Clinical and germline risk factors for multiple treatment-related toxicities in pediatric acute lymphoblastic leukemia

Treatment-related toxicity (TRT) causes morbidity in acute lymphoblastic leukemia (ALL). A minority of patients suffer multiple TRT (mTRT). We characterized the incidence and risk factors for ALL mTRT in 1,240 patients between 1998-2013. The mTRT incidence was 10.7% with the most common mTRT combination being bone and neurotoxicity in 40%. There was no difference in leukemia-free survival (LFS), event-free (EFS), or overall survival (OS) following mTRT. Five clinical/laboratory factors (older age (≥10 years), female sex, high-risk leukemia, low albumin and elevated γ glutamyl transferase (GGT) during induction therapy) and one germline *MUC16* single nucleotide polymorphism (SNP) (rs78342591; P=2.24x10^{-8}) were associated with mTRT risk.

The burden of TRT can be devastating for patients and clinicians. The occurrence of mTRT has not been well studied but can impair chemotherapy delivery and may be associated with an increased relapse risk. It is unknown what predisposes individuals to mTRT. Possible susceptibilities include organ dysfunction, delayed drug excretion, drug-drug interactions, genetic predisposition, constitutional syndromes and physiological factors such as age or sex. mTRT is likely exacerbated by intensive ALL therapy. Genome-wide association studies (GWAS) have identified germline risk factors associated with TRT but have focused on individual TRT. In ERASE (Evaluation of Risk of ALL Treatment-related Side-Effects), we undertook a retrospective study of Australian pediatric ALL patients diagnosed between 1998-2013, including annotation of treatment, survival, TRT and a germline GWAS (*Online Supplementary Tables S1, S2*). This analysis focused on mTRT, their impact on survival, and identifying clinical and germline factors associated with mTRT risk. The ERASE study including the GWAS have been published.[1,2] mTRT was defined as experiencing ≥2 TRT and controls as 0 or 1 documented TRT and who were followed for ≥18 months from diagnosis. The mTRT phenotype included bone (osteonecrosis or fractures), central or peripheral neurotoxicity, symptomatic venous thromboembolism (VTE) and insulin requirement. The mTRT GWAS cohort included 707 individuals, with five excluded due to lack of mTRT information, leaving 64 mTRT cases and 638 controls. The number of directly genotyped and imputed SNP with a minor allele frequency (MAF) >0.05% was 10999498 and with a MAF>2% was 7780980.

The median age was 59 months (range, 9-218 months) with a median follow-up of 78 months (range, 3-186 months). The 5-year OS, EFS and LFS of the ERASE cohort was 92±0.8%, 83.8±1.1% and 85.6 ±1.1%. mTRT occurred in 133 of 1,240 (10.7%) with the majority being CTCAE grade ≥2 severity (123/1240, 9.9%). The incidence of individual TRT included neurotoxicity in 7.6% (94/1240), insulin requirement in 6.9% (85/1,240), bone toxicity in 6.0% (75/1,240) and VTE in 5.5% (68/1,240) (Table 1). Bone and neurotoxicity was the most frequent combined mTRT. There was no difference in LFS, EFS or OS in mTRT patients (N=133), compared to controls (N=1,107). The 5-year LFS was 88,8±2,9% (mTRT), *versus* 85,9±1.1% (control, P=0.276), 5-year EFS was 84.9±3.3% (mTRT) *versus* 84.2±1.2% (control, P=0,595) and 5-year OS was 89.1±2.9% (mTRT) *versus* 92.5±0.9% (no control, P=0.138) (*Online Supplementary Figure S1*).

Risk factors for mTRT were assessed using univariable and multivariable logistic regression analyses. Twenty-six of 38 factors were significant in univariable analysis. Univariable associations with the mTRT phenotype included factors present at diagnosis and treatment during the early dose-intensive phases of chemotherapy (Table 2). Eighteen variables were carried into multivariable regression and five were independently associated with mTRT: age ≥10 years, female sex, high-risk ALL treatment, low serum albumin (<20 g/L during induction/consolidation),

Table 1. Incidence of individual toxicities and combinations of multiple toxicities observed in the ERASE cohort (N=133).

Toxicity	N affected	% of mTRT cohort
Incidence of individual treatment related toxicity		
Neuropathy	94	70.7
Insulin requirement	85	63.9
Bone toxicity	75	56.4
Venous thromboembolism	68	51.1
Combinations of multiple treatment related toxicities		
Bone + neurotoxicity	53	39.8
Neurotoxicity + insulin requirement	22	16.5
VTE + neurotoxicity	13	9.8
Bone + neurotoxicity + insulin requirement	13	9.8
VTE + bone toxicity	12	9.0
Bone toxicity + insulin requirement	11	8.3
VTE + bone + neurotoxicity	5	3.8
VTE + insulin requirement	1	0.8
VTE + bone toxicity + insulin requirement	1	0.8
VTE + neurotoxicity + insulin requirement	1	0.8
VTE + bone + neurotoxicity + insulin requirement	1	0.8

mTRT: multiple treatment-related toxicities; VTE: venous thromboembolism.

elevated GGT (>5x upper limit of normal during induction/consolidation) (Table 2).

The GWAS identified 28 candidate SNP (P<5x10^{-6}), mapping to eight genes including *MUC16, SMYD3, FAM155A, UQCRFS1, FMO1, PIGF, LOC105371611, LOC105372352* (Table 3). Most candidate SNP (20/28) were associated with a reduced odds ratio of mTRT. Three SNP, associated with increased mTRT risk fell within *MUC16* introns (rs78342591, rs62118276

Table 2. Univariable and multivariable analysis of risk factors associated with multiple treatment-related toxicities.

Variable	Univariable			Multivariable		
	P	OR	95% CI	*P*	OR	95% CI
Sex: female	0.345	-	-	0.029	1.80	1.06-3.04
Treatment platform: BFM* *vs.* COG	<0.001	2.12	1.4-3.19	-	-	-
T-immunophenotype	0.012	1.83	1.14-2.95	-	-	-
Age ≥10 years	<0.001	6.84	4.68-10.0	<0.001	3.91	2.26-6.73
WCC at diagnosis	0.026	1.002	1.000-1.003	-	-	-
CNS3 at diagnosis	0.005	3.29	1.43-7.59	-	-	-
High-risk group: HR/VHR[a]	<0.001	4.36	3.0-6.34	<0.001	2.87	1.59-5.16
Peak urate[b]	0.002	3.42	1.59-7.35	-	-	-
Tumour lysis[b]	<0.001	2.86	1.74-4.70	-	-	-
Bilirubin at diagnosis	<0.001	1.04	1.02-1.06	-	-	-
GGT at diagnosis	<0.001	1.01	1.005-1.013	-	-	-
Abnormal peak creatinine >2x baseline[c,d]	0.005	2.70	1.34-5.45	-	-	-
Peak bilirubin[d]	<0.001	1.01	1.01-1.02	-	-	-
Peak bilirubin >3x ULN[d]	<0.001	5.21	2.83-9.58	-	-	-
Lowest albumin[d]	<0.001	0.9	0·87-0·93	-	-	-
Lowest serum albumin <20 g/L[d]	<0.001	2.66	1·71-4·13	0.026	1.95	1.08-3.52
Peak GGT[d]	<0.001	1.002	1.001-1.002	-	-	-
Peak GGT >5x ULN[d]	<0.001	4.98	3.07-8.09	<0.001	3.76	2.14-6.62
Peak ALT[d]	0.006	1.001	1.000-1.001	-	-	-
Peak ALT >5x ULN[d]	<0.001	2.04	1.37-3.03	-	-	-
Confirmed infection[d]	0.002	1.88	1.26-2.81	-	-	-
Positive blood culture[d]	0.024	1.56	1.06-2.29	-	-	-
Weight at diagnosis: Z score, CDC	0.01	1.24	1.05-1.46	-	-	-
Weight at diagnosis >95th centile	0.009	1.86	1·16-2·97	-	-	-
BMI at diagnosis >95th centile	0.001	2.34	1.41-3.87	-	-	-
BMI at diagnosis: Z score, CDC	0.003	1.26	1.08-1.47	-	-	-
BMI at end of consolidation: Z score, CDC	0.038	0.85	0.73-0.99	-	-	-

Thirty-eight variables were assessed in univariable analysis, relating to baseline diagnostic factors (N=6), treatment response (N=1), biochemical parameters at baseline and during induction/consolidation (N=19), infection during induction/consolidation (N=3), and anthropometric values at diagnosis or during induction/consolidation (weight, body mass index "BMI") (N=9). Univariable and multivariable modeling was conducted with a Bonferroni correction for multiple comparisons so that a P<0.0013 (0.05/38) was considered significant. For risk modeling, individuals with incomplete data were excluded. Categorical variables were assessed using Pearson χ^2 analysis. Variables with a significance level P<0.20 were assessed in multivariable modeling by backward elimination. The multivariable analyses were adjusted for age and sex. The least significant factor was removed at each stage, until all factors in the model were independently significant (2-tailed P<0.05) and the model was significant (overall model P<0.05, Hosmer-Lemeshow value P>0.05). *BFM reference cohort. [a]High-risk group comprised high risk and very high-risk patients which were compared to the non-high-risk group comprising of standard-, medium-, average- or low-risk patients, as defined by their respective protocols. [b]Value during induction. [c]Peak creatinine value as compared to baseline creatinine at diagnosis, or 2x the upper limit of normal if the presenting creatinine at diagnosis was above the normal range. [d]Values during induction/consolidation. OR: odds ratio; CI: confidence interval; COG: Children's Oncology Group; BFM: Berlin-Frankfurt-Munster; WCC: white cell count; CNS3: central nervous system involvement; HR: high-risk; VHR: very high-risk; GGT: γ-glutamyl transferase; ALT: alanine aminotransferase; BMI: body mass index; CDC: Centers for Disease Surveillance and Control Growth Charts; ULN: upper limit of normal.

and rs2341321). One reaching genome-wide significance (rs78342591; P=2.24x10^{-8}) (Table 3). Four SNP in *SMYD3* were associated with increased mTRT risk (Table 3). The *MUC16* rs78342591 risk allele (C) was examined with 640 individuals with informative data. Individuals with at least one rs78342591 risk allele C accounted for 17 of 64 (26.6%) of the GWAS cohort of children affected by mTRT. Four individuals were homozygous for the risk allele, with 50% (2/4) experiencing mTRT. Seventy-three individuals were heterozygous for the risk allele (CT), with 20.5% (15/73) experiencing mTRT. In contrast, 563 patients were homozygous for the non-risk allele (TT) with 8.3% (47/563) ex-

Table 3. Top single nucleotide polymorphisms associated with multiple treatment-related toxicities phenotype in the ERASE cohort.

Chromosome	Position	SNP	Non effect allele	Effect allele	MAF	*P*	OR	OR 95% CI (lower)	OR 95% CI (upper)	Gene[a]	Location
1	2774381	rs12567869	G	A	0.20	1.34x10^{-6}	0.14	0.05	0.36	-	-
1	171204809	rs12405613	A	G	0.38	3.21x10^{-6}	0.36	0.23	0.58	*LOC105371611*	intronic
1	171207408	rs7513485	T	C	0.38	3.40x10^{-6}	0.36	0.23	0.58	*LOC105371611*	intronic
1	171208014	rs2421710	C	T	0.38	3.45x10^{-6}	0.36	0.23	0.58	*LOC105371611*	intronic
1	171208094	rs2421711	C	T	0.38	3.46x10^{-6}	0.36	0.23	0.58	*LOC105371611*	intronic
1	171209900	rs35152982	A	C	0.38	3.72x10^{-6}	0.36	0.23	0.58	*LOC105371611*	intronic
1	171216717	rs7520777	C	G	0.40	4.51x10^{-6}	0.37	0.23	0.58	*FMO1*	intronic
1	246355668	rs10924537	T	C	0.29	1.82x10^{-6}	3.50	1.96	6.23	*SMYD3*	intronic
1	246355795	rs12407828	C	T	0.29	3.05x10^{-6}	3.39	1.91	6.00	*SMYD3*	intronic
1	246356128	rs2333991	A	G	0.21	4.17x10^{-6}	4.37	2.10	9.10	*SMYD3*	intronic
1	246356200	rs2333992	G	T	0.29	3.95x10^{-6}	3.39	1.90	6.04	*SMYD3*	intronic
2	46807991	rs2276554	T	C	0.13	4.60x10^{-6}	0.13	0.04	0.42	*PIGF*	intronic
4	25062315	rs11723040	T	A	0.27	4.29x10^{-6}	0.28	0.15	0.51	-	-
5	60919428	rs56300029	C	T	0.28	4.45x10^{-6}	2.87	1.83	4.50	-	-
7	80894904	rs117511099	G	A	0.02	1.11x10^{-6}	4.75x10^{-30}	8.43x10^{-57}	2.67x10^{-3}	-	-
7	80905279	rs117698731	C	T	0.02	1.52x10^{-6}	2.62x10^{-30}	1.89x10^{-57}	3.63x10^{-3}	-	-
13	108289235	rs67586898	ATATAT	A	0.36	3.53x10^{-6}	0.33	0.20	0.55	*FAM155A*	intronic
14	53685357	rs61986921	C	A	0.23	4.09x10^{-6}	0.28	0.15	0.52	-	-
14	53769396	rs4573847	A	G	0.16	5.65x10^{-7}	0.14	0.06	0.38	-	-
16	13815870	rs179606	G	A	0.35	1.96x10^{-6}	0.33	0.20	0.54	-	-
16	13818107	rs179609	G	T	0.35	1.91x10^{-6}	0.33	0.20	0.54	-	-
19	9020185	rs78342591	T	C	0.08	2.24x10^{-8}	5.89	3.23	10.74	*MUC16*	intronic
19	9027313	rs62118276	A	G	0.06	6.09x10^{-8}	6.11	3.25	11.48	*MUC16*	intronic
19	9029511	rs2341321	A	G	0.06	6.63x10^{-8}	5.88	3.16	10.94	*MUC16*	intronic
19	29693669	rs142959560	GA	G	0.15	4.46x10^{-6}	0.15	0.05	0.42	-	-
19	29700027	rs71960487	GAC	G	0.15	4.46x10^{-6}	0.15	0.05	0.42	*UQCRFS1*	intronic
19	29712441	rs35484580	C	T	0.15	4.53x10^{-6}	0.15	0.05	0.42	*LOC105372352*	non-coding transcript variant
19	29744818	rs201622525	CTCT	C	0.12	1.61x10^{-6}	0.07	0.02	0.31	-	-

There was 1 single nucleotide polymorphism (SNP) at genome-wide significance (<5x10^{-8}) located within *MUC16*· In total, there were 28 SNP below a *P* significance threshold <5x10^{-6}. The table is ordered according to chromosome and sequential position (assembly GRCh37/hg19) [a]The annotated gene was determined by cross referencing Refseq, ensembl 74 and UCSC database information (hg19, 2015 update), accessed through SNPnexus (2012 update). The SNPnexus database (http://www·snp-nexus·org) is kept synchronized with the UCSC human genome annotation database (http://genome·ucsc·edu). Where there was discrepancy or the gene was uncertain, a search was performed manually using NCBI dbSNP build 149·SNP with a minor allele frequency (MAF) <2% were excluded. Functional annotation was determined using NCBI dbSNP build 149. SNP with an odds ratio (OR) of 0.00 were excluded as were SNP with an OR 95% confidence interval (CI) that included 1. The 95% CI for the OR is the range of values between "OR 95% CI (lower)" through to "OR 95% CI (upper)"· *P* value thresholds are: <1x10^{-5} is suggestive of an association and <5x10^{-8} is the threshold for genome-wide significance.

periencing mTRT. Splicing analysis using Introme predicted the introduction of a polypyrimidine tract-binding protein (PTB) binding site from the rs62118276 SNP.

The ERASE study collected mTRT data across two major ALL treatment platforms, creating an opportunity to undertake the first study of clinical and genetic risk factors for mTRT in pediatric ALL. At least 10% of ALL patients experienced mTRT, but mTRT did not impact on ALL survival, a finding, whilst counterintuitive, aligns with the observation of Yeoh and co-workers who did not observe an increase in relapse risk in ALL patients experiencing treatment delay during the intensive phase of ALL therapy.[3]

The strongest independent risk factor for mTRT was older age (≥10 years), which is a risk factor for VTE, osteonecrosis, fractures, methotrexate neurotoxicity, vincristine-induced neuropathy and insulin requirement.[2,4-8] The association between high-risk ALL and mTRT is likely correlated with dose intensity and/or cumulative chemotherapy dosing. Female sex was an independent significant risk factor for mTRT, but female sex has not consistently been identified as a TRT risk factor across different studies.[4,5,9] There was an association between hypoalbuminemia and mTRT, independent of risk group and age, pointing to a link between therapy intensity and serum albumin, as low serum albumin often occurs during severe illness. Hypoalbuminemia is a likely consequence of treatment with asparaginase, malnourishment and/or underlying disease severity. A tentative association between albumin and osteonecrosis has been reported.[5] Hypoalbuminemia has been associated with delayed methotrexate clearance.[10] Treatment-related GGT elevation was associated with mTRT. Elevated GGT has been identified as a risk factor for symptomatic VTE[11] as well as decreased survival in multiple cancers including breast, ovarian, endometrial and melanoma treated with checkpoint inhibitors.

The mTRT GWAS identified 28 SNP mapping to eight genes with *P* values $<5x10^{-6}$. Six loci were associated with a reduced mTRT risk and two with increased mTRT risk. One SNP, rs78342591, reached genome-wide significance. *MUC16* encodes a large transmembrane, mucinous, glycoprotein normally found on bronchial, endometrial, ovarian and corneal epithelia.[12] Multiple *MUC16* functions have been identified including as an anti-microbial barrier, providing immune-protection from the innate immune system, enhancing metastasis and cancer cell proliferation and when knocked down promoting apoptosis and cell cycle arrest.[12] All *MUC16* SNP identified in the GWAS are intronic, raising the hypothesis that the SNP might influence *MUC16* splicing. Although Introme analysis did not link these SNP with a high probability splicing change,[13] the rs62118276 SNP is predicted to introduce a polypyrimidine tract-binding protein (PTB) binding site. PTB regulates alternative splicing by exon inclusion/exclusion. Within the Expression Atlas, *MUC16* is expressed within the liver and kidney but not within bone, postnatal brain, nerve cells, vascular endothelium, or hematopoietic cells. The role of *MUC16* in mTRT remains to be clarified. We hypothesize that dysregulated hepatic and renal *MUC16* expression following cytotoxic chemotherapy exposure results in dysregulated local cytokine production and inflammation increasing the risk of treatment-related toxicity.

This study has several limitations arising from the retrospective design and findings will require validation. Following the ERASE study, we are collecting data on two additional Australian ALL cohorts, one retrospective and one prospective, to replicate these findings. Data were collected by retrospective chart review, a resource- and time-intensive methodology which limits data collection to information easily and reproducibly documented in the medical record. With electronic medical records, automatically extracting adverse events in ALL patients has been demonstrated by the Children's Oncology Group,[14] suggesting that automated collection of relevant TRT in the future is feasible. There are substantial differences between the risk stratification and treatment algorithms used in different ALL treatment platforms. The data analysis was as recorded by the treating clinician and center based on the local risk stratification and treatment allocation without adjusting for differences between protocols (*Online Supplementary Table S2*). Toxicities analyzed in ERASE reflect those occurring at a reasonable frequency (≈5%) and consistently captured. Replication followed by functional validation of the *MUC16* SNP on chemo-toxicity may provide clearer evidence regarding the mechanism of ALL mTRT.

Although blinatumomab is effective and well tolerated in patients with B-ALL,[15] most ALL treatment platforms are adding blinatumomab to existing chemotherapy rather than substituting chemotherapy with blinatumomab suggesting that TRT from conventional chemotherapy will continue to be a problem for the foreseeable future. Functional validation and biomarker studies may provide tools for early diagnosis and intervention in children who are at high-risk of mTRT. This study provides clinically relevant information that can be used for counseling ALL patients and their families, regarding factors that may lead to increased risk of mTRT. Adolescent girls diagnosed with high-risk ALL have the highest chance of mTRT. Through improved understanding of clinical and germline factors associated with mTRT risk, it may be possible to devise strategies to reduce mTRT.

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Contributions

Study conceptualization and design, literature search, funding acquisition, project administration, data collection, data analysis, data interpretation, writing, writing original draft, writing review and editing by GM, TNT and MKM. Data collection, data analysis, writing reviewing and editing by MCJQ, SMacG, CM and PB. Resources, investigation, writing - review and editing by CG, JG, RS, DB, FA, RC, DC, RSK and LDP.

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Data-sharing statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

References

1. Mateos MK, Tulstrup M, Quinn MC, et al. Genome-wide association meta-analysis of single-nucleotide polymorphisms and symptomatic venous thromboembolism during therapy for acute lymphoblastic leukemia and lymphoma in Caucasian children. Cancers (Basel). 2020;12(5):1285.
2. Mateos MK, Marshall GM, Barbaro PM, et al. Methotrexate-related central neurotoxicity: clinical characteristics, risk factors and genome-wide association study in children treated for acute lymphoblastic leukemia. Haematologica. 2022;107(3):635-643.
3. Yeoh A, Collins A, Fox K, et al. Treatment delay and the risk of relapse in pediatric acute lymphoblastic leukemia. Pediatr Hematol Oncol. 2017;34(1):38-42.
4. te Winkel ML, Pieters R, Hop WC, et al. Prospective study on incidence, risk factors, and long-term outcome of osteonecrosis in pediatric acute lymphoblastic leukemia. J Clin Oncol. 2011;29(31):4143-4150.
5. Kawedia JD, Kaste SC, Pei D, et al. Pharmacokinetic, pharmacodynamic, and pharmacogenetic determinants of osteonecrosis in children with acute lymphoblastic leukemia.

Blood. 2011;117(8):2340-2347; quiz 2556.
6. Bhojwani D, Sabin ND, Pei D, et al. Methotrexate-induced neurotoxicity and leukoencephalopathy in childhood acute lymphoblastic leukemia. J Clin Oncol. 2014;32(9):949-959.
7. Grace RF, Dahlberg SE, Neuberg D, et al. The frequency and management of asparaginase-related thrombosis in paediatric and adult patients with acute lymphoblastic leukaemia treated on Dana-Farber Cancer Institute consortium protocols. Br J Haematol. 2011;152(4):452-459.
8. Tuckuviene R, Ranta S, Albertsen BK, et al. Prospective study of thromboembolism in 1038 children with acute lymphoblastic leukemia: a Nordic Society of Pediatric Hematology and Oncology (NOPHO) study. J Thromb Haemost. 2016;14(3):485-494.
9. Diouf B, Crews KR, Lew G, et al. Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. JAMA. 2015;313(8):815-823.
10. Reiss SN, Buie LW, Adel N, Goldman DA, Devlin SM, Douer D. Hypoalbuminemia is significantly associated with increased clearance time of high dose methotrexate in patients being treated for lymphoma or leukemia. Ann Hematol. 2016;95(12):2009-2015.
11. Mateos MK, Trahair TN, Mayoh C, et al. Risk factors for symptomatic venous thromboembolism during therapy for childhood acute lymphoblastic leukemia. Thromb Res. 2019;178:132-138.
12. Zhang M, Cheng S, Jin Y, Zhao Y, Wang Y. Roles of CA125 in diagnosis, prediction, and oncogenesis of ovarian cancer. Biochim Biophys Acta Rev Cancer. 2021;1875(2):188503.
13. Sullivan PJ, Gayevskiy V, Davis RL, et al. Introme accurately predicts the impact of coding and noncoding variants on gene splicing, with clinical applications. Genome Biol. 2023;24(1):118.
14. Miller TP, Getz KD, Li Y, et al. Rates of laboratory adverse events by course in paediatric leukaemia ascertained with automated electronic health record extraction: a retrospective cohort study from the Children's Oncology Group. Lancet Haematol. 2022;9(9):e678-e688.
15. Hodder A, Mishra AK, Enshaei A, et al. Blinatumomab for first-line treatment of children and young persons with B-ALL. J Clin Oncol. 2024;42(8):907-914.1.