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Kathleen E A Felton, University of Alberta
Christopher Porter, Emory University
Jun J Yang, St. Jude Children's Research Hospital

Journal Title: Expert Review of Precision Medicine and Drug Development

Volume: Volume 3, Number 6

Publisher: Taylor & Francis | 2018-11-02, Pages 339-341

Type of Work: Article | Post-print: After Peer Review

Publisher DOI: 10.1080/23808993.2018.1517026

Permanent URL: https://pid.emory.edu/ark:/25593/vh5vv

Final published version: http://dx.doi.org/10.1080/23808993.2018.1517026

Accessed November 5, 2022 6:25 PM EDT
The genetic risk of second cancers: should the therapy for acute lymphoblastic leukemia be individualized according to germline genetic makeup?

Kathleen E.A. Felton¹, Christopher C. Porter²,* Jun J. Yang³,*

¹Department of Pediatrics, University of Alberta, Edmonton, AB, Canada
²Aflac Cancer and Blood Disorders Center, Children’s Healthcare of Atlanta and Department of Pediatrics, Emory University School of Medicine, Atlanta, GA, USA
³Departments of Pharmaceutical Sciences and Oncology, St. Jude Children’s Research Hospital, Memphis, TN, USA

Keywords
acute lymphoblastic leukemia; germline genetics; second cancers; TP53; treatment individualization

Risk adapted combination chemotherapy has improved the prognosis for pediatric acute lymphoblastic leukemia (ALL) such that more than 85% of children are expected to live disease-free for at least 5 years after diagnosis [1]. Early cooperative group trials identified older age and high white blood cell count as risk factors for adverse outcomes, and subsequent trials demonstrated improvements in survival with more intensive regimens for those with high-risk disease. The incorporation of genetic subtypes (based on gross chromosomal abnormalities and molecular genomic features) and minimal residual disease status (MRD) into risk stratification has further improved cure rates of this cancer in children [2]. More recently, high-throughput genomic profiling of leukemia identified a plethora of novel prognostic factors and raised the prospect of targeted therapy for specific oncogenic mutations. Armed with such information, clinicians are now better positioned than ever to tailor therapy for maximal efficacy while minimizing side effects.

Studies of germline genomics in children with ALL have also provided insight about leukemia pathogenesis and treatment. Germline polymorphisms in TPMT and NUDT15 alter the metabolism of 6-mercaptopurine, a key component of successful ALL therapy [3]. In addition, genome-wide association studies and studies of familial leukemia have uncovered common and rare inherited genetic factors related to ALL susceptibility.
respectively [4]. For example, germline mutations in \textit{ETV6} are associated with a unique syndrome of thrombocytopenia and predisposition to B-ALL [5,6].

Li Fraumeni syndrome (LFS), caused by germline mutation in \textit{TP53}, is another cancer predisposition syndrome associated with leukemia [7]. LFS is the prototypical autosomal dominant cancer predisposition syndrome, in which 50% of affected women and men develop cancer by age 31 and 46, respectively, and almost 100% develop cancer by age 70 for both sexes [8]. While patients may develop a wide range of cancers, certain tumors are particularly associated with LFS. For example, the diagnosis of choroid plexus carcinoma or adrenocortical carcinoma in a child, should warrant consideration of genetic counseling and testing for germline mutation in \textit{TP53}. Similarly, almost 50% of children with low-hypodiploid ALL harbor germline \textit{TP53} mutations [9].

Hypodiploid ALL has long been associated with a poor prognosis in children, prompting some to advocate for hematopoietic stem-cell transplantation in first remission [10]. However, the finding of LFS in a large subset of these patients raises the possibility that germline genetics (in addition to the somatic aneuploidy) contribute to the dismal outcomes in this population [9]. In a recent study by Qian et al of 3801 children with ALL, 26 (0.7%) were found to have pathogenic variants in \textit{TP53} in the germline. Children with pathogenic \textit{TP53} variants were strikingly more likely to have hypodiploid ALL than those without pathogenic variants (65.4% vs 1.2%, p<0.001). Pathogenic variants were also associated with inferior event-free survival and overall survival (hazard ratio, 4.2 and 3.9, p<0.001 and p<0.001, respectively). Germline \textit{TP53} pathogenic variants remained prognostic in multivariable analyses that included ancestry, age and leukocyte count at diagnosis and presence of MRD at end of induction therapy. Even after excluding hypodiploid ALL, germline \textit{TP53} pathogenic variants were still associated with poor event free and overall survival (HR 5.4, P=0.0002 and HR 6.1, P=0.0004, respectively), pointing the robust effects of this germline genetic factor on treatment outcomes. Importantly, pathogenic germline \textit{TP53} variants were linked to a strikingly higher risk of second malignant neoplasm (SMN), as 25.1% of those with pathogenic mutations developed a SMN, compared to only 0.7% in those without. This higher risk remained when examining only those with hypodiploid ALL [11].

SMN is a devastating late effect for survivors of childhood and adult cancers. The cumulative incidence of SMN within 25 years of diagnosis of childhood cancer is 3.6 – 3.9%, or a ~6-fold increased risk of new malignancy compared to the general population [12]. Although radiation is more clearly related to the development of second solid tumors, chemotherapy appears to particularly contribute to therapy-related leukemia. For example, topoisomerase inhibitors (e.g., etoposide) are associated with the development of therapy-related myeloid neoplasia (t-MN) with \textit{KMT2A} (\textit{MLL}) rearrangement. The combination of chemotherapy and radiation therapy increases the risk of SMN. Notably, greater exposure to antimetabolites 6-mercaptopurine (6MP) increases the risk of therapy-related myeloid neoplasm (t-MN) t-MN in children treated for ALL [13]. However, contrary to the prevailing hypothesis that chemotherapy induces widespread DNA damage, including mutation of \textit{TP53}, the genomes of t-MN harbor similar global mutation burden as \textit{de novo} AML [14]. In addition, \textit{TP53} mutations can be found in sub-clonal populations prior to the onset of t-MN,
and it is now believed that chemotherapy effectively selects for mutant hematopoietic stem/progenitor cells with a competitive advantage [15].

The study by Qian et al provides one of the first systematic, large-scale analyses of the contribution of TP53 germline genetics to the development of SMN in children, although smaller studies, including those of adults, have suggested that individuals with second malignancies may have underlying cancer predispositions. Among 37 pediatric cancer survivors in the Childhood Cancer Survivor Study who experienced second cancers without a history of familial cancer predisposition syndrome, 10 (27%) had germline variants in TP53, although none was considered as pathogenic [16]. Studies of adults with t-MN suggest that ~20% harbor mutation in cancer predisposition genes, most involved in DNA damage response [17].

These data, and the increasing use of targeted or genome-wide genetic testing of tumor and germline tissues, raise the question of whether clinicians can further personalize therapy to reduce short- and long-term side effects, based on germline genetics. This is already being done in many settings during ALL therapy, with routine testing of TPMT, (and less commonly NUDT15), and preemptive alteration of 6MP dosing based on the result [4]. However, this is more challenging in the context of cancer predisposition genes. For example, TP53 directly influences the cellular response to DNA damage, which is the ultimate mechanism of action of most chemotherapeutics and radiation and therefore germline TP53 mutation not only contribute to leukemia response but also toxicities such as second cancer. However, the omission of the agents most implicated in the development of t-MN (e.g. topoisomerase inhibitors) might increase the risk of relapse of the original disease. Furthermore, it is possible that SMN may actually represent a second primary malignancy unrelated to therapy, particularly in an individual with a cancer predisposition. Complicating the question is the different molecular consequences and pathogenicity of the wide variety of TP53 mutations, which are not completely elucidated.

Nonetheless, existing and emerging data may help guide the clinician treating a patient with LFS and ALL. First, hypodiploid ALL, irrespective of germline TP53 mutation status, can be cured with intensive chemotherapy without hematopoietic stem cell transplant (HSCT), if early response can be achieved (i.e., <0.01% MRD in the bone marrow mononuclear fraction) at the end of remission induction [10]. Conversely, those with detectable MRD had very poor outcomes, despite intensive chemotherapy. Thus, it seems reasonable to avoid the potential toxicity of myeloablative chemotherapy and total body irradiation for HSCT in a patient with LFS and ALL if there is no detectable MRD. Although in this single institution clinical study, MRD in those hypodiploid patients was eliminated only in the context of very intensive induction therapy that may not be employed broadly, the development of more sensitive measures of MRD with next-generation sequencing techniques [18] may soon provide clinicians with more confidence to forego HSCT in this context. Justification for avoiding transplant is also augmented by the fact that 100% of the LFS patients who developed SMN reported by Qian et al had received HSCT (although clinical information about the SMN in those without LFS is not available for comparison). For those with LFS and ALL, in whom undetectable MRD cannot be achieved, consideration of more innovative therapy is warranted. These patients may benefit from immunomodulatory agents earlier in
therapy, although this would not necessarily abrogate the need for HSCT. Consideration of non-total body irradiation (TBI) conditioning regimens for HSCT is particularly important, but to date, TBI conditioning regimens demonstrate better outcomes than those without [19].

There is more clarity, or at least consensus, on surveillance strategies for those with leukemia predisposition syndromes [20,21]. Generally, for those syndromes in which acute leukemia is not typically preceded by dysplasia, including LFS, screening with complete blood counts (CBC) annually may be all that is required; although those with a prior history of chemotherapy and/or abnormal CBC should be followed more closely, including with bone marrow evaluation.

Looking forward, it is likely that more patients with leukemia predisposition syndromes will be identified prior to or soon after the diagnosis of leukemia. While it may not be practical to perform randomized trials studying different interventions for these patients, it will be critical to include them in prospective clinical trials to collect clinical and biological data from them.

Acknowledgments

Funding

This manuscript has received funding from the National Institutes of Health (U01CA176063, R01GM118578, P50GM115279).

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