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Solid organ transplantations in childhood cancer survivors: an unrealised research potential

Do anti-cancer and immunosuppressive agents cause cancer in man? What is the effect of these agents on existing cancers? These key fundamental questions were raised in 1972 by Penn and Starzl in their article entitled 'The effect of immunosuppression on cancer'.[1] Resulting speculations, which are highly relevant for the topic of solid organ transplantation in childhood cancer survivors, are considered by Andrew C Dietz and colleagues[2] in *The Lancet Oncology*.

With the advent of multimodal therapy, survival from childhood cancer has improved over the past 50 years, now reaching more than 80% at 5 years after diagnosis in developed European countries.[3] However, treatments are harsh and might cause serious adverse effects later in life.[4] High-dose irradiation and exposures to chemotherapeutic drugs might lead to treatment-induced end-organ failure and consequently the need for organ transplantation. To prevent rejection of organ transplants, post-transplant immunosuppressants are used, which might lead to additional adverse outcomes.

The question raised in 1972 concerning the role of immunosuppressants for facilitating tumour development is still an ongoing concern, and one of the most severe long-term complications of immunosuppression in the transplant population is de novo malignancies. In the particular case of cancer survivors undergoing transplantation, the occurrence of immunotherapy-associated relapse of the primary cancer or development of secondary malignancies is of great concern as this population have already proved the potential to develop cancers. Several studies have reported that pre-transplant malignancy in adult patients with cancer is associated with an increased risk of developing de novo malignancies after solid organ transplantation compared with those without malignancies.[5] Yet, the magnitude of this problem in childhood cancer survivors undergoing solid organ transplants is still to be assessed.

Similar to other transplant candidates, childhood cancer survivors undergo a thorough evaluation process before transplantation and survivors must be in tumour remission for some time, depending on the type of cancer, before being considered for transplantation.[6] Very limited evidence is available to guide decision making on whether and when the childhood cancer survivor should undergo transplant surgery. So far, the decision seems to be based on extrapolations from the evidence obtained in adult patients with cancer, which might not be appropriate.

In *The Lancet Oncology*, Dietz and colleagues[2] provide new insight into this field. Using the unique resources within the Childhood Cancer Survivor Study (CCSS), the authors provide novel data on kidney, heart, liver, and lung transplantations in childhood cancer survivors—an area to date only touched upon in case reports and small case series. Aimed at defining the incidence of, risk factors for, and survival after end-organ failure and transplantation, a retrospective cohort of 13 318 5-year survivors of childhood cancer diagnosed between 1970 and 1986 below age 21 years were linked to a database of US organ transplants revealing that 100 CCSS participants went on to receive 103 transplants later in life, with an additional 67 survivors being placed on the waiting list for an organ. Organ-specific radiation and chemotherapy exposures were shown to increase the risk of requiring solid organ transplantations following cure of childhood cancer. Furthermore, post-transplant survival outcomes showed that an organ transplant should be considered for 5-year survivors with life-threatening end-organ failure.

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Evidence has been accumulated since the 1970s and results of large population-based studies have documented that childhood cancer survivors have a 3 times higher risk of being diagnosed with a second malignancy following cancer treatment than the general population.[7] Furthermore, overwhelming evidence in adult patients with cancer suggests that immunosuppression increases the risk of post-transplant cancer.[8] However, no evidence is available concerning the risk of a subsequent cancer in childhood cancer survivors when treated with immunosuppressive agents.

Childhood cancers differ substantially from adult cancers, in tissue origin, risk factors, and treatment protocols.[9] This raises the question of whether immunosuppressive protocols should be modified in childhood cancer survivors, or whether these survivors should be treated as patients with adult cancers.

Elevated risk of cancer in patients receiving immunosuppressive medications has been reported among adult kidney transplant recipients with risk estimates two to 12 times higher than population comparisons, whereas a risk 30 times higher has been reported in childhood transplant recipients.[10] These findings might indicate that childhood cancer survivors who have had a transplant in childhood have a very high risk of second cancers, but for those having the transplant later in life, cancer risk is still unknown.

More research should be vigorously pursued to learn about appropriate immunosuppression in this high-risk group. From a clinical perspective, until this knowledge is available, monitoring for de novo or recurrent malignancies to prevent or detect and treat cancers at an earlier stage is of primary concern.

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Targeting lineage plasticity in prostate cancer

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In cancer biology, the term lineage plasticity denotes a process by which cancer cells change from one morphological and functional cell type to another (and back), under the influence of particular environmental pressures. In the context of prostate cancer therapy, lineage plasticity refers to a shift in cellular phenotype from an androgen receptor-dependent adenocarcinoma to an androgen receptor-indifferent neuroendocrine or small-cell carcinoma, which might occur as a consequence of ongoing androgen deprivation therapies.[1] These neuroendocrine prostate cancers are difficult to define histologically (except in the case of pure small-cell prostate cancers) but are clinically characterised by inadequate responses to androgen deprivation therapy and novel hormonal therapies. Early data have suggested that patients with these neuroendocrine prostate tumours might also have suboptimal responses to taxane chemotherapies, perhaps showing greater sensitivity to platinum agents.