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Testicular function of survivors of childhood cancer: A comparative study between ifosfamide- and cyclophosphamide-based regimens ☆

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ABSTRACT

Purpose: This study aimed at comparing gonadal toxicity of ifosfamide versus cyclophosphamide received during childhood.
Methods: The evaluation was based on basal FSH measurement. LH and testosterone were also measured in most of the patients. One hundred patients had received ifosfamide and 59 had received cyclophosphamide.
Results: Median age at treatment was 11.2 years. The median interval since treatment was 10.7 years (range 4.1–20.2) and median age at evaluation was 21.4 years (17.5–36.1). The median dose of ifosfamide and of cyclophosphamide was 54 g/m^2 (18–114) and 8.3 g/m^2 (4.6–22), respectively. All but two males had normal testosterone levels. FSH was abnormal in 28/59 patients (47.5%) after receiving cyclophosphamide and was within the normal range in 94/100 patients (94%) after receiving ifosfamide.
Conclusions: These results show that ifosfamide is associated with a lower risk of gonadal damage than cyclophosphamide. The risk of abnormal FSH increased with the cumulative dose of cyclophosphamide.

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1. Introduction

Over the past two decades, continuing therapeutic progress in the management of childhood malignancies has resulted in a dramatic decline of mortality and in a greater number of long-term childhood cancer survivors. For instance, the 5-year survival rate of patients with localised sarcomas now exceeds 70%. Thus, the emphasis on the management of childhood cancer has shifted from cure at any cost to the one in which the quality of life after treatment has become increasingly important.

Although fertility problems do not become apparent until after puberty, there is no doubt that alkylating agents (cyclophosphamide, procarbazine, chlorambucil, nitrogen mustard, melphalan) can lead to infertility and sub-fertility in later life which compromise the quality of life.[1–5] These agents are effective through their action against more rapidly dividing cells, which include cancer cells as well as testicular germ cells. The latter are killed or damaged at the stage of differentiating spermatogonia.[6] These agents cause a certain degree of oligozoospermia to azoospermia associated with increased levels of follicular stimulating hormone (FSH).

The alkylating agent ifosfamide, a structural analogue of cyclophosphamide, was progressively introduced in first-line therapy for soft-tissue sarcomas as well as bone sarcomas during the 1980s. The reasons for recourse to ifosfamide were its relatively mild myelotoxicity enabling its use at a high dose and its encouraging activity in patients previously treated with cyclophosphamide, suggesting a lack of complete cross-resistance between these two key drugs.

Compared with the well-established effects of other alkylating agents on fertility, data are still scant about the effects of ifosfamide in this regard.

We evaluated the gonadal function of adult male survivors who were treated during childhood or adolescence with ifosfamide as the only alkylating agent. These results were compared with those observed in a previous cohort of males treated with cyclophosphamide.

2. Methods

Testicular function was assessed by measuring baseline plasma FSH and luteinising hormone (LH) levels. Ideally, gonadal function should be evaluated by a sperm count and this procedure is easily accepted exclusively in males on the brink of fatherhood. The serum FSH level is strongly correlated with the sperm count,[7,8] even if normal FSH may be associated with azoospermia. We therefore decided to explore a large group of males on the basis of FSH levels rather than to explore a very small and selected group of males using a spermogram.

In addition to LH and FSH levels, plasma testosterone concentration was measured for patients treated with ifosfamide. Such values were not available for the previously evaluated patients treated with cyclophosphamide. Serum FSH and LH levels were considered abnormal when they were above the laboratory upper limit of the normal range. Testosterone levels were considered abnormal when they were below the lower limit of the normal range. A semen analysis was proposed and performed at the request of the patients.

The ratio of the doses of cyclophosphamide and ifosfamide with equivalent alkylating activity has been assumed to be between 3.45, based on the measurement of plasmatic levels,[9] and 4 or 4.3 on a clinical basis.[10,11] We therefore retained a ratio equal to 4 to compare ifosfamide and cyclophosphamide doses.

3. Patients

Male patients considered eligible for the present study had to have received cyclophosphamide or ifosfamide as the only alkylating agent. They could have received platinum chemotherapy but not any other alkylating agents (e.g. procarbazine, chlorambucil, nitrogen mustard, melphalan, busulfan, thiotepa or any nitrosoureas). Patients who had received pelvic, gonadal or cranial radiation were not eligible.

Group I consisted of patients treated with ifosfamide between 1984 and 2000 in seven French paediatric oncology centres and selected from databases of several studies carried out according to SFCE (Société Française des Cancers de l'Enfant) or SIOP (International Society of Paediatric Oncology) protocols. The study population included patients with osteosarcoma treated in OS87[12] and OS94[13] SFCE protocols, patients with Ewing's sarcoma enrolled in EW84, EW93 SFCE protocols,[14] and patients with soft-tissue sarcomas treated in MMT84, MMT89 SIOP protocols.[15,16]

Group C consisted of patients treated with cyclophosphamide between 1973 and 1991 in a single institution (Institut Gustave Roussy, Villejuif) whose data have been partially published.[1,17]

All patients had a 5-year follow-up from the end of therapy and were aged >17 years at the time of the study.

Enrolment in this study was proposed by the patient's paediatric oncologist either during consultation visits to the cancer centre or via letters describing the goal of the study for discharged patients. Most of the survivors were explored in the different centres where they had been treated. A few were investigated in a laboratory closest to their home.

As gonadal evaluation was part of the usual follow-up of patients after chemotherapy in keeping with good clinical practice, no informed consent was requested by the French national IRB. Nevertheless, patients provided their consent for data collection.

4. Data collection

Diagnosis and treatment data were abstracted from the hospital records and included age at the time of the initial diagnosis, the pathologic diagnosis and site, date of completion of therapy after primary disease or relapse, cumulative doses of chemotherapy, the field and dose of radiotherapy and the type of surgery, if any.

Group I: In all ifosfamide-based protocols, this drug was administered via a short infusion over one to three hours, for two to four consecutive days per course with concomitant 24-h continuous intravenous fluid hydration and mesna at a dose of 120% of the respective ifosfamide dose. The daily dose of ifosfamide was 3 g/m^2, and the total dose per cycle ranged from 6 to 12 g/m^2. Cumulative doses per protocol ranged from

18 to 60 g/m^2. For several reasons such as a relapse, some patients received higher doses. The cumulative median dose was 54 g/m^2 (range 18–114 g/m^2)

Group C: Cyclophosphamide was administered via a short infusion. Doses per cycle ranged from 1.0 to 1.5 g/m^2. The median cumulative dose was 8.3 g/m^2 (range from 4.6 to 22.0 g/m^2)

5. Statistics

Bivariate associations between the type, dose of alkylating agents and hormonal results were assessed using chi-squares.

6. Results

One hundred patients treated with ifosfamide (group I) and 59 patients treated with cyclophosphamide (group C) were investigated. Patient characteristics are shown in Table 1.

Among the 147 potentially evaluable patients for investigations after ifosfamide, 47 were not evaluated for various reasons: four had already fathered children, five had had investigations before the beginning of the study, one had psychological problems. Clinicians felt that it was not possible to request investigations for those patients. The others either were lost to follow-up or did not reply to the letter. The characteristics of those patients were similar to those of their evaluated counterparts in terms of age at treatment, cumulative doses of Ifosfamide, and potential follow-up.

Apart from the diagnosis (patients with non-Hodgkin's lymphomas were exclusively in group C), patients in both groups had similar characteristics. Median age at treatment was 12 years (range 0.5–20.7) in group I and 9.8 years (range 0–17.6) in group C. Median age at investigation was 22.5 years (range 17.3–36.1) in group I and 19.5 years (range 17.5–28.6) in group C. The median time after the end of treatment was 8.5 years (range 5–16.5) in group I and 12 years (range 5.4–20.5) in group C (Table 1).

No patient in either cohort had a previous history or actual presence of cryptorchidism, orchidectomy, varicocele or malignant disease of the testis.

Median cumulative doses of ifosfamide and cyclophosphamide were, respectively, 54 g/m^2 (range 18–114 g/m^2) and 8.3 g/m^2 (range 4.6–22.0 g/m^2) (Table 2).

Patients were stratified according to the cumulative doses received in both groups. In group I, 29 patients had received less than 36 g/m^2 of ifosfamide, 11 patients had received between 36 and 47.9 g/m^2, while the majority of patients ($n = 60$) had received more than 48 g/m^2 (range: 18–114 g/m^2). Of these 60 patients, 27 had received a cumulative dose exceeding 60 g/m^2. In group C, 28 patients had been treated with less than 9 g/m^2 of cyclophosphamide, 15 patients had received between 9 and 11.9 g/m^2 and 16 patients had received more than 12 g/m^2 (Table 1).

In addition to alkylating agents, 42 of the 159 patients had received either cisplatinum or carboplatinum.

According to hormone measurements, a significantly higher proportion of males had an abnormal FSH value in group C than in group I. Of 59 patients treated with cyclophosphamide, 28 (47.4%) had abnormal FSH levels compared to only six of 100 (6%) patients treated with ifosfamide ($p = 0.0001$). A subgroup analysis according to cumulative chemotherapy doses is shown in Table 2.

The difference in the rates of gonadal damage as assessed by FSH concentrations is more pronounced in the subgroups of patients who had received higher equivalent cumulative doses of the two alkylating drugs: elevated FSH levels were observed in 14/16 (87.5%) patients treated with more than 12 g/m^2 of cyclophosphamide versus 5/60 (8.3%) patients who had received more than 48 g/m^2 of ifosfamide ($p < 0.0001$). Overall, 70% of the patients who had received more than 9 g/m^2 of cyclophosphamide had an abnormal FSH value as compared to 7% of the patients who had received more than 36 g/m^2 of ifosfamide.

Among the group of patients treated with ifosfamide, testosterone concentrations were in the normal range in all but two evaluated patients, 17.5 and 26.5 years old, respectively, at the time of the investigation, with normal LH and FSH and low testosterone concentrations. LH was elevated in 14/100 (14%) evaluated patients.

At the time of hormone measurement, 8/59 patients treated with cyclophosphamide had fathered at least one child

Table 1 – Patients characteristics.

	Cyclophosphamide	Ifosfamide
Number	59	100
Diagnosis		
Soft tissue sarcomas	11	68
Osteosarcomas	12	27
Ewing's sarcomas	5	5
Non-Hodgkin's lymphomas	28	0
Other diagnosis	3	0
Age at diagnosis*	9.8 years (0–17.6)	12 years (0.5–20.7)
Age at follow-up*	19.5 years (17.5–28.6)	22.5 years (17.3–36.1)
Follow-up intervals*	8.5 years (5–16.5)	12 years (5.4–20.5)
Cumulative doses*	8.3 g/m2 (4.6–22)	54 g/m^2 (18–114)

* Data expressed as medians (range).

Table 2 – FSH results in patients treated with cyclophosphamide or ifosfamide, according to cumulative doses.

Cyclophosphamide			Ifosfamide		
Cumulative doses	No. pts	No. with abnormal FSH	Cumulative doses	No. pts	No. with abnormal FSH
<9 g/m^2	28	21.4% (6/28)	<36 g/m^2	29	3.4% (1/29)
9–11.9 g/m^2	15	53.3% (8/15)	36–47.9 g/m^2	11	0% (0/11)
⩾12 g/m^2	16	87.5% (14/16)	⩾48 g/m^2	60	8.3% (5/60)
Total	59	47.4% (28/59)		100	6% (6/100)

versus 6/100 patients in the ifosfamide group. The median cumulative dose in group C was 8.3 g/m^2 versus 54 g/m^2 in group I. Median age at treatment was 14 years in both groups (range 9–19 years in cohort I; 8–18 years in cohort C).

Adding cisplatinum or carboplatinum to alkylating agents had no impact on testicular function.

7. Discussion

Diagnostic precision, therapy and supportive care have resulted in a growing number of childhood cancer survivors and nowadays, 5-year survival rates of sarcomas range from 60% to 70%. Clinical research is now focusing on the incidence of late effects resulting from cancer treatments in order to decrease the consequent physiological and psychosocial morbidities. Since chemotherapy and radiotherapy may lead to impairment of spermatogenesis, infertility is a significant issue among survivors.

Gonadotoxicity of most alkylating agents, especially cyclophosphamide, has been widely described in the literature.[3,17–23] Long-term male gonadal damage following cyclophosphamide-containing regimens has been shown to be dose-dependent with up to 70% or 80% of patients being affected by abnormal FSH levels after treatment with a cumulative dose of the drug exceeding 9 g/m^2.[20,24] Despite its efficacy against solid tumours in children and its use for more than 20 years, very few studies have addressed the issue of male sterility in patients treated with ifosfamide. Clinicians who counsel patients receiving ifosfamide therefore often extrapolate gonadotoxicity data from cyclophosphamide evaluations.

Longhi et al. evaluated 96 male childhood patients surviving an osteosarcoma. Sixteen out of 96 patients had received ifosfamide as a single alkylating agent and had accepted to undergo a semen analysis. The median ifosfamide cumulative dose was 42 g/m^2 (range: 24–60 g/m^2) and median follow-up was 6 years. Fourteen patients were azoospermic, one patient was oligospermic and one patient was normospermic. The incidence of azoospermia related to ifosfamide versus no ifosfamide was considered statistically significant although definitive conclusions are prohibited given the small number of patients who accepted semen testing. Patients who were normospermic had a longer follow-up of 13.5 years compared with 6 years in the azoospermic group.[25] The patients who had received ifosfamide in that study had a shorter median follow-up than the patients we investigated (6 years versus 12 years). Experience shows that patients can improve from azoospermia to oligospermia or normospermia sometimes after more than 10 years.[26,27]

The only published comparative study aimed at evaluating the long-term effects on testicular function of ifosfamide versus cyclophosphamide was conducted on 33 male survivors of childhood cancer (follow-up: 7–23 years) and was based on a semen analysis, the hormonal status and testicular Doppler ultrasound. Eight patients had received cyclophosphamide-containing regimens and 25 patients had received ifosfamide-containing regimens. Patients treated with cyclophosphamide had a higher mean level of FSH than patients treated with ifosfamide. All subjects treated previously with cyclophosphamide had azoospermia or severe oligospermia associated with increased FSH levels, and sperm counts were significantly higher in the ifosfamide group as compared to the cyclophosphamide group ($p < 0.001$), suggesting that ifosfamide treatment seems to be safer in terms of testicular function and fertility.[28]

Based on the results recently reported by the British group, a dose relationship can be assumed for ifosfamide-induced gonadal damage akin to that following treatment with cyclophosphamide. Among 32 male cancer survivors with a sperm test and hormonal measurements, no gonadal dysfunction was seen at a total ifosfamide dose of <60 g/m^2. Two-thirds who had received more than 60 g/m^2 were subfertile and 31% had elevated FSH supporting evidence of germ cell failure.[29]

The limitation of our study is the lack of sperm counts in our patients and the possibility that azoospermia may be observed despite a normal FSH value. However, this is counterbalanced by the size of the group evaluated, i.e. 100 patients treated with ifosfamide. We could also compare their plasma FSH level with the results of a group of patients treated with cyclophosphamide.

The very low incidence of abnormal FSH observed after a long follow-up in the cohort treated with ifosfamide shows that ifosfamide is safer than cyclophosphamide for testicular function when given at a moderate dose, the median dose being 54 g/m^2. In addition, the common protocols used for the treatment of sarcomas use a cumulative dose of cyclophosphamide exceeding 9 g/m^2 which, according to our data, is associated with a very high risk of gonadal damage and possible infertility (70% in the present study). By contrast, the ifosfamide dose used in European protocols for soft-tissue sarcomas is 54 g/m^2, which represents a low risk of gonadal damage (7% in the present study). These results cannot be extrapolated to patients receiving high doses of ifosfamide. The current Euro-Ewing trial for localised tumours is addressing the question of the efficacy and the long-term toxicity of 104 g/m^2 cumulative dose of ifosfamide as compared to 60 g/m^2 of ifosfamide combined with cyclophosphamide (10.5 g/m^2). The potential renal toxicity of ifosfamide should also be taken into consideration when choosing the alkylating agent to include in a protocol.

Conflict of interest statement

None declared.

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