ORIGINAL ARTICLE

Restoration of ovarian function after chemotherapy for osteosarcoma

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Aim: To evaluate ovarian function after modern intensive multi-agent chemotherapy for osteosarcoma given during childhood or adolescence.
Methods: After discontinuation of treatment, 10 female osteosarcoma survivors were followed up for 1.5–14 (median 4.6) years. Their age at diagnosis was a median of 12.9 (range 6–15) years and at the last follow up 18.6 (range 16–22). The main follow up included recording of their pubertal and menstrual status and of sex hormone determinations.
Results: Prior to diagnosis, 5/10 had had their menarche, and one had it while on therapy. At discontinuation of chemotherapy, ovarian function had severely deteriorated; none of the girls experienced regular menstrual cycles. However, during follow up, significant restoration of ovarian function was evident. At the last follow up, 9/10 patients were menstruating spontaneously. During follow up, four patients, three of whom had received high doses of alkylating agents, presented with clear hypergonadotrophism with high FSH levels (14.4–132 IU/l). Three of these four patients initiated menstruation after their gonadotrophin levels normalised.
Conclusions: The modern multi-agent chemotherapy applied for osteosarcoma impairs ovarian function. Normalisation of ovarian function is common, even in cases with severe hypergonadotrophic hypogonadism, but may only occur after several years off chemotherapy. Regular assessment of ovarian function and cautious use of hormone replacement therapy are important in patients with chemotherapy induced gonadal damage.

Intensive modern multi-agent chemotherapy has dramatically improved the prognosis of patients with osteosarcoma. Today, more than 60% of these patients can expect long term survival and a definitive cure.[1–3] Of the multiple late complications after anticancer therapy, ovarian impairment is a common late effect.[4] Many studies have examined ovarian function in survivors of leukaemia, Hodgkin's disease, and brain tumours. Although gonadal damage is mostly related to radiotherapy (for example, total body irradiation preparative for stem cell transplantation), intensive chemotherapy may also cause such damage. Because of the relative radioresistancy of the tumour, radiotherapy is not utilised for osteosarcoma. Instead, the chemotherapy regimens applied for osteosarcoma have gradually become more and more intensive. Today, they include high cumulative doses of metotrexate, ifosfamide, and cisplatin—doses not routinely employed in regimens for leukaemia, lymphomas, and brain tumours. The aim of this study was to evaluate ovarian function in young females after aggressive modern treatment for osteosarcoma in childhood or adolescence.

PATIENTS AND METHODS

This was a retrospective cohort study of all consecutive female long term survivors of osteosarcoma in childhood or adolescence treated from 1984 to 1999 at the Hospital for Children and Adolescents, University of Helsinki, Finland. There were 10 girls or young women, who had been a minimum of 1.5 years off therapy and were older than 16 at the last follow-up. During chemotherapy, no measures were taken to protect the ovaries.

Four different chemotherapy protocols had been applied: CCG 782, ISG/SSG I, SSG II, and a modified Rosen T10.[1 5 6] Table 1 lists the cumulative doses of the drugs. In addition to chemotherapy, all patients underwent orthopaedic surgery (table 1).

After chemotherapy, the patients were followed up at 3–12 month intervals. In addition to information concerning the malignancy, we recorded growth, pubertal development, and menstrual history. Pubic hair and breast development were staged according to Tanner.[7] Follicle stimulating hormone (FSH), luteinising hormone (LH), and oestradiol levels were measured when clinically indicated. Serum FSH (reference range 1–12 IU/l in the follicular phase) and LH (2–10 IU/l in the follicular phase) concentrations were measured by time resolved immunofluorometric assays, and oestradiol (0.11–0.44 nmol/l in the follicular phase, levels <0.02 nmol/l, not detectable) by direct radioimmunoassay.[8 9]

RESULTS

Key characteristics of the patients

Median age of patients at diagnosis was 12.9 years (range 6.4–15.2). The last follow up was at 18.6 (range 16.2–21.8) or 4.6 years (range 1.5–13.6) after discontinuation of therapy (table 1).

Pubertal and menarcheal status at diagnosis

At diagnosis, three patients were prepubertal, five were in mid-puberty, and two had completed their pubertal development. Of the 10 girls, five had had their menarche prior to diagnosis; two of them had irregular menstrual cycles (table 2).

Pubertal status, menarcheal status, and biochemistry at completion of chemotherapy and at last follow up

One patient had her menarche while on chemotherapy. At discontinuation of therapy, none had regular menstruation.

Abbreviations: FSH, follicle stimulating hormone; HRT, hormone replacement therapy; LH, luteinising hormone

Table 1 Key characteristics of 10 female patients treated for osteosarcoma, with cumulative doses of chemotherapeutic agents

Patient	Age at diagnosis (y)	Duration of treatment (y)	Age at last follow up (y)	Follow up time (y)	Site of tumour	Type of surgery	MTX (g/m^2)	CTX (g/m^2)	IFO (g/m^2)	VP-16 (g/m^2)	CDDP (mg/m^2)	ADM (mg/m^2)	B (mg/m^2)	D (mg/m^2)	VCR (mg/m^2)
1	6.4	1.2	21.2	13.6	Dist. femur	Amputation	61	5.8	–	–	740	450	140	5.8	–
2	10.7	1.5	16.2	4	Dist. femur	Amputation	56	3.6	17.0	1.2	330	300	90	3.6	–
3	11.4	1.0	17.9	5.5	Prox. humerus	Limb salvage with fibulograft	86	–	54.5	2.2	600	380	–	–	–
4	11.8	0.9	17.7	5	Dist. femur	Limb salvage with endoprosthesis	8	5.0	–	–	630	410	120	5.0	–
5	12.6	1.2	21.8	8	Prox. femur	Hemipelvectomy	18	–	63.5	3.5	710	350	–	–	–
6	13.1	1.2	19.2	4.9	Dist. radius	Limb salvage with fibulograft	126	4.8	–	–	–	390	90	6.6	6.3
7	14.8	1.3	17.6	1.5	Prox. humerus	Limb salvage with fibulograft	24	4.8	60.4	2.0	670	320	90	4.4	–
8	15.1	0.9	20.4	4.4	Prox. tibia	Amputation	55	–	35.1	2.0	350	220	–	–	–
9	15.2	0.9	18.9	2.8	Pelvic girdle	Hemipelvectomy	20	–	28.5	1.0	230	150	–	–	–
10	15.3	1.0	18.3	2	Dist.radius	Limb salvage with fibulograft	48	3.7	9.0	0.5	600	290	90	3.7	–

MTX, high dose methotrexate; CTX, cyclophosphamide; IFO, ifosfamide; VP-16, etoposide; CDDP, cisplatin; ADM, doxorubicin; B, bleomycin; D, dactinomycin; VCR, vincristine.

Table 2 Menstrual activity before and after chemotherapy in 10 young girls with osteosarcoma

Patients	Age at diagnosis (y)	Tanner stage at diagnosis	Age at M2 (y)	Age at menarche (y)	Amenorrhoea at end of therapy	Duration of off-therapy amenorrhoea (y)	Irregular menses at end of therapy	Irregular menses at last follow up	Regular menses at last follow up	Highest FSH level recorded (IU/l)	Last FSH level recorded (IU/l)
Premenarcheal at diagnosis											
1	6.4	M1 P1	11.5	12.8					*	3.8	3.1
2	10.7	M1 P1	13.4	15				*		5.4	3.8
3	11.4	M2–3 P2	<11.4	12			*†		*†	132.0	5.5
4	11.8	M2 P1	<11.8	13.5					*	11.0	–
5	12.6	M1 P1	16.2(HRT)	16.7(HRT)				*†		14.9	4.6
Postmenarcheal at diagnosis											
6	13.1	M3 P3		<13			*		*	4.6	–
7	14.8	M4 P4		12	*†	1.0 (HRT)			*†(HRT)	51.2	9.3 (HRT)
8	15.1	M5 P5		11			*	*		4.6	3.8
9	15.2	M4 P4		11	*	0.3			*	7.8	2.9
10	15.3	M5 P5		13–14	*†	<1.0			*†	127.2	5.0

*Positive history for; †patients with hypergonadotrophic hypogonadism during follow up; HRT, on hormone replacement therapy.
Normal range for FSH in follicular phase, 1–12 IU/l.

Three girls were amenorrhoeic, and three had irregular menstrual cycles. The amenorrhoea has been transient in two patients, each for a total duration of less than a year after discontinuation of therapy. All originally prepubertal patients have experienced menarche, although one needed hormone replacement therapy (HRT) to support her pubertal development. At the last follow up, of the 10 patients, six had regular menstruations, while three had irregular menstrual cycles. One patient was still on HRT 1.5 years off chemotherapy (table 2).

During follow up, four patients have presented with clear hypergonadotrophism, as evidenced by high FSH levels (14.4–132 IU/l), high LH levels (13.7–49.8 IU/l), and non-measurable oestradiol levels (<0.02 nmol/l). Three of these four subjects have subsequently initiated menstruation and now have normalised gonadotrophin and oestradiol levels. The fourth remains on HRT (table 2). Three of the four patients with hypergonadotrophic hypogonadism represent those with the highest cumulative doses of ifosfamide (patients 3, 5, and 7; table 1).

DISCUSSION

We report a single centre study of ovarian function in 10 survivors of osteosarcoma treated during childhood or adolescence. Although this cohort was small, it does show the impact of intensive multi-agent chemotherapy on ovarian function. At discontinuation of chemotherapy, no girls had regular menstrual cycles, although five had been menstruating at time of diagnosis. An encouraging finding is that this disturbance seemed to be transient: at the last follow up, six of the 10 patients had regular menstrual cycles, and three had irregular ones. Normalisation of high gonadotrophin and low oestradiol levels heralded the new start of menstrual cycles.

Following cytotoxic chemotherapy, ovarian failure is not uncommon. Damage is strongly age and dose dependent. With increasing age, progressively smaller doses are required to induce permanent amenorrhoea. The incidence of ovarian dysfunction also varies according to the chemotherapy regimen applied.[10] High doses of alkylating agents such as cyclophosphamide are especially toxic to the ovaries.[11] Gonadal damage caused by cisplatin seems to be reversible,[12] but we are aware of no other reports on gonadotrophin and oestradiol levels in patients treated for osteosarcoma.

Age and pubertal/menarcheal status were important determinants for menstrual activity during chemotherapy. Those girls postmenarcheal at diagnosis seemed to suffer more extensive damage (table 2), than did those premenarcheal at diagnosis. Ovarian damage in prepuberty will in general result in delayed puberty and primary amenorrhoea. When ovarian failure occurs during or after pubertal maturation, arrested puberty, secondary amenorrhoea, and menopausal symptoms are often evident.[13] Younger patients generally continue with normal ovarian function after the cytotoxic insult, but they may undergo premature menopause.[14] In our series this may be documented with time.

A proportion of girls and women initially amenorrhoeic after treatment experience recovery of ovarian function.[10 15–18] Normal menstruation and fertility may return, even in cases with biochemical evidence of premature ovarian failure.[10 15] We have thus far no indicators that would allow us to identify this subgroup. In addition, the mechanisms underlying this recovery of ovarian function are unclear.

Reduction in the number of ovarian follicles and impaired follicular maturation occur in cancer patients independent of pubertal age. In addition, focal and diffuse cortical fibrosis appears in the ovaries after cessation of multi-agent chemotherapy, even when no radiotherapy has been applied to the pelvis.[19 20] Development of ovarian dysfunction over time correlates with the number of oocytes destroyed. Older patients have a smaller remaining pool of oocytes before cytotoxic treatment and are therefore more likely to become permanently amenorrhoeic. Damage to the germ cells leads both to the loss of endocrine function as well as to germ cell failure and infertility, because of structural and functional interdependence within the follicle between oocyte and the sex hormone producing granulosa and thecal cells. Likewise, toxic injury to the granulosa cells results in oestrogen insufficiency as well as in oocyte death. During intensive chemotherapy and resultant arrested follicle maturation, no negative feedback by ovarian sex steroids and inhibin on FSH and LH secretion occurs. After cytotoxic therapy, follicles sensitive to the increased FSH levels are recruited. Follicle maturation initiates sex hormone production, and FSH and LH levels return to normal. Our data indicate that after discontinuation of cytotoxic chemotherapy, the duration of this hypergonadotrophic window may range from less than one year to several years. Observations from longitudinal studies confirm the existence of this phenomenon.[16–18]

In female cancer survivors chemotherapy alone (even with alkylating agents) has shown no apparent effect on fertility.[21] This is also true for long term survivors of osteosarcoma,[22 23] but long term follow up is crucial for assessing the impact of chemotherapy treatment on their fertility.[24]

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