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Post-treatment sperm cryopreservation practices in childhood and young adult cancer survivors

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Abstract

Research question: What are current practices regarding post-treatment fertility preservation in male childhood cancer survivors (CCS) who have not benefited from pre-therapeutic fertility preservation in France, as well as in other European countries?

Design: A survey study was addressed to all fertility preservation centers in France (n=30) and to European fertility specialists (n=9 in 5 European countries). It included 8 clinical cases and 40 questions, to assess the effect of age at diagnosis, type of treatment (alkylating-agents, orchidectomy, testicular radiotherapy) and sperm parameters on the probability of post-treatment fertility preservation proposal. Demographic characteristics of the responding practitioner were also collected.

Results: The practices analysis in France showed that a post-treatment sperm cryopreservation was proposed by 100% of fertility specialists in cases of severe oligoasthenoteratozoospermia, 77-88% in cases of moderate oligoasthenoteratozoospermia and in 65-77% in cases of sperm motility and vitality impairment. In cases of normal sperm parameters, 27-54% of fertility specialists would propose post-treatment sperm cryopreservation. These results did not differ significantly according to the type of treatment received or to the responder-related factors. The practices of European specialists were also guided by sperm parameter results, with 44-67% of responders who would propose sperm cryopreservation in cases of moderate/severe sperm parameters alterations.

Conclusion: Post-treatment semen analysis could be widely proposed to CCS who have not benefited from pre-therapeutic fertility preservation, in order to propose post-treatment fertility preservation in cases of persistent moderate/severe sperm parameter alterations. Guidelines would be important to homogenize practices and to encourage oncologists to refer CCS to fertility visits.

Keywords: Sperm Cryopreservation, testicular biopsy, childhood cancer survivors, infertility, follow-up studies, oligospermia.

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Introduction

The overall childhood cancer survival rate has increased in recent decades, with a current 5-year survival rate around 80% (Miller et al., 2019). This has led to a growing population of long-term childhood cancer survivors (CCS). Pediatric treatments are mainly intensive and multimodal, combining surgery, chemotherapy and radiation therapy, resulting in a high risk of sequelae and late complications (Allen et al., 2018) with as many as 75% of CCS having at least one late effect in adulthood (Geenen et al., 2007; Hudson et al., 2013) and over one-quarter a severe or life-threatening adverse event before the age of 50 years (Oeffinger et al., 2006).

Male fertility alteration is one of the most frequent late effects in CCS with significant impact on quality of life, psychosocial distress, anxiety and low self-esteem (Knapp et al., 2011; Levine et al., 2010). The impact of cancer treatments on fertility depends on the cancer itself, cumulative doses of chemotherapy and especially of alkylating agents (estimated by the “cyclophosphamide equivalent dose”, CED, a standardized epidemiological tool for assessing the cumulative dose of exposure to various alkylating agents), exposure to radiation therapy and surgeries (Balduzzi et al., 2017; Borgmann-Staudt et al., 2012; Bujan et al., 2014, 2013; Chow et al., 2016; Romerius et al., 2011). Sperm parameter alterations are observed after exposure to CED $>4,000$ mg/m² and are common after CED $>8,000$ mg/m² (Green et al., 2014b). Several studies based on a low number of patients concluded that the impact varies according to the type of alkylating agent used, and in particular there is a lower risk of gonadic toxicity with ifosfamide compared with cyclophosphamide (Garolla et al., 2006;

Ridola et al., 2009). In case of testicular exposure to radiation therapy, although the highest dose limit beyond which permanent azoospermia becomes unavoidable remains uncertain, doses above 2 Gy increase the recovery time of spermatogenesis and the risk of permanent azoospermia is significant above 6 Gy (Skinner et al., 2017). Even though there are many established risk factors, the recovery of spermatogenesis in male CCS is also depending on individual susceptibility factors and remains difficult to predict (Green et al., 2014a).

Pre-therapeutic fertility preservation is recommended in all males patient affected by cancer but is limited by the available procedures. In adolescents and young adults, sperm cryopreservation is an efficient fertility preservation method, but it could be not feasible due to pre-treatment critical clinical conditions, abnormal initial sperm parameters or initial refusal of the patient or his parents (Daudin, 2015; Kamischke et al., 2004; Rives et al., 2022; Wyns et al., 2015). Moreover, this procedure is not applicable in prepubertal patients, who can benefit only from testicular tissue cryopreservation, with fertility restoration techniques still experimental (Picton et al., 2015). In these scenarios, post-treatment semen analyses and banking could be suggested at adulthood. Post-treatment fertility preservation could also be encouraged due to the risk of second event that may impair fertility such as second malignancies (Meadows et al., 2009; Tukenova et al., 2012) or late relapses (Thebault et al., 2021). Unfortunately, there is no recommendation regarding post-treatment fertility preservation for male CCS who did not benefit from pre-therapeutic sperm preservation (Hudson et al., 2021; “Préservation de la fertilité et cancer - Thésaurus - Ref: RRETHESCATFERT21,” n.d.; Skinner et al., 2017).

The aim of this survey was to assess and analyze the professional practices in France compared with other European countries regarding post-treatment fertility preservation in male s CCS who have not benefited from pre-therapeutic fertility preservation at cancer diagnosis and who have persistent abnormal sperm parameters in adulthood at least 1 year after the end of cancer treatment, without immediate paternity desire.

Material and methods

Description of the survey

This study was an international survey addressed to all fertility preservation centers in France (CECOS, *Centre d'Étude et de Conservation des Oeufs et du Sperme*, n=30) and to several European fertility specialists contacted through the PanCare network (n=9 in 5 European countries: Belgium, Greece, Italy, Switzerland and the United Kingdom) conducted between June 2022 and August 2022. One response per center was expected.

The survey consisted of 8 different fictive standardized clinical cases corresponding to different risk-levels of fertility alteration, due to variations in the type of cancer, the age at diagnosis and the type of treatment received (cumulative doses of chemotherapy, orchidectomy, radiotherapy on the testis) (Table-1 and Supplementary materials). The risk of sperm parameter alterations regarding therapeutic exposures was defined as follows:

(a) low-risk, in cases of alkylating agents exposure with CED <4,000mg/m² without testicular radiation therapy nor orchidectomy, (b) moderate-risk, in cases of CED between 4 and 12,000mg/m² or orchidectomy but without testicular radiation, (c) high-risk, in cases of CED >12,000mg/m² (except exposure to ifosfamide only (Ridola et al., 2009)) or exposure to testicular radiation therapy. In all the clinical cases, five scenarios were presented corresponding to five different semen analyses: normal sperm parameters, moderate oligo-astheno-teratozoospermia (OAT) (with a sperm concentration between 5 and 10 M/ml), severe OAT (with a sperm concentration between 0 to 1 M/ml), normal concentration (≥ 16 M/ml) but alteration of the motility and vitality of spermatozoa, and azoospermia (World Health Organization, 2021). For each situation, a standardized binary question (yes/no) was asked: “In this situation, would you propose a sperm cryopreservation (for scenarios 1 to 4) / a testicular biopsy (for situation 5, azoospermia)?” The order of presentation of the clinical cases was defined at random but was the same for all responders.

Demographic characteristics of the responding practitioner were also collected: sex, age at survey completion, years of experience (less than 5 years of experience, between 5 and 10 or more than 10) and work area, corresponding either to the 6-areas defined by the interregional hospital organization for French pediatric oncology or to other European countries.

This survey did not include patients but only physicians questioned about their clinical practices. Consequently, no ethics committee advice was required according to the French national laws. Study data were collected and managed using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Gustave Roussy (Harris et al., 2009; Harris et al., 2019).

Statistical analyses

Descriptive statistics were used to characterize the study responder's profile and to evaluate the number of positive and negative responses to each of the questions of the 8 clinical cases. A two-level hierarchical linear mixed model was used to identify potential factors affecting the probability of cryopreservation. In this model, the cryopreservation center was considered the upper-level, and the clinical case the base-level. The covariates concerning the risk-level of fertility alteration (age at diagnosis, cumulative doses of alkylating agents expressed as CED, orchidectomy and radiotherapy on the testis) and the sperm parameters were entered in a multivariable analysis. We then studied the effect of responders' profiles by adding in the multivariable model the study responder characteristics (sex, age at survey completion, years of experience and work area) with the previously identified covariates identified as significantly associated with the proposal of fertility preservation. All tests were two-sided with alpha set to 0.05. The statistical analyses were performed with *SAS 9.4* (SAS Institute, Cary, NC, USA).

Results

Of the thirty French CECOS centers contacted between June and August 2022, twenty-six (87%) fully completed the survey. Moreover, 9 European fertility specialists from 5 different countries (Belgium, Greece, Italy, Switzerland, and the United Kingdom) among the specialists contacted via the PanCare network also fully completed the survey. The characteristics of the respondents are described in Table-2.

Sperm cryopreservation practices in France

Table-3 shows the percentage of responders who would propose a secondary post-treatment fertility preservation with sperm cryopreservation or testicular biopsy according to the risk of fertility alteration and to the results of semen analysis. Regarding the responses of specialists working in French clinics, in cases of severe OAT, all the specialists (26/26) would propose sperm cryopreservation, regardless of treatment exposures and risk of relapse (Table-3, scenario-3). In cases of moderate OAT or impairment of sperm motility and vitality, 77-88% and 65-77% of fertility specialists would propose sperm cryopreservation, respectively (Table-3, scenarios 2 and 4). In cases of normal sperm parameters, the proportion of specialists who would propose sperm cryopreservation was lower, varying according to clinical cases from 27% (case-3: moderate dose of alkylating agents without RT or orchidectomy) to 54% (case-4: unilateral orchidectomy without alkylating agents and case-8: high risk of relapse with moderate doses of alkylating agents) (Table-3, scenario-1).

In multivariate analyses, only sperm parameters and age at diagnosis were significantly associated with the proposal of secondary fertility preservation with sperm cryopreservation (Table-4). The odds ratios (OR) of moderate and severe OAT were 1.5 (1.4-1.6) and 1.8 (95%CI=1.7-1.9), respectively, compared with a normal count ($p<0.0001$). Alterations of sperm motility and vitality were also associated with the proposal of sperm cryopreservation with an OR of 1.4 (95%CI=1.3-1.5). Concerning clinical characteristics detailed in the clinical cases resuming the risk of fertility alteration, a higher age at diagnosis (15 years-old vs. 5

years-old) was significantly associated with a higher probability of sperm cryopreservation proposal (OR=1.1, 95%CI=1.0-1.2, p=0.013). The cumulative dose of alkylating agents (p=0.30), orchidectomy (p=0.65) and testicular radiation therapy (p=0.26) were not associated with a higher probability of sperm cryopreservation proposal. After adjustment for semen analysis (sperm count and alterations of motility and vitality) and age at diagnosis, no responders' characteristics were significantly associated with fertility preservation proposal (sex p=0.67, age at survey completion p=0.71, years of experience p=0.69, work area p=0.62, Supplementary Table-1).

Testicular biopsy practices in France

In cases of azoospermia, 42 to 54% of fertility specialists would propose testicular biopsy (Table-3 scenario-5). In multivariate analyses, the clinical characteristics detailed in the clinical cases were not associated with the proposal of secondary fertility preservation with testicular biopsy (Table-5). Responders' characteristics were also not associated with the proposal of testicular biopsy (sex p=0.80, age at survey completion p=0.32, years of experience p=0.92, work area p=0.69, Supplementary Table-2)..

Fertility preservation practices in Europe

Table 6 presents the descriptive analysis of European answers (n=9). In case of moderate and severe OAT, 44%-67% of the specialists would propose sperm cryopreservation, regardless of treatment exposures and risk of relapse (Table 6, scenarios 2 and 3). In cases of normal sperm parameters, the proposition of sperm cryopreservation was less frequent (0-33%; Table 6, scenario 1). In cases of azoospermia, 33-56% of fertility specialists would propose testicular biopsy (Table 6, scenario 5). In all scenarios, we observed that post-treatment fertility preservation practices differ mainly according to semen analysis results.

Discussion

The present study is the first national survey addressing post treatment sperm cryopreservation practices in France. It showed that the proposal of post-treatment fertility preservation was related to semen analysis results (sperm count, vitality, and motility) and not to the treatment exposures.

The unanimous attitude of specialists in recommending sperm cryopreservation in cases of severe OAT is clearly highlighted in the survey's answers. Attitudes are more heterogeneous in cases of moderate OAT and qualitative sperm alterations. However, the majority of fertility specialists would propose secondary sperm cryopreservation in cases of persistent quantitative (77-88%) or qualitative (65-77%) alterations of sperm parameters, independently of the past exposure to gonadotoxic treatments. This trend is confirmed by the results of the European survey, in which fertility specialists would propose sperm cryopreservation in case of persistent quantitative (44-67%) alterations of sperm parameters, regardless of treatment-related risk of gonadotoxicity.

In cases of normal sperm parameters, fertility specialists in France would propose sperm cryopreservation in 31 to 54% of the cases. Past-treatment exposures did not influence the probability of sperm cryopreservation proposal, which varied from 31% in the case of no gonadotoxic treatment exposure to 42% in the case of exposure to high dose of alkylating agents. Responders proposed sperm cryopreservation at the highest rates in the scenarios where the risk of second events, which could impair sperm parameters, is the highest. Indeed, the rate was 54% in the case of unilateral orchidectomy, with the risk of damage to the only residual testis, and in the case of high risk of relapse, with the potential need of secondary gonadotoxic treatments (Meadows et al., 2009; Thebault et al., 2021; Tukenova et al., 2012).

The reasons why one-third of the fertility specialists would propose sperm cryopreservation after childhood cancer to patients with normal sperm parameters and in the absence of past gonadotoxic treatment exposure could be explained in two ways. One reason could be ethical,

considering the right to have access to fertility preservation independently of the clinical situation, in the same manner as men and women have access today in France to fertility preservation independently of the clinical situation (“Article L2141-2 - Code de la santé publique - Légifrance,”). Another reason could be the risk of subsequent malignant events, which is increased in all CCS (Friedman et al., 2010).

In cases of azoospermia, testicular biopsy may be a solution for infertility, with the possibility of testicular sperm extraction (TESE) from testicular tissues, and intra cytoplasmic sperm injection (ICSI) procedure. This technique leads to successful results and should be offered to azoospermic cancer survivors who did not cryopreserve sperm prior to their gonadotoxic treatments (Dar et al., 2018). However, the probability of finding spermatozoa could vary widely according to the type and doses of anticancer treatments received in childhood and the results of hormonal tests in adulthood (e.g. male CCS treated at pre pubertal age with Busulfan-Melphalan for high risk neuroblastoma have in nearly all cases in adulthood prepubertal testicular size, with testosterone secretion but lack of Sertoli function leading to a very low estimated probability of finding spermatozoa (Haghiri et al., 2021)). In cases of positive biopsy, the rate of successful pregnancy after TESE in cancer survivors is the same as non-cancer azoospermic patients (Levi-Setti et al., 2020). In this survey, TESE would be offered in about 50% of azoospermia cases. However, in the absence of paternity desire, proposing such a procedure is questionable due to its potential to affect hormonal secretions in patients with chemotherapy-related testicular damage including hormonal deficiency prior to proposal of the TESE procedure. A specific investigation of this procedure would be interesting in order to assess its availability in the different centers and its current indications in male CCS.

It is also important to add that even if the best practice guidelines are followed for the semen analysis, there is an error margin that cannot be set to zero. This may be due to both subjectivity in interpreting results and variability of semen samples according to biological

and lifestyle factors (Douglas et al., 2021; Tomlinson, 2016). Some studies suggest performing two consecutive semen analyses to confirm a diagnosis in cases of male infertility (Blickenstorfer et al., 2019). This is an important variable to take into consideration when delivering results and proposing secondary fertility preservation.

Compared with France, practices of EU specialists tended to be different with a lower rate of post-treatment fertility preservation proposal, especially in cases of severe sperm parameters alteration (100% vs. 44-67%). The differences in legislation and cost of cryopreservation could explain these results. In France, sperm cryopreservation costs 40,5 euros per year and is free of charge for the patient in case of treatment altering fertility or medically assisted procreation, without any limit of storage duration, until the age of 60. The non-medical sperm cryopreservation is possible between the age of 29 and 45 years old, its cost is also 40.50 euro per year and can be stored until the age of 60 (“Article 3 - LOI n° 2021-1017 du 2 août 2021 relative à la bioéthique - Légifrance,” ; “Article R2141-38 - Code de la santé publique - Légifrance,”). This regulation is different in other European countries such as England or Switzerland where post therapeutic cryopreservation is at the patient's expense.

In conclusion, this survey suggests the importance for pediatric oncologists to systematically propose a fertility visit with semen analysis to all their adult CCS patients who have been exposed to gonadotoxic treatment. The aims of such a visit would be to inform CCS about the risk of fertility impairment, to perform semen analysis and to discuss post-treatment fertility preservation according to its results for patients who have not benefited from pre-therapeutic fertility preservation. In cases of persistent severe OAT, secondary post-treatment sperm cryopreservation could be widely proposed. However, guidelines would be useful to homogenize the practices of post-treatment fertility preservation (sperm cryopreservation and testicular biopsy).

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