Author's response to reviews

Title: Impact of age, leukocyte count and day 21-bone marrow response to chemotherapy on the long-term outcome of children with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in the pre-Imatinib era: results of the FRALLE 93 study

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Author's response to reviews: see over
Dear Dr Dunckley,

Thank you for the opportunity to send revision notes regarding our manuscript entitled “Impact of age, leukocyte count and day 21-bone marrow response to chemotherapy on the long-term outcome of children with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia in the pre-Imatinib era: results of the FRALLE 93 study” MS 9189200572225740.

We carefully read the reviewers’ comments and suggestions and modified the paper accordingly. Please find below a point-by-point response to the referees’ comments and a list of the text modifications. As you and two reviewers strongly advised, we asked a copyediting service for English language corrections.

I hope the revised version will meet the requirements for publication in BMC Cancer.

Looking forwards to hearing from you.

Sincerely yours

Docteur V. GANDEMER
Point-by-point response

Reviewer John Doyle:

Major compulsory revisions

1) Clearly indicate which analyses are performed using the entire cohort and which are performed using only the 26 that entered remission with initial therapy.

All analyses are performed using the entire cohort of 36 patients except for DFS analysis. We thus indicated in the legend of Figure 2 that results concerned only the 26 patients who achieved remission. We also notified in Table 2 that the whole cohort of 36 patients was used.

2) Include a table or discussion that indicates the outcomes for different treatment groups.

Statistical comparisons of different groups of treatment were not performed due to the small number of patients in each group. Nevertheless, as suggested by Vaskar Saha, we constructed a flow diagram explaining the treatment and the outcome of each patient.

Please see the new Figure 1

“All seven children were then transplanted (2 matched related transplants, 4 matched unrelated transplants and one autologous transplantation); outcomes are described in Figure 1. Of the other children with CR observed after induction, five of the six children with an HLA-matched sibling received alternate courses of R3 and COPADM treatment before allogeneic bone marrow transplantation (one toxic death occurred before graft). Eight children received an autologous transplant, five a mismatched related transplant and two others a matched unrelated transplant (Figure 1).”

3) Include some discussion of statistical methods.

A paragraph concerning the statistical tests has been included in the manuscript.

“Analysis was based on an intent-to-treat principle. CR rates were compared using Fisher's exact test. Censored endpoints were estimated by the non parametric Kaplan-Meier method, and then compared by the log-rank test. Multivariate analyses were carried out to define the set of informative prognostic factors, using regression models adapted to the endpoint, namely the logistic model for CR rates, and Cox model for OS and EFS. Type I error was fixed at 5%. All tests were two-tailed. Statistical analysis was performed using SAS 9.1 (SAS, Inc, Cary, NC).”

Minor essential revisions:

1) Occasionally state Table 1 when you mean Table 2.

We reviewed all table references and changed as follow:
• Page 8: “We did not find any differences between the effects of including patients at two different time periods (before or after July 1996) and the addition of one dose of daunorubicin and two doses of asparaginase (but the numbers of children within each group are small) (Table 2).”

• page 8 (now page 9): “Table 2 summarizes the main endpoints…”

Discretionary revisions:

1) reorganize the introduction:
We changed the order of the sentences as suggested:

“The Philadelphia chromosome (Ph1) is detectable in 2% to 5% of children with acute lymphoblastic leukemia (ALL) [1,2]. The detection of a Philadelphia chromosome remains a major prognostic factor of induction failure. Despite the steady improvement in the management of ALL in children, Ph1-ALL is associated with high rates of relapse or resistance to treatment [3,4,5]. This disease is heterogeneous in terms of clinical parameters such as leukocyte count, age at diagnosis, and initial steroid response [4,6]. A slow early response to conventional therapy has also been reported as indicative of a poor prognosis [2].”

Reviewer Vaskar Saha

Major compulsory revision
i. I would suggest a detail table listing each patient and their outcome or a consort type flow diagram is constructed....

We added a flow chart of the Ph1-positive patients of the FRALLE 93 (Figure 1) which describes the treatment and the outcome of each patient for each group of treatment.

ii. The difference in outcome between the two induction regimens may not be statistically significant due to the small numbers or to the tests used.

With the small number of patients, the power of the tests can not be sufficient for detecting a significant difference and we notified this fact.

“We did not find any differences between the effects of including patients at two different time periods (before or after July 1996) and the addition of one dose of daunorubicin and two doses of asparaginase (but the numbers of children within each group are small) (Table 2).”

Minor essential revision

iii. We modified the Table number page 8 (now page 9): “Table 2 summarizes the main endpoints…”

iv. We deleted line 3-4 page 9 as suggested.
Reviewer P Gaynon

i. Page 6, R3 bloc is not defined or referenced

R3 and COPADM courses were now defined page 6 and we referenced also the Table 1 where the details of chemotherapy were described.

"Children with an HLA-matched sibling received alternating courses of R3 (Cytarabine, Etoposide, Dexamethasone) and COPADM (Vincristine, Methotrexate, Doxorubicin, Cyclophosphamide, Prednisone) therapy (for a total of 3 courses of treatment) before an allogeneic bone marrow transplantation (Table1)."

Reviewer R Maziarz

1. Description of these 36 children and how they were managed is quite incomprehensible when describe in the text of the manuscript.

We constructed as suggested by two other reviewers a flow diagram explaining the treatment and the outcome of each patient (see Figure 1).

“All seven children were then transplanted (2 matched related transplants, 4 matched unrelated transplants and one autologous transplantation); outcomes are described in Figure 1. Of the other children with CR observed after induction, five of the six children with an HLA-matched sibling received alternate courses of R3 and COPADM treatment before allogeneic bone marrow transplantation (one toxic death occurred before graft). Eight children received an autologous transplant, five a mismatched related transplant and two others a matched unrelated transplant (Figure 1)"

2. Within the abstract, the last sentence should include the exact P value.

"We also observed a non statistically significant difference (p=0.14) in outcome between these groups for transplanted patients (5-year DFS: 83% ±14% and 33±15%, respectively)."

3. Reference 14 should be given more detailed discussion ... the reader will want to see these data described in detail within the manuscript.

and 6. Within the discussion the authors could propose how they might use the indicator data.

The following sentences have been included within the discussion:

“Indeed, the COG AALL0031 study showed that continuous administration of Imatinib given in combination with intensive chemotherapy backbone resulted in a significant improvement in early EFS. More specifically cohort 5 who received 340 mg/m2 of Imatinib for 280 days with chemotherapy only had a similar two years EFS as compared to the
cohort of patients who underwent stem cell transplantation (32 patients) either according to the protocol (MRD-21 patients) or from MUD (11 patients)."[14].

“The combination of available tools, including minimal residual disease assessment, with these easily measured predictive features could be useful for refining the indications for bone marrow transplantation [19-22]. Thus, if the long term follow-up of the AALL0031 non randomized study was confirmed, good risk patients could be spared by transplantation.”

4. **Within the Table 1, the pro-phase treatment week should be included**

The “prophase” is notified and corresponds to treatment given before Day 8 ie: Prednisone 60 mg/m2 on D1-D8 and intrathecal therapy before D4

<table>
<thead>
<tr>
<th>Induction</th>
<th>Prednisone 60 mg/m2/d PO on D1-8, 40 mg/m2/d on D8-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine</td>
<td>1.5 mg/m2 IV (max, 2 mg) on D8, D15, D22, D29</td>
</tr>
<tr>
<td>Daunorubicin§</td>
<td>40 mg/m2 IV on D8, D9, D10, D15</td>
</tr>
<tr>
<td>L-Asparaginase§</td>
<td>10,000 U/m2 IM or IV on D20, D22, D24, D26, D28, D31, D33, D35</td>
</tr>
<tr>
<td>intrathecal therapy*</td>
<td>before D4, D8, and D15</td>
</tr>
</tbody>
</table>

5. **In the results section, the beginning of the paragraph 4 should be corrected to read “Table2”**

We modified Table number page 8 (now page 9): “Table 2 summarizes the main endpoints...”

**Editor and general comments**

**Ethics**

We specified in the text page 6 that

“This study was approved by the ethics committee of the Hôpital Saint Louis, France (accepted April 29, 1993). All patients, or their parents, provided informed consent in accordance with the Declaration of Helsinki.”

**Quality of Written English**

We performed language corrections with the help of a professional service (Axel Edelman & associates).