Publishers page: [http://dx.doi.org/10.1016/S2352-3026\(18\)30181-9](http://dx.doi.org/10.1016/S2352-3026(18)30181-9)
<[http://dx.doi.org/10.1016/S2352-3026\(18\)30181-9](http://dx.doi.org/10.1016/S2352-3026(18)30181-9)>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



Commentary for LANCET HAEMATOLOGY on manuscript:

Treatment of Pediatric Philadelphia Positive Acute Lymphoblastic Leukemia with imatinib: an Intergroup, Open-label, Single-Arm Clinical Trial (EsPhALL2010)

Biondi et al.

Manuscript number: THELANCETHAEMATOLOGY-D-18-00319R2

Title of commentary:

Striking the balance between TKI and transplant in pediatric Ph+ALL

Author and Correspondence:

Professor Oliver Ottmann
Head of Haematology
Division of Cancer and Genetics
Room 160, 7th Floor, A-B Link
School of Medicine
Cardiff University
Heath Park
Cardiff
CF14 4XN
Tel: 02920742375
Fax: 02920744655
E-mail: OttmannO@Cardiff.ac.uk

Commentary:

Before the advent of tyrosine kinase inhibitor (TKI) therapy, BCR-ABL1/Philadelphia chromosome positive ALL (Ph+ALL) carried an exceptionally poor prognosis and was a definite indication for allogeneic hematopoietic stem cell transplantation (HSCT). Adding TKI to frontline therapy improved survival and transplantation was increasingly reserved for poor responders in paediatric patients. The study by Biondi et al. in this issue of *Lancet Haematology*(1) confirms previous findings that earlier initiation and prolonged, continuous TKI administration together with intensive chemotherapy increase morphologic and molecular response rates in Ph+ ALL.(2, 3) Notably, response in the EsPhALL2010 trial compared favorably with the preceding study particularly in poor risk patients, with similar overall and disease-free survival.(4) This supports the tenet that reliance on HSCT can be reduced without compromising outcome but relapse, treatment-associated mortality and morbidity remain serious limitations in transplanted and in chemotherapy-only cohorts.

Which patients actually benefit from HSCT? Best outcomes in terms of DFS occurred in the good risk (GR) group achieving early minimal residual disease (MRD) negativity, whereas MRD poor risk (PR) patients and those with higher WBC count who underwent HSCT in first CR had inferior (albeit not statistically significant) DFS. This challenges the widely accepted transplant strategy for children with Ph+ALL, with implications for designing future treatment of poor risk patients. GR patients fared significantly better with HSCT in terms of relapse incidence and event-free survival (EFS) but not overall survival, an observation that differs substantially from adult Ph+ALL, where avoidance of relapse is critical. Although deferring HSCT to more advanced disease is accepted practice in children owing to the efficacy of salvage therapy, the outcome of these patients reported by Biondi et al. remains unsatisfactory.

Given its non-randomized study design and the changing indications for HSCT during protocol accrual, the EsPhALL2010 study does not conclusively resolve the controversy surrounding eligibility for HSCT. Post amendment, poor risk pts were not transplanted in case of a good MRD response, but MRD data were available for only about half of patients enrolled, and pre-transplant MRD values were often lacking. Thus, it is unclear how the indications for HSCT (poor MRD response) would have been determined in patients without having at least one MRD analysis performed during therapy. Moreover, the potential of post-transplant intervention with TKI has most likely not been fully exploited in this trial.

MRD measurements were based on quantitation of immunoglobulin(Ig)/T-cell receptor (TCR) gene rearrangements rather than on quantitation of BCR-ABL1 transcripts. Recent studies have demonstrated that results generated by these methods may be discordant, particularly in cases with p210^{BCR-ABL1}.(5, 6) As the underlying biological differences are likely to be clinically relevant and have implications for treatment, future MRD testing should employ both methods in parallel.

The relevance of biologic and genetic factors in pediatric and adult Ph+ALL has become increasingly appreciated but is hardly addressed by this EsPhALL trial. A negative impact of high WBC ($>1 \times 10^5/\mu\text{l}$) was noted but the molecular mechanisms underlying the inferior outcome of these patients, or those in the GR group who nevertheless experience late relapses remain elusive. Similarly, the study did not evaluate the role of recurrent genomic alterations such deletions in IKZF1 which have been linked to inferior outcome in several studies, including a COG trial of dasatinib plus chemotherapy,(7) or applicability of the recently described inverse correlation between number of genetic lesions and outcome to this population.(8) It therefore remains unclear whether presence of these genetic lesions

correlates with MRD response, WBC at diagnosis or outcome in relation to HSCT or non-transplant therapy. Such integrated analysis of MRD, genomic and clinical data will be needed to identify novel, independent biomarkers for outcome in future trials.

Improving outcomes requires increasing treatment efficacy while reducing the toxic death rate associated with current intensive regimens. Published data in adult Ph+ALL demonstrate lower early morbidity and mortality without compromising long-term outcome when imatinib is combined with minimal chemotherapy during induction.(9) More potent TKI may further augment rates and depth of molecular response.(10) Conversely, post-remission treatment intensity remains important for treatment with curative intent. Addition of novel treatment elements able to induce MRD negativity while adding only moderate toxicity, e.g. immunotherapy, has the potential to improve post-transplant outcome particularly of PR patients who did not benefit from HSCT, or even obviate the need for HSCT. It is plausible that such novel regimens will also benefit the group of GR patients when incorporated into frontline therapy. Evaluation of novel therapeutic interventions and algorithms for clinical decisions in this rare subgroup of childhood ALL will require ambitious, multinational trials exemplified by this study of the EsPhALL consortium.

References

1. Biondi A. Treatment of Pediatric Philadelphia Positive Acute Lymphoblastic Leukemia with imatinib: an Intergroup, Open-label, Single-Arm Clinical Trial (EsPhALL2010). *Lancet Haematol.* 2018.
2. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, et al. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. *Leukemia.* 2014;28(7):1467-71.
3. Wassmann B, Pfeifer H, Goekbuget N, Beelen DW, Beck J, Stelljes M, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). *Blood.* 2006;108(5):1469-77.
4. Biondi A, Schrappe M, De Lorenzo P, Castor A, Lucchini G, Gandemer V, et al. Imatinib after induction for treatment of children and adolescents with Philadelphia-chromosome-positive acute lymphoblastic leukaemia (EsPhALL): a randomised, open-label, intergroup study. *Lancet Oncol.* 2012;13(9):936-45.
5. Bruggemann M, Kotrova M. Minimal residual disease in adult ALL: technical aspects and implications for correct clinical interpretation. *Blood Adv.* 2017;1(25):2456-66.
6. Nagel I, Bartels M, Duell J, Oberg HH, Ussat S, Bruckmueller H, et al. Hematopoietic stem cell involvement in BCR-ABL1-positive ALL as a potential mechanism of resistance to blinatumomab therapy. *Blood.* 2017;130(18):2027-31.
7. Slayton WB, Schultz KR, Kairalla JA, Devidas M, Mi X, Pulsipher MA, et al. Dasatinib Plus Intensive Chemotherapy in Children, Adolescents, and Young Adults With Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia: Results of Children's Oncology Group Trial AALL0622. *J Clin Oncol.* 2018;36(22):2306-14.
8. Pfeifer H, Raum K, Markovic S, Nowak V, Fey S, Oblander J, et al. Genomic CDKN2A/2B deletions in adult Ph(+) ALL are adverse despite allogeneic stem cell transplantation. *Blood.* 2018;131(13):1464-75.
9. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, et al. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. *Blood.* 2015;125(24):3711-9.
10. Jabbour E, Kantarjian H, Ravandi F, Thomas D, Huang X, Faderl S, et al. Combination of hyper-CVAD with ponatinib as first-line therapy for patients with Philadelphia chromosome-positive acute lymphoblastic leukaemia: a single-centre, phase 2 study. *Lancet Oncol.* 2015;16(15):1547-55.