614.ACUTE LYMPHOBLASTIC LEUKEMIAS: THERAPIES, EXCLUDING TRANSPLANTATION AND CELLULAR IMMUNOTHERAPIES | NOVEMBER 5, 2021

First Results of the Risk-Adapted, MRD-Stratified GMALL Trial 08/2013 in 705 Adults with Newly Diagnosed Acute Lymphoblastic Leukemia/Lymphoma (ALL/LBL)

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Abstract

In the past decade outcome of adult ALL was improved significantly using pediatric-based chemotherapy in combination with risk-adapted stem cell transplantation (SCT) and targeted therapies. The GMALL Trial 08/2013 (NCT02881086) for patients (pts) aged 18-55 years (yrs) with newly diagnosed ALL/LBL has a BFM-based 2-phase induction, up to 8 cycles of PEG-asparaginase (ASP) with up to 7 cycles of HDMTX, HDAC, a reinduction phase and conventional maintenance up to 2.5 yrs. Two cycles Nelarabine are implemented for standard risk (SR) T-ALL. Pts with B-precursor-ALL (B-ALL) receive Rituximab independent of CD20 expression (Ph+ only if CD20+). Ph+ ALL pts receive Imatinib and a dose reduced induction (Vincristine, Dexamethasone, ASP). ASP is scheduled in induction 1 (IP1) (d 20) and 2 (d 34 for Ph+ and d 44 for Ph-) and dose is adapted to risk factors for hepatotoxicity. Pts with BMI>30 and/or liver steatosis receive 500 U/m ^{2}, whereas 2000 U/m ^{2} is the standard dose. It is recommended to withhold the 2 nd dose of ASP in case of clinically relevant ASP-associated toxicities. Pts with high-risk (HR) features (WBC > 30,000/µl in B-ALL, pro B-ALL-, KMT2A rearrangement, early/mature T-ALL) or Ph+ ALL are considered for SCT in CR1 after 1 st consolidation (C1). Pts with MolFail (table 1) after C1 are candidates for targeted therapy (Blinatumomab, Nelarabin) followed by SCT. Randomization (R) 1 evaluates CNS irradiation versus ith. prophylaxis in B- ALL/LBL. R II compares SCT versus SR therapy in HR pts with MolCR after induction. Both randomizations are blinded and not available for analysis. The trial is ongoing and scheduled to recruit 950 pts.

Between 8/2017-4/2021 770 pts from 78 centers were included and 705 were evaluable. The median age was 35 (18-55) yrs, 638 had ALL (B,Ph-: 55%, Ph+: 20%, T: 25%,) and 67 pts LBL (B:12%; T:88%). For ALL the hematologic (Hem) CR rate after C1 was 93% and the MolCR Rate 61% (75% mol. response) (table 1). Hem/CR rate was 72% in LBL with 21% PR. PET CT was negative in half of the LBL PR cases. The lowest HemCR rate was observed in early T-ALL (83%) together with a MolCR rate of 45% (71% mol. response).

In Ph- pts 2000 U/m ^{2} as first dose ASP was administered in 66%, 500 U/m ^{2} in 24%, no ASP in 1% and other doses in 9%. In pts with Ph+ ALL the respective numbers were 61%, 21%, 6% and 13%. For the 2nd dose the numbers were 43%, 21%,13% and 22% for Ph- and 41%, 24%, 13% and 22% for Ph+ pts. Bilirubine increases grade III/IV were observed in Ph- ALL in 18% of the cases treated with 500 U/m ^{2} vs 24% for 2000 U/m ^{2}. In Ph+ ALL the respective numbers were 5% vs 3%. GOT/GPT grade III/IV increases were observed 29% of Ph- ALL pts treated with 500 U/m ^{2} vs 25% of those with 2000 U/m ^{2}. The respective numbers for Ph+ ALL were 24% and 40%.

At a median follow-up of 23 mo, the overall survival (OS) for all pts (N=705) was 88% and 76% at 1 and 3 yrs resp (subgroups see table 1). OS was correlated to age, 87%, 74%, 69% and 73% at 3 yrs for pts aged 18-25, 26-35, 36-45 and 46-55 yrs resp. SR T-ALL reached an OS of 86% at 3 yrs with a conventional and nelarabine based consolidation. 79% of pts with an indication for SCT were transplanted (64 sibling, 174 MUD). The OS of SCT pts after SCT was 75% at 3 yrs.

63 pts with MolFail became candidates for a targeted therapy, which was realized in 89% of the cases. The molecular response was evaluable in 51 pts and reached 55% (N=40) and 18% (N=11) after one cycle of Blinatumomab or Nelarabin resp. Pts with MolFail (N=63) achieved an OS of 84% at 1y and 72% at 3 years resp (71% for Ph- and 76% for Ph+).

This large, ongoing prospective multicenter trial provides promising preliminary results. This applies also to those aged 45-55 yrs underlining that adult pts beyond the variable AYA definitions can benefit from pediatric-based therapy. Intensive and individualized ASP therapy was feasible. Whereas high HemCR rates were observed in nearly all subgroups, MolCR rates ranged from 41-74% and a relevant proportion remained MRD low positive underlining the need for detailed MRD classification. MRD-based targeted treatment was realized in a high proportion of pts. Responses to Blinatumomab in MolFail were lower compared to previous trials. Responses to Nelarabine in MolFail T-ALL pts were only 18%. OS of MolFail pts however was promising with the combination of targeted therapy and SCT. Thus, SCT is still a key component, contributing to improved outcomes although the overall proportion of SCT was lower than in previous GMALL trials.

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Figure 1

Table 1: Total Outcome and Subgroups for ALL

	Total	B-ALL/Ph-	B-ALL/Ph+	T-ALL	B/T SR[4]	B/T HR[4]
Evaluable for Hematologic Response (N) [1]	599	326	122	151	261	217
Hematologic CR	93%	94%	95%	89%	96%	88%
Early death	4%	5%	3%	5%	3%	7%
Failure/PR[2]	3%	1%	2%	7%	1%	4%
Evaluable for Molecular Response (N) [3]	542	306	116	120	248	178
Molecular CR	61%	65%	41%	67%	74%	54%
Molecular Failure	19%	18%	28%	11%	10%	25%
Molecular Low positive	14%	11%	17%	20%	12%	16%
Molecular not evaluable	6%	6%	13%	3%	4%	5%
N Overall Survival	638	350	128	160	276	234
Overall Survival 1y	88%	88%	85%	88%	94%	81%
Overall Survival 3y	76%	77%	74%	74%	85%	65%

[1]Evaluable pts with response evaluation after consolidation I; evaluable is defined as response evaluation after induction II or early death.
[2] including residual extramedullary disease
[3] Pts with evaluable MRD test after consolidation I; calculated in relation to CR pts; Molecular CR (MolCR): MRD negative with sensitivity of at least 0.01%; Molecular Failure (MolFail): MRD positive above 0.01%; Low positive: MRD below 0.01%; Molecular not evaluable: Negative with sensitivity less than 0.01% or positive but not quantifiable. Molecular response: MolCR or low positive
[4] Risk groups defined by pre-treatment characteristics, excluding MRD response, SR/HR= Ph/BCR-ABL-negative

Figure 1: Overall Survival for ALL and LBL - GMALL Study 08 (N=705)

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OffLabel Disclosure:
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