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Chemotherapy De-Escalation Does Not Alter the Effectiveness of Therapy for Ph+ Acute Lymphocytic Leukemia in the Era of Tyrosine Kinase Inhibitors

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INTRODUCTION

The Russian group working with ALL applies the protocol based on a less intensive and also non-interruptive approach. The addition of tyrosine kinase inhibitors (TKI) to chemotherapy has dramatically improved the long-term outcome in Ph+ ALL. But how intensive chemotherapy it should be, is still the matter of debate. We have conducted three consecutive trials in Ph+ ALL aiming to evaluate the efficacy of more and less intensive chemotherapy approaches in combination with constant non-stop 600 mg Imatinib.

AIM

To analyze the effectiveness of RALL–2009+TKI, RALL–2012+TKI and RALL-2012m protocols.

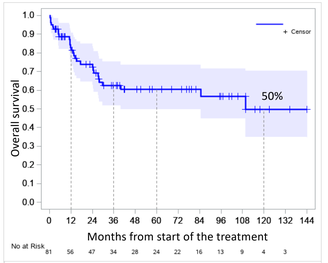
METHOD

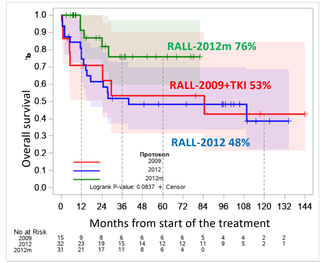
From 2010 January to 2024 May, 81 new Ph+ ALL cases were diagnosed in 4 centers of the RALL–group. From 2010 to 2012, 15 pts were treated according to RALL–2009 protocol (ClinicalTrials.gov; NCT01193933) with concurrent administration of Imatinib. Since 2012 till 2018 32 pts were included in RALL–2012 protocol, based on de-escalation chemotherapy approach in RALL-2009+ TKI study. Since 2018 till now 31 pts were included in RALL–2012m protocol, based on the next step of de-escalation chemotherapy approach. And 3 patients were treated not by the RALL protocols (pregnancy or clinical trial – ponatinib 3001). All protocols suggested the shift to Dasatinib after non-achievement of MolCR on day 70 of treatment. MolCR was stated if *bcr/abl* chimeric transcript was <0,01% by PCR with 10^{-4} sensitivity. All patients were considered as candidates for allogeneic HSCT if HLA-identical donor was available. 32 pts (40%) underwent allo-HSCT as the first-line therapy.

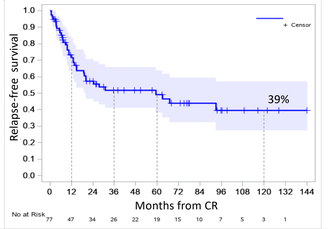
RESULTS

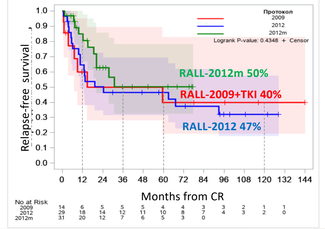
MolCR **o**n day 70 was achieved in 36%, 43% and 33% in RALL–2009 (4 of 11), RALL–2012 (14) and RALL-2012m (9 of 27), respectively. Death on therapy (within 2 months of induction/consolidation) was registered in 2(6%) cases on less intensive RALL-2012, 3(20%) cases on RALL–2009, nobody on RALL-2012m. Hematological CR was achieved in 71 (91%) of 78 pts (except four early deaths and 2 refractory cases). Allo–HSCT in 1CR was carried out in 5pts of RALL–2009 protocol pts, in 16pts of RALL–2012 and in 11pts of RALL-2012m.

The long-term outcome on protocols (RALL–2009, RALL–2012 and RALL-201m) was similar: 5yOS – 53% vs 48% vs 76 (p=0,08), 5yRFS – 40% vs 47% vs 50% (p=0,43), respectively. In order to evaluate the impact of allogeneic HSCT we performed a comparison of transplanted and non-transplanted patients by a landmark analysis. The land mark was chosen as the median time from CR to allo-HSCT – 4,3 mo (3-16 mo). So, the 5y RFS from land mark was 45% for non-transplanted patients and from day of HSCT - 65% in transplanted (p=0,48).









CONCLUSIONS

De-intensification of the chemotherapy does not affect the effectiveness of Ph-positive acute lymphocytic leukemia therapy in the era of tyrosine kinase inhibitors.

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