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Acute leukemia risk associated with low dose radiation

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The association with radiation exposure in childhood and subsequent risk of development of acute leukemia, as well as other cancer types, is well known¹. Appreciation of this link has, over the past decade, led to a decrease in the use of computerized tomography (CT) testing in children in part due to the dissemination of education and guidelines for reducing pediatric imaging radiation exposure^{2,3}. Therapy related myeloid neoplasm, the development of either Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML), following exposure to therapeutic radiotherapy treatment, is well described and has a poor prognosis⁴. The impact of low dose (ie: less than 100mSv) radiation exposure, such as that conceivable from repeated CT imaging⁵, on the risk of subsequently developing acute leukemia was however less clear. In this issue of *Lancet Haematology* the work from Little and colleagues⁶ convincingly suggests, using data from nine cohorts totaling over a quarter of a million children (including 137 cases of acute leukemia and MDS), that even low dose radiation exposure is associated with low, but quantifiable, increased risk of acute leukemia.

Many unknowns remain. What are the biological and clinical characteristics of these acute leukemias developing in the context of pediatric exposure to low dose radiation? Are there any cytogenetic or mutational signatures that would allow correct classification of a leukemia as low-dose radiation-induced? Acute leukemia patients with such low-level radiation exposure would have previously not have been classified as having a therapy-related neoplasm. What is the response to treatment and clinical outcome of patients diagnosed with acute leukemia in the context of prior low-dose radiation exposure? Are the characteristics of the MDS and AML cases such that it would be appropriate to include them in the therapy related myeloid neoplasm diagnostic category? How do the acute lymphoblastic leukemia cases compare with those currently considered therapy-related⁷?

It is increasingly recognized that inherited susceptibilities to cancer and particularly leukemia exist⁸, together with improved understanding of the polygenic basis of variability in radiosensitivity⁹. It is therefore of particular interest to determine why only some exposed

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to low-dose radiation develop MDS or acute leukemia and if there are genomic explanations beyond chance alone to explain this. Identification of those most susceptible to acute leukemia after radiation would allow the threshold for radiation exposure to be raised in such individuals together with close post-dose hematological monitoring likely for at least ten years. Such a biomarker or classification would also serve to correctly reassure those not in this highly vulnerable group who required clinically-indicated radiation. Importantly, cancer patients and survivors were excluded from this study but may be at particular high risk for radiation-associated leukemia, they are among the highest recipients of repeated low dose radiation exposure in the form of CT imaging and may also have genetic and other risk factors that make them particularly in jeopardy of developing a secondary malignancy such as acute leukemia.

What are the practical immediate implications of this work for hematologists? Firstly, CT scanning currently continues to be an essential clinical tool for diagnosis even in the pediatric setting. As the authors state; this work re-enforces rather than challenges existing radiation protection guidelines. It may however stimulate reflection and allow conversations to ensure local radiology facilities are practicing according to best principles^{2,3} to consistently limit radiation doses used for essential tests to the lowest possible level while also reducing variation by benchmarking to reference standards⁵. Our feeling is that minimizing radiation exposure, particularly in children, is prudent while also recognizing that the benefit for CT imaging for a strong medical indication outweighs risk¹⁰. Secondly, it should stimulate translational and clinical research into the questions described above and more. Thirdly, it will allow for better quantification in risk estimates when discussing with patients and their families. On the basis of the model presented these risks present an important public health challenge, but at a population level thousands of additional CT scans would be expected to create one new case of acute leukemia or MDS. Finally, it should provide additional motivation for the continued development of radiation-minimized medicine practice and the careful identification and protection of those most at risk from toxicity. As acute leukemia physicians we would much rather prevent than have to treat leukemia, and this important study helps identify an important modifiable factor by showing that even exposure to low doses of ionizing radiation in children is associated with a measurable increased risk of subsequent acute leukemia.

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