Documents

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Evaluating testicular tissue for future autotransplantation: focus on cancer cell contamination and presence of spermatogonia in tissue cryobanked for boys diagnosed with a hematological malignancy

(2024) *Human Reproduction*, 39 (3), pp. 486-495.

DOI: 10.1093/humrep/dead271

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Abstract
STUDY QUESTION: What is the contamination rate by cancer cells and spermatogonia numbers in immature testicular tissue (ITT) harvested before the start of gonadotoxic therapy in boys with a hematological malignancy? SUMMARY ANSWER: Among our cohort of boys diagnosed with acute lymphoblastic leukemia (ALL) and lymphomas, 39% (n ¼ 11/28) had cancer cells identified in their tissues at the time of diagnosis and all patients appeared to have reduced spermatogonia numbers compared to healthy reference cohorts. WHAT IS KNOWN ALREADY: Young boys affected by a hematological cancer are at risk of contamination of their testes by cancer cells but histological examination is unable to detect the presence of only a few cancer cells, which would preclude autotransplantation of cryobanked ITT for fertility restoration, and more sensitive detection techniques are thus required. Reduced numbers of spermatogonia in ITT in hematological cancer patients have been suggested based on results in a limited number of patients. STUDY DESIGN, SIZE, DURATION: This retrospective cohort study included 54 pre- and peri-pubertal boys who were diagnosed with a hematological malignancy and who underwent a testicular biopsy for fertility preservation at the time of diagnosis before any gonadotoxic therapy between 2005 and 2021. PARTICIPANTS/MATERIALS, SETTING, METHODS: Among the 54 patients eligible in our database, formalin-fixed paraffin-embedded (FFPE) testicular tissue was available for 28 boys diagnosed either with ALL (n ¼ 14) or lymphoma (n ¼ 14) and was used to evaluate malignant cell contamination. Hematoxylin and eosin (H&E) staining was performed for each patient to search for cancer cells in the tissue. Markers specific to each patient's disease were identified at the time of diagnosis on the biopsy of the primary tumor or bone marrow aspiration and an immunohistochemistry (IHC) was performed on the FFPE ITT for each patient to evidence his disease markers. PCR analyses on the FFPE tissue were also conducted when a specific gene rearrangement was available. MAIN RESULTS AND THE ROLE OF CHANCE: The mean age at diagnosis and ITT biopsy of the 28 boys was 7.5 years (age range: 19 months–16 years old). Examination of ITT of the 28 boys on H&E stained sections did not detect malignant cells. Using IHC, we found contamination by cancerous cells using markers specific to the patient's disease in 10 of 28 boys, with a higher rate in patients diagnosed with ALL (57%, n ¼ 8/14) compared with lymphoma (14%, n ¼ 2/14) (P-value < 0.05). PCR showed contamination in three of 15 patients who had specific rearrangements identified on their bone marrow at the time of diagnosis; one of these patients had negative results from the IHC. Compared to age-related reference values of the number of spermatogonia per ST (seminiferous tubule) (Spg/ST) throughout prepuberty of healthy patients from a simulated control cohort, mean spermatogonial numbers appeared to be decreased in all age groups (0–4 years: 1.49 ± 0.54, 4–7 years: 1.08 ± 0.43, 7–11 years: 1.56 ± 0.65, 11–14 years: 3.37, 14–16 years: 5.44 ± 3.14). However, using a cohort independent method based on the Z-score, a decrease in spermatogonia numbers was not confirmed. LIMITATIONS, REASONS FOR CAUTION: The results obtained from the biopsy fragments that were evaluated for contamination by cancer cells may not be representative of the entire cryostored ITT and tumor foci may still be present outside of the biopsy range. WIDER IMPLICATIONS OF THE FINDINGS: ITT from boys diagnosed with a hematological malignancy could bear the risk for cancer cell reseeding in case of autotransplantation of the tissue. Such a high level of cancer cell contamination opens the debate of harvesting the tissue after one or two rounds of chemotherapy. However, as the safety of germ cells can be compromised by gonadotoxic treatments, this strategy warrants for the development of adapted fertility restoration protocols. Finally, the impact of the hematological cancer on spermatogonia numbers should be further explored. STUDY FUNDING/COMPETING INTEREST(S): The project was funded by a grant from the FNRS-Télévie (grant n◦. 7.4533.20) and Fondation Contre le Cancer/Foundation Against Cancer (2020-121) for the research project on fertility restoration with testicular tissue from hemato-oncological boys. The authors declare that they have no conflict of interest. © 2024 Oxford University Press. All rights reserved.

Author Keywords
cancer; fertility preservation; leukemia; lymphoma; spermatogonia quantity

Index Keywords
common acute lymphoblastic leukemia antigen, eosin, formaldehyde, hematoxylin, paraffin, tumor marker; adolescent, Article, autotransplantation, B cell acute lymphoblastic leukemia, bone marrow biopsy, Burkitt lymphoma, cancer cell, cancer patient, child, cohort analysis, controlled study, cryopreservation, data base, diffuse large B cell lymphoma, fertility preservation, gene rearrangement, hematologic malignancy, human, human tissue, immunohistochemistry, lymphoblastoma, major clinical study, male, paraffin embedding, prepuberty, preschool child, primary tumor, retrospective study, school child, seminiferous tubule, spermatogonium, T cell acute lymphoblastic leukemia, testis biopsy, testis tissue, tumor biopsy

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Publisher: Oxford University Press

ISSN: 02681161
CODEN: HUREE
PubMed ID: 38227814
Language of Original Document: English
Abbreviated Source Title: Hum. Reprod.
2-s2.0-85186379089
Document Type: Article
Publication Stage: Final
Source: Scopus