Editorial

Editorial on the role of "Genetic mediators of neurocognitive outcome in survivors of childhood acute lymphoblastic leukemia"

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Abstract: With current chemotherapy regimen favorable event free survival rates can be achieved for children and adolescents with acute lymphoblastic leukemia (ALL). Besides others, neurocognitive late effects come more and more into the focus of attention. Especially, as first reports indicate that the omission of cranial irradiation (CRT) did not solve the problem of neurocognitive deficits. The report by Krull and colleagues analyzed the association of neurocognitive outcome and a large set of potentially predisspoing polymorphisms. The authors identified significant associations between specific polymorphisms and neurocognitive outcome. However, the consequences of such testing need to be discussed carefully.

Keywords: Acute lymphoblastic leukemia (ALL); neurocognitive outcome; predisposing polymorphisms

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Survival and event free survival of children and adolescents with acute lymphoblastic leukemia (ALL) increased dramatically during the last decades and reached 85-95%. This benefit in survival was mainly achieved by the use of modern poly-chemotherapy regimen. One of the prices of this progress in survival is a relevant rate of late complications after the end of treatment. Most relevant or most common late effects are second cancers, osteonecrosis, endocrine dysfunctions, and cardial abnormalities (1-6). Recent protocols reduced or even omitted cranial irradiation (CRT) which was accused as one of the most relevant treatment elements associated with late complications, such as second cancers (1,5), short stature (7), obesity (8), pubertal abnormalities and neurocognitive late effects (9-11). The latter late effect comes more and more into focus of attention. It is expected that the neurocognitive outcome of ALL survivors will improve after the reduction or omission of CRT. But recent data obtained in patient cohorts treated without CRT showed neurocognitive deficits in ALL survivors compared to the expected rate based on the normative sample (12). How to go on from that point? Given the observation that eradication of CRT does not solve the problem of attention deficits and cognitive late effects after ALL treatment, this remains a relevant question.

Krull and colleagues recently reported a study aiming at the identification of single nucleotide polymorphisms (SNPs) associated with neurocognitive outcome of ALL patients (13). The 42 investigated SNPs were related to antifolate and glucocorticoid chemotherapy and oxidative stress on the one hand and SNPs, reported to be associated with attention problems in cohorts of individuals without cancer on the other hand. The study was performed at St. Jude children's hospital. There, a total of 408 pediatric patients were enrolled in the ALL trial Total XV (14). Of these, 345 patients participated in a neurocognitive assessment at least one during the course of therapy and 243 had an assessment two years after completion of consolidation therapy. The testing included common tests for general intelligence, processing speed, working memory, sustained attention and variability of reaction time added by parent-reported attention problems. The evaluable 243 patients represented approximately 60% of all patients enrolled in St. Jude. Given the characteristics of age, sex, race, and

treatment arm, the available cohort was representative for the whole cohort. The analyzed SNPs were chosen according to their relevance for the folate pathway, steroid receptors, general drug metabolism, oxidative stress or for attention deficits in the general population.

As a first relevant result Krull and colleagues showed that the ALL survivors two years after completion of consolidation showed attention deficits, both by neurocognitive testing and by parent's reports. Similar results have been reported earlier by the same group (12). The authors hypothesize that the attention problems are related to multiple factors, including treatment intensity as well as SNPs in genes related to antifolate chemotherapy, oxidative stress, and CNS integrity. To analyze the impact of specific SNPs, the respective genotypes were correlated with the results of neurocognitive testing. These analyses revealed several statistically significant associations. For example, SNPs in *Methionine Synthase (MS)* were associated with decreased attentiveness and slowed response speed. MS is relevant for the metabolism of homocysteine to methionine. It was discussed by the authors that in patients treated with methotrexate (MTX), variants of MS might be associated with an increased risk to hyperhomocysteinemia which again increases the risk for vascular abnormalities including vascular abnormalities the CNS. In the current study however, the authors did not provide data on homocytein levels or other data directly linking MS variants to impaired neurocognitive outcome after MTX treatment. Such approaches might be feasible. For instance Radtke and colleagues showed in another study that SNPs in candidate genes relevant for the MTX and folate pathway were associated with MTX pharmakokinetics, toxicity and outcome of 499 children treated according to the trial ALL-BFM 2000 (15). SNPs in the genes MTHFR, SLC19A1 and TYMS were candidate genes included in both analyses, the one by Krull *et al.* and the one by Radtke *et al.* Therefore one the next steps evaluating of the impact of specific SNPs for neurocognitive late effects of ALL treatment might be the conduction of studies analyzing the mechanisms of the genetic variants in their role for the cognitive outcome.

But already today it must be discussed how to translate the results reported by Krull *et al.* into future treatment strategies? In general, two options might be considered: one possible way would be to screen all newly diagnosed pediatric ALL patients for SNPs associated with the metabolism of specific drugs. And given the genotype of the patient, the dosage of the specific drugs might be modified accordingly. In most cases that would mean a reduction of dosages aiming to reduce neurocognitive late effects. But what about significant associations of neurocognitive outcome with SNPs that can not be related to a specific drug. E.g., the association of attention problems with MAOA and APOE-4 variants which are known to be associated with attention deficits in non-cancer patients? And how to proceed in cases with favorable and unfavorable SNPs in parallel? Which cohort of patients would be available for such an approach to reduce treatment in order to minimize neurocognitive late effects? Will such a dose reduction increase the risk of relapse for those patients? To answer these and multiple other questions, several clinical trials will be necessary, especially as the impact of SNPs might not be the same for different treatment approaches and results can not be transferred from one trial to another.

Krull and colleagues propose a second option to transfer their results into clinics by concluding that preventive approaches of early cognitive intervention to enhance attention networks (16) are to be discussed to prevent neurocognitive late effects in ALL survivors.

Given the results reported and the complexity of the problem one might even go one step further and ask whether such preventive approaches should be made available for all pediatric ALL patients, irrespective of genetic predispositions for neurocognitive late effects?

No doubt, the analyses of SNPs and their predisposing role for neurocognitive late effects clearly promote the efforts to prevent such complications in the future. And these studies are highly relevant to understand the mechanisms of these late effects. But in parallel with such molecular studies, systematic efforts to prevent neurocognitive late effects in patients treated today need to be supported.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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