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by Mark Litzow

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The real world of acute lymphoblastic leukemia

Mark R. Litzow

Division of Hematology

Mayo Clinic

Rochester, MN 55902 USA

Email: litzow.mark@mayo.edu

In this issue of the journal Lazzarotto and colleagues describe the outcome of 421 adults between the ages of 18 and 80 years (median 42 years) with Philadelphia chromosome negative acute lymphoblastic leukemia (Ph-ALL) who received treatment outside of a clinical trial from 39 centers who are part of the Campus ALL network in Italy[1]. The treatment they received was according to the chemotherapy regimen utilized in the GIMEMA LAL1913 protocol[2]. The regimen is a BFM-style regimen with an induction course followed by 7 additional courses that include 3 courses of high dose methotrexate and cytarabine and 4 additional courses of therapy similar to the induction cycle followed by 24 months of maintenance therapy. Pegaspargase at a dose of 2000 IU/m^2 was added to courses 1, 2, 5, and 6 for patients aged from 18 to 65 years, with dose reductions in patients aged >55 years. Lazzarotto et al, compared their results to those of 203 patients treated on the LAL1913 protocol[2]. They found that they achieved a higher complete remission (CR) rate in their patients at the end of induction at 94% compared to 85% for the LAL1913 patients (p =0.004). However, rates of achievment of MRD negativity by RT-PCR for immunoglobulin and T-cell receptor gene rearrangements at the end of induction and after course 3 of chemotherapy were significantly lower in their cohort compared to the LAL1913 patients (46% vs 56%, p=0.04, and 72% vs 80%, p=0.04, respectively). Despite this, the overall and disease-free survival (OS and DFS) rates in their cohort were nearly identical to those seen in the LAL1913 study [OS 67% vs 67%, p=0.94 (Figure); DFS 57% vs 63%, p=0.17, respectively]. Propensity score matching was done between the two cohorts to balance varying risk factors and with this weighting OS and DFS remained similar between the two cohorts. A major difference in outcome was the higher rate of pegaspargase-related hepatic toxicity $\geq$2 in the Campus ALL network cohort compared to the LAL1913 patients (25% vs 12%, p=0.0003, respectively).

A common belief in the medical community is that patients treated on clinical trials have better outcomes than patients who do not participate in clinical trials[3]. The results of this Campus ALL network study would appear to counter this belief. The authors and clinicians caring for this cohort of patients are to be congratulated for the excellent results they have achieved in this study. This “real-life” study falls into the realm of the expanding field of “real-world evidence” (RWE) reports found in the literature. Real world evidence is produced by analyzing data collected from routine clinical practice and can provide insights into multiple areas of clinical medicine including, but not limited to health economics, epidemiology, and the safety and effectiveness of treatment[4]. In March of 2016 the United States Food and Drug Administration (FDA) indicated that they would use RWE in regulatory decision-making in a document entitled “Prescription Drug User Fee Act (PDUFA) for 2018-2022”. Legislation in the United States that same year, the 21st Century Cures Act, provided that RWE could be used in place of evidence

from randomized clinical trials to support approval for new clinical agents if judged to be appropriate by the FDA. Since then there has been a burgeoning literature on the topic of RWE with some inconsistencies in how the term is applied[5]. And while the data provided in the report that is the subject of this editorial will not support any new drug approvals it is an important proof of concept that RWE can confirm that the results seen in a controlled clinical trial can be applied in the community and achieve results similar to or better than that found in a clinical trial.

Of note, this report from the Campus ALL network and the LAL1913 trial did not incorporate the use of any immunotherapeutic agents in the treatment regimen. Agents like blinatumomab, a bi-specific T cell engager molecule, and inotuzumab ozogamicin, a CD22 antibody drug conjugate, are increasingly being utilized in the frontline setting in phase 2 and more recently phase 3 trials[6-8] and have the potential to further improve outcomes. A recently reported randomized phase 3 trial conducted by the National Clinical Trials Network in the United States in patients with MRD negative Ph-ALL added 4 cycles of blinatumomab to 4 cycles of consolidation chemotherapy and compared the outcome of this regimen to patients who received the 4 cycles of consolidation chemotherapy alone. The trial demonstrated a 3 year OS of 85% for the blinatumomab+chemotherapy group compared to 68% for the chemotherapy group alone ($p=0.002$)[8]. These results led the FDA to approve blinatumomab for a new indication of use in consolidation treatment. The use of agents like blinatumomab and inotuzumab ozogamicin and possibly chimeric antigen receptor T-cell (CAR-T) therapy in the frontline setting have the potential of not only improving response rates, but also allowing reduced use of chemotherapy with the potential to lessen toxicity and improve outcomes and quality of life for patients. It also raises the hope that we can shorten the duration of the long course of chemotherapy that patients with ALL currently endure. The Campus ALL network study shows that excellent outcomes in ALL can be achieved outside the realm of a clinical trial and complements, though does not lessen, the importance of conducting clinical trials to bring further advances to the encouraging improvements we have seen in ALL therapy in recent years.

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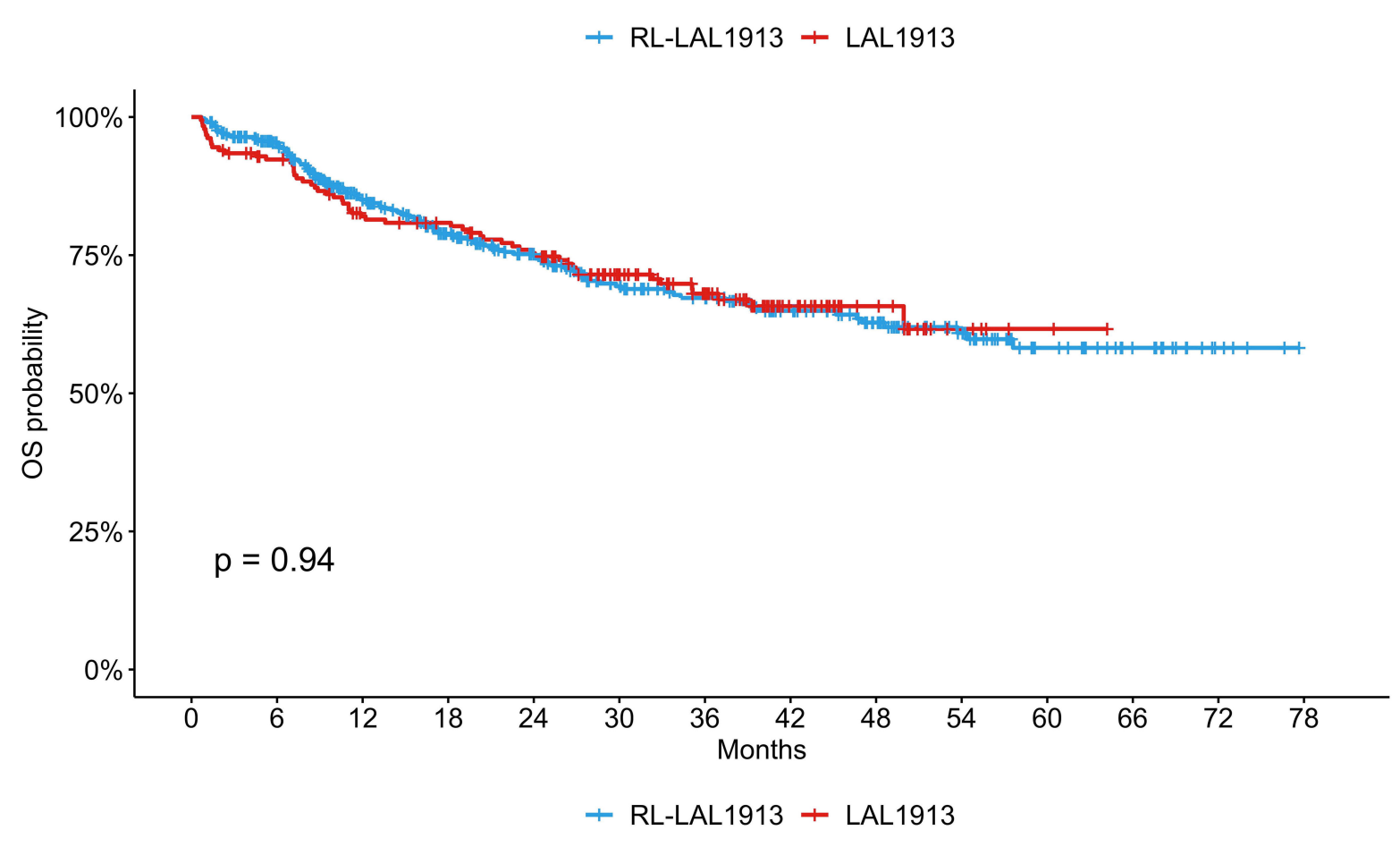
Figure: Overall survival of the entire population[1].

Abbreviation: RL-LAL1913=Real Life data reported in the manuscript for Campus ALL network patients treated according to the LAL1913 protocol.


RL-LAL1913
LAL1913
100%
75%
50%
25%
0%
OS probability
p = 0.94
0
6
12
18
24
30
36
42
48
54
60
66
72
78
Months
RL-LAL1913
LAL1913