Prevention of irreversible chemotherapy-induced ovarian damage in young women with lymphoma by a gonadotrophin-releasing hormone agonist in parallel to chemotherapy*

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To examine whether the concomitant administration of a gonadotrophin-releasing hormone agonist (GnRHa) during combination chemotherapy to young women with lymphoma may facilitate preservation of gonadal function, a prospective clinical protocol was undertaken in 18 cycling women with lymphoma, aged 15–40 years. Thirteen patients suffered from Hodgkin disease (HD) and 5 from non-Hodgkin lymphoma. After informed consent a monthly injection of depot D-TRP⁶-GnRHa was administered for a maximum of 6 months starting prior to chemotherapy. Most of these patients (15/18) were treated with the MOPP/ABV(D) combination chemotherapy followed by mantle field irradiation in 10 patients. Hormonal profile [luteinizing hormone (LH), follicle stimulating hormone (FSH), oestradiol, testosterone, progesterone, insulin-like growth factor (IGF)-1, prolactin] was taken before the GnRHa/chemotherapy co-treatment, and monthly thereafter until resuming spontaneous ovulation and menses. This group of prospectively treated lymphoma patients was compared to a matched control group of 18 women (aged 17–40 years) who have been treated with chemotherapy, mostly MOPP/ABV (14/18), with (11) or without (7) mantle field radiotherapy. Fourteen had Hodgkin's and four non-Hodgkin's lymphoma. Gonadal function was determined clinically, hormonally (LH, FSH, oestradiol, progesterone), and sonographically. Two of the patients in each group died from refractory disease. Of the remaining 16 patients, 15 (93.7%) resumed spontaneous ovulation and menses within 3–8 months of termination of the combined chemotherapy/GnRHa co-treatment. In contrast, only seven (39%) of the 18 similarly treated patients in the control group (chemotherapy without GnRHa) resumed ovarian cyclic activity (regular menses). The other 11 experienced premature ovarian failure (POF) (61%). Our preliminary data suggest a possible significant protective effect of GnRHa

co-treatment with chemotherapy from irreversible ovarian damage (POF).
Key words: amenorrhea/chemotherapy/fertility/GnRHa/premature ovarian failure (POF)

Introduction

Hodgkin's disease is the most common malignancy in the population aged 15–24 years (Glaser, 1994). Prolonged survival is now expected for a high proportion of young patients treated with cytotoxic chemotherapy for advanced Hodgkin's and non-Hodgkin's lymphoma. This is due to the introduction of effective chemotherapy such as mechlorethamine, vincristine–oncovin, prednisolone, and procarbazine (MOPP) or adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) and its variants (De Vita *et al.*, 1970; Sherins, 1993).

Infertility represents one of the main long-term consequences of combination chemotherapy given for Hodgkin's disease, non-Hodgkin's lymphoma, and other malignancies (Muller and Stahel, 1993; Glaser, 1994). The impairment of gonadal function after chemotherapy is much more frequent in men than in women, occurring in up to 90% of postpubertal males (Johnson *et al.*, 1985). Since dividing cells are known to be more sensitive to the cytotoxic effects of alkylating agents than are cells at rest, it has been suggested that inhibition of the pituitary–gonadal axis would reduce the rate of spermatogenesis and oogenesis and thereby render the germinal epithelium less susceptible to the effects of chemotherapy (Sutcliffe, 1979; Johnson *et al.*, 1985; Sherins, 1993). The possibility of administering an adjuvant treatment that might limit the gonadal damage caused by an otherwise successful treatment programme is therefore attractive (Waxman *et al.*, 1987). Glode *et al.* (1981) tested this hypothesis using a murine model and concluded that an agonistic analogue of GnRH appeared to protect male mice from the gonadal damage normally produced by cyclophosphamide. It may be that decreased secretion of the pituitary gonadotrophins, by decreasing gonadal function, could protect against the sterilizing effects of chemotherapy.

Although previous suggestions were made (Glode *et al.*, 1981; Chapman and Sutcliffe, 1986; Krepart and Lotocki, 1986; Sherins, 1993), claiming that primordial germ cells fare better than germ cells that are part of an active cell cycle, this hypothesis has not been clinically tested. Despite encouraging preliminary results in experimental animals and humans, none of the previous approaches has been proved effective (Sherins, 1993). Whereas several investigators have demonstrated that

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GnRHa inhibit chemotherapy-induced ovarian follicular depletion induced by chemotherapy in the rat (Glode *et al.*, 1981), uncertainty remains that the same effects may not occur in humans and other primates. The latter species have lower concentrations of ovarian GnRH-receptors and may not necessarily exhibit the same response as rats. Ataya *et al.* (1994) have found that GnRHa protected the ovary against cyclophosphamide-induced damage in Rhesus monkeys, by significantly decreasing the total amount of follicles lost during the chemotherapeutic insult, and by decreasing the daily rate of follicular decline.

Based on this rationale, we have undertaken a prospective evaluation to determine whether GnRHa administration before and during combination chemotherapy for lymphomas could preserve post-treatment fertility in women by inducing a prepubertal hormonal state.

Materials and methods

A prospective clinical protocol was taken in 18 normally cycling women with either Hodgkin's (13) or non-Hodgkin's lymphoma (five), aged 15–40 years. Eligibility criteria included Hodgkin's disease or non-Hodgkin's lymphoma, regular cycles and normal gonadotrophins, age 15–40 years and no previous chemo- or radiotherapy. This protocol was approved by the Helsinki II committee for human experimentations of the Rambam Medical Center, and Israel's Ministry of Health. After informed consent, a monthly injection of 3.75 mg depot D-Trp^6-GnRHagonist (Decapeptyl CR Ferring, Malmo, Sweden) was administered i.m. in the early follicular phase of the menstrual cycle, starting 7–10 days before chemotherapy, until its conclusion, or for a maximum of 6 months. Two patients (non-Hodgkin's lymphoma) died, and two have been recently (within 6 months) out of the treatment protocol. Of the 16 who concluded the treatment protocol, 13 were treated with the MOPP, mechlorethamine (Mustargen Merck, Sharp & Dohme, Westpoint, PA, USA), Oncovin (vincristine: Abic, Netanya, Israel), prednisolone (Ultracorten H: Ciba-Geigy, M Jacobsohn, Tel-Aviv, Israel), procarbazine (Natulan: Roche, Devries Ltd, Tel-Aviv, Israel), and ABV(D), adriamycin (doxorubicin: Pharmacheme, Lapidot, Hertzlia, Israel), bleomycin (Lundbeck A/S, Lapidot, Hertzlia), vinblastin (Blastovin: Teva, Netanya) [with (1) or without (7) dacarbazine (Deticene: Roger-Bellon, Chimnter, Netanya, Israel)] combination regimen, and the remaining three with a similar combination CHOP, cyclophosphamide (Cytophosphan Taro, Haifa, Israel), adriamycin, vincristine, and prednisone (Rekah, Holon, Israel) (DeVita *et al.*, 1985). In the control group, 14 patients received the MOPP/ABV(D) chemotherapeutic combination, one was treated with CHOP, one woman received 'C (cyclophosphamide)–MOPP' and one ABV only (Table I).

Of the 16 patients in the study group, and the 18 patients in the control group, 13 and 11 respectively were also irradiated receiving 'mantle' radiotherapy (whereby the ovaries are outside the irradiated field).

Hormonal profile for follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol, testosterone, progesterone, insulin-like growth factor-1 (IGF-1), and prolactin was evaluated before starting the GnRHa/chemotherapy co-treatment, and monthly thereafter (for FSH, LH, oestradiol) until resuming spontaneous ovulation and menses, and at 3–6 month intervals until 36 months after chemotherapy. The hormonal measurements were performed using commercial radioimmunoassay kits as previously described (Blumenfeld *et al.*, 1992).

This group of prospectively treated lymphoma patients was compared to historical, consecutive matched control group of 18 regularly cycling women (aged 17–40 years) who had been treated in the same medical centre with a similar chemotherapeutic regimen, mostly MOPP (or C-MOPP)/ABV(D) (14/18), with (11) or without (7) mantle radiotherapy. The control group represented the 18 consecutive patients who were treated immediately prior to the initiation of the GnRHa/chemotherapy co-treatment, or in parallel, in cases who preferred not to join the study protocol. Fourteen women in this group suffered from Hodgkin's disease and the remaining four had non-Hodgkin's lymphoma. These 18 women who were similarly treated except for the GnRHa co-treatment, served as a historical control group, and were referred for evaluation of hormonal status and gonadal function at 10–80 months after completing chemotherapy (without GnRHa co-treatment). The two groups, the GnRHa/chemotherapy group (study group) and the chemotherapy without GnRHa co-treatment (control group) were compared for age, regularity of the menstrual cycle before, during, and after the chemotherapeutic regimen, number of menstrual days before treatment and afterwards, and period of time (months) from completion of chemotherapy to return of menstrual bleeding. The two groups were also compared for suggestive evidence of ovarian folliculogenesis and ovulation on ultrasonographic examination (transvaginal or abdominal), occurrence of amenorrhoea, and regularity or irregularity of the menstrual cycle after chemotherapy. Also, concentrations of FSH, LH, oestradiol, progesterone, and prolactin after chemotherapy, time from chemotherapy to hypergonadotrophic ovarian failure, number of chemotherapeutic courses, duration of chemotherapy, radiotherapy adjuvant treatment or not, duration of radiotherapy, and radiation dose were compared. Additional parameters for comparison were: recurrency, bone marrow transplantation and necessity of additional chemotherapy, splenectomy, treatment associated side effects (alopecia, rash, mucositis, sore throat, thyroid dysfunction, neutropenia, leukopenia, anaemia, thrombocytopenia, infection, arthralgia, hot flashes during and/or after treatment, vaginal dryness), and duration of remission.

All these data were computerized and a comparison between the study and control groups was performed using analysis of variance (ANOVA), Mann–Whitney test, Student's t-test, and SPSS computerized statistical analysis. Statistical significance was considered when $P < 0.05$.

Results

Of the 18 patients in the study group, two failed to achieve remission. Chemotherapy was therefore continued beyond 6 months, but they died from the disease. Of the remaining 16 women in the study group, 15 (93.7%) resumed spontaneous ovulation and menses within 3–8 months of termination of the GnRHa/chemotherapy co-treatment. The oldest patient in the study group, a 40 year old woman, experienced hypergonadotrophic amenorrhoea and ovarian failure, 4 months after treatment. In contrast, only seven of the 18 (39%) similarly treated patients in the control group (chemotherapy without GnRHa) resumed cyclic ovarian activity (regular menses) ($P < 0.05$, Table I). The other 11 (61%) experienced premature ovarian failure (POF) and were menopausal (Figure 1).

The median FSH concentration, 4–9 months after completion of the GnRHa/chemotherapy co-treatment group was 7.2 (mean $\pm$ SD: 12.5 $\pm$ 16.4) IU/l compared to 31.5 (36 $\pm$ 25.2) IU/l in the control group ($P = 0.003$), and the median LH concentrations 4.1 (mean $\pm$ SD: 5.9 $\pm$ 8.1) and

Table 1 Comparison of GnRHa/chemotherapy co-treated women and their controls

	GnRHa/chemotherapy n	Control 16	P 18
Mean age (years) ± SD (range)	23.4 ± 6 7 (15–40)	25 8 ± 7 8 (17–40)	NS
Median age (years)	20	23	NS
Hodgkin's disease	13	14	NS
Non-Hodgkin's lymphoma	3	4	NS
MOPP/ABV(D)	13/16	14/18	NS
Radiotherapy, no. of patients (%)	13/16 (81%)	11/18 (61%)	NS
Follow-up (years)			
Range	0 5–4	1.5–8	NS
Mean (±SD)	1 7 ± 1	7 ± 4 9	NS
Median	1.5	5	NS
POF[a]	1/16 (6 3%)	11/18 (61%)	<0.01

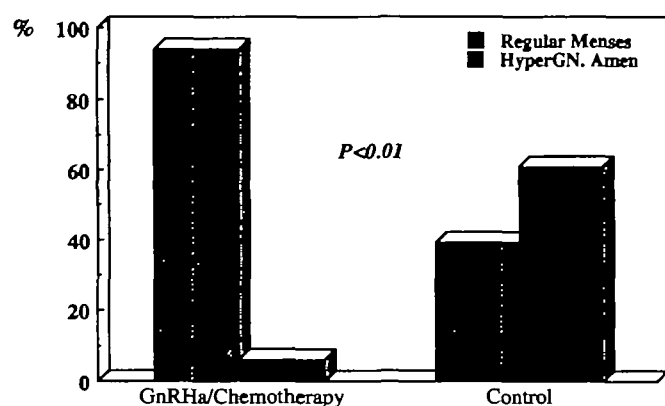[a]POF = Premature ovarian failure

Figure 1. Incidence of hypergonadotrophic amenorrhoea and premature ovarian failure (POF), versus regular cyclic ovarian activity in the GnRHa/chemotherapy co-treatment (study) group, as compared to the chemotherapy 'alone' (control) group.
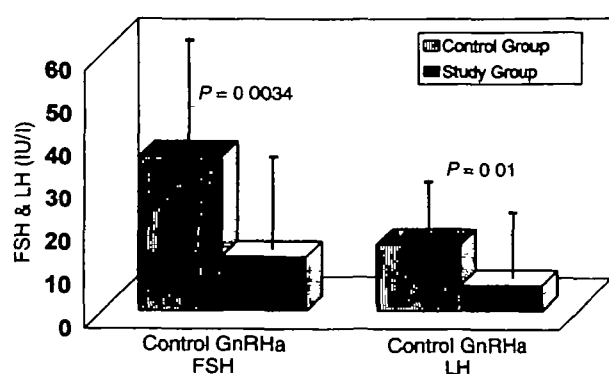

Figure 2. Mean ± SD concentrations of follicle stimulating hormone (FSH) and luteinizing hormone (LH) 4–9 months after completion of chemotherapy in the GnRHa/chemotherapy (study) group versus the control group

11.3 (15.4 ± 10.1) respectively (P = 0.01) (Figure 2). The median and mean (±SD) age of the patients in the study group was 20 (23.1 ± 6.7) years versus 23 (25.8 ± 7.8) in the control group (NS). The radiation dose per patient in the study group was 2320 ± 1521 centi-Grey versus 1882 ± 1983 centi-Grey in the control group (NS) (Table II). The mean dosage of the used chemotherapeutic agents which are most frequently associated with premature ovarian failure (Sherins, 1993),

cyclophosphamide and mechlorethamine were not statistically different between the two groups (Table II).

Only four out of 16 patients in the study group and 10 out of 18 in the control group received cyclophosphamide. The total dose of cyclophosphamide in these four patients in the study group ranged from 609 to 4500 mg/m^2, compared to a range of 531–14531 mg/m^2 in the study group. Neither the mean, nor the median and range of cyclophosphamide dosage between the two groups was statistically significant (P > 0.05; Mann–Whitney). All the four patients in the study group who received cyclophosphamide resumed ovarian menstrual function, whereas only four of the ten patients who received cyclophosphamide in the control group returned to ovulate, and six experienced POF. Due to the wide dose variability in cyclophosphamide administration we established dose intervals for cyclophosphamide (0, 0–1000, 1001–4000, ≥4001 mg/m^2) and determined the proportion of patients who experienced POF in each dose interval. In the patients who did not receive cyclophosphamide the POF rate was one out of 14 (7%) in the study group compared to five out of eight (62.5%) in the control group. In the cyclophosphamide dose interval of <1000 mg/m^2, the POF rate was none out of two in the study group versus one out of three (33%) in the control group. No patients in the study group received 1001–4000 mg/m^2 cyclophosphamide, whereas three out of four (75%) turned menopausal in the control group in this dose interval. Lastly, none of the two patients in the study group who received >4000 mg/m^2 cyclophosphamide was menopausal versus two out of three (66.6%) in this dose interval in the control group.

All but one of the 16 surviving patients in the study group experienced spontaneous menses, with mid-luteal progesterone concentrations compatible with ovulation, progesterone > 5 ng/ml (15.9 nmol/l). During the GnRHa/chemotherapy co-treatment the concentrations of LH, oestradiol, and progesterone decreased to almost prepubertal levels (Figure 3). However, within 1–3 months after the last GnRHa depot injection, an increase in LH and FSH concentrations was measured, followed by several weeks later in an increase in oestradiol and progesterone concentrations (Figure 3) to within normal levels. In three patients in the study group the FSH levels transiently increased to 20–43 IU/l on one examination at 2–6 months after the last GnRHa injection but returned to

Table II. Mean ± SD and median dosage of chemotherapeutic agents and radiotherapy dosage used in the control and study groups

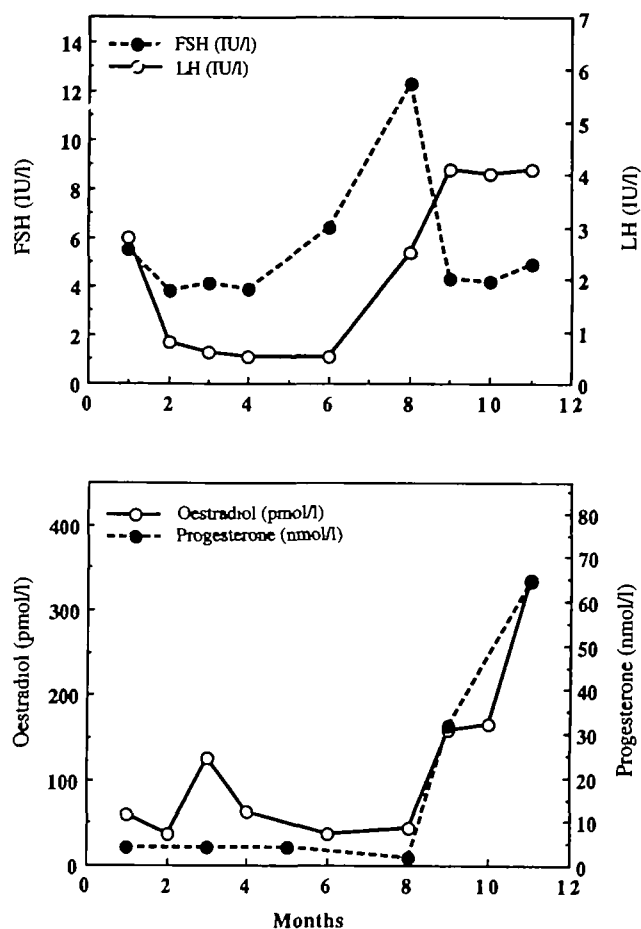| Dosage of chemotherapeutic agent (mg/m²)	Control group		Study group		P
	Mean ± SD	Median	Mean ± SD	Median	
Cyclophosphamide	2133 7 ± 3640	565.6	781.2 ± 1646	0	NS (0 18)
Mechlorethamine	25 5 ± 17.5	27 3	23 1 ± 12 1	27 8	NS (0 6)
Radiation dosage (centi-Grey)	1882 2 ± 1983	1300	2320 ± 1521	3060	NS (1)

Months

Figure 3. Concentrations of follicle stimulating hormone (FSH), luteinizing hormone (LH), oestradiol and progesterone before, during and after completion of the GnRHa/chemotherapeutic co-treatment in a representative patient in the study group. The co-treatment was administered from months 1–6

within normal levels (1–12 IU/l) thereafter, with normal LH, oestradiol, and progesterone concentrations, compatible with spontaneous ovulatory ovarian activity. Moreover, three of these 16 women conceived spontaneously four times, about 3–4 years after the co-treatment protocol, and were delivered of three healthy normal term neonates The fourth gestation was terminated due to social reasons

Transvaginal or abdominal sonographic examinations on the 16 surviving patients in the study group detected either one (or more) dominant ovarian follicle, of 16–25 mm diameter at midcycle, and/or presence of corpus luteum, in the luteal phase in all but the one woman who developed POF. Evidence for ovulation was achieved in only seven of the 18 women in the

control group (two conceived and in five hormonal, sonographic criteria or both were compatible with, or suggestive of, ovulation).

There was a significant correlation between the age at diagnosis and the probability to develop POF [$R = 0.47$; $P = 0.047$ (11/18 in the control group and 1/16 in the study group developed POF)]. However, no significant correlation was found between the occurrence of POF and the dosage of cyclophosphamide ($R = 0.138$; $P = 0.58$) or that of mechlorethamine ($R = 0.17$; $P = 0.5$), in our group of patients.

There were no significant changes in the levels of prolactin, testosterone, and IGF-1 during the GnRHa/chemotherapy co-treatment regarding baseline levels or post-treatment follow up, or significant differences in these hormone levels between the two groups.

Discussion

Advances in the treatment of all stages of Hodgkin's and non-Hodgkin's lymphoma with chemotherapy and irradiation have led to a long-term survival of more than 70% of patients (Longo, 1990; Kreuser et al., 1992). The improved long-term survival of relatively young patients treated for lymphoma, focused attention to the gonadal toxicity of the combined chemo- and radiotherapy. Many drugs used in the treatment of cancer have profound and lasting effects on gonadal function (Sherins, 1993). Both germ cell production and endocrine function may be affected, not infrequently in an irreversible manner. The magnitude of the effect varies with the drug class, the total dose administered, and the age and pubertal status of the patient at the time of therapy (Sherins, 1993). Drugs most frequently associated with ovarian failure are divided into three classes (Sherins, 1993) (1) those which definitely are associated with gonadal toxicity: cyclophosphamide, L-phenyl-alanine mustard, busulfan, and mitrogen mustard; (2) those which are unlikely to cause gonadal toxicity: methotrexate, 5-fluorouracyl, and 6-mercaptopurine, and (3) those drugs whose gonadal toxicity is unknown: doxorubicin, bleomycin, vinca alakloids (vincristine and vinblastin), cisplatin, nitrosoureas, and cytosine, arabinoside (Sherins, 1993) In one study (Koyama et al., 1977) amenorrhoea occurred after a mean cyclophosphamide dose of 5200 mg in all patients >40 years, whereas younger women experienced amenorrhoea only after a mean total dose of 9300 mg Furthermore, menstrual cyclicity returned within 6 months after cessation of chemotherapy in half of women under the age of 40 years (Koyama et al., 1977). Similar age-related phenomena have been noted after adjuvant chemotherapy with L-phenylalanine mustard (Fisher et al., 1979; Sherins, 1993).

Unlike the profound effects of MOPP combination chemotherapy on testicular function (Sherins, 1993), MOPP produces ovarian dysfunction and amenorrhoea in only 40–50% of treated women (Sherins *et al.*, 1975; Horning *et al*, 1981; Sherins, 1993). Whereas 86% of men had azoospermia after the COPP/ABVD regimen (Kreuser *et al.*, 1992), only 48–77% of women receiving chemotherapy for lymphoma exhibited hypergonadotrophic amenorrhoea and ovarian failure (Kreuser *et al.*, 1992). Moreover, a long-term follow-up of 240 children, 15 years of age or younger, treated by MOPP for Hodgkin's disease showed azoospermia in 83% of the boys, whereas only 13% of the girls suffered ovarian failure (Ortin *et al.*, 1990). The chances of maintaining gonadal function following combined modality treatment are significantly greater among girls than boys (Ortin *et al.*, 1990; Sherins, 1993) At variance with the results reported in adults, the MOPP chemotherapy in girls with Hodgkin's disease did not induce ovarian failure (Bakchine *et al.*, 1986). Since ovarian function was preserved in most long-term survivors who were treated prepubertally for lymphoma (Bakchine *et al.*, 1986; Ortin *et al.*, 1990), but only for a minority of similarly treated adult patients (Kreuser *et al.*, 1992), it is clinically logical and therefore tempting to create temporarily a prepubertal milieu in women in the reproductive age before and during the chemotherapeutic insult.

It has been reported that 64% of adult female patients undergoing cancer therapy experienced one or more of the symptoms of ovarian failure (Kreuser *et al.*, 1990). Whereas previous studies (Johnson *et al.*, 1985) suggested profound gonadal toxicity in men after adjuvant chemotherapy in patients with and without GnRHa protection, for malignant lymphoma (Johnson *et al.*, 1985; Sherins, 1993), the situation in females may be completely different. Ataya *et al.* (SGI abstract, 1994) have recently shown, in female Rhesus monkeys, that GnRHa may protect the ovary from cyclophosphamide induced gonadal damage. Administration of GnRHa in parallel to cyclophosphamide has significantly decreased the daily rate of follicular decline and the total number of follicles lost during the chemotherapeutic insult, as compared to cyclophosphamide alone (without GnRHa). This preliminary experience in Rhesus monkeys is in keeping with our clinical results, whereby only one 40 year old woman of the 16 surviving patients who completed the study protocol was menopausal after the GnRHa/ chemotherapy co-treatment (6.3%), as compared to a 61% (11/18) rate of POF in the chemotherapy without GnRHa (control) group.

Our preliminary experience is promising. Whereas 15 out of 16 (93.7%) of the survivors of the chemotherapy (with or without radiotherapy) who received the GnRHa co-treatment resumed ovulatory menses, only seven of the 18 women who were treated with chemotherapy with or without mantle irradiation had normal ovarian function and more than half of these women (11 out of 18; 61%) had premature ovarian failure (POF) and hypergonadotrophic amenorrhoea. This rate of POF is in keeping with the findings of previous publications (Kreuser *et al.*, 1992; Sherins, 1993). However, another GnRHa, buserelin failed to preserve fertility in all men and four of eight women treated with cytotoxic treatment for Hodgkin's disease (Waxman *et al.*, 1987). A possible explana-

tion to the differing results between this study (Waxman *et al.*, 1987) and ours, is the possibility that the pituitary–ovarian desensitization achieved by buserelin in Waxman *et al.*'s (1987) study was incomplete, thus the prepubertal milieu was not adequately imitated. In our study the hormonal profile during the GnRHa and chemotherapy was compatible with profound ovarian suppression, possibly explaining the different results. As opposed to young girls, since prepubertal boys receiving chemo- and radiotherapy suffered azoospermia, there is little rationale to expect a significant benefit from the GnRHa co-treatment in men (Bakchine *et al.*, 1986; Byrne *et al.*, 1987; Ortin *et al*, 1990). Contradictory to the apparent protective effect of GnRHa co-treatment with chemotherapy, no protection from ovarian damage caused by irradiation to rats could be provided by the agonist (Jarrell *et al.*, 1991).

The severity of gonadal toxicity after chemotherapy and irradiation depends on dosage levels and intervals, cytotoxic range, and age (Horning *et al.*, 1981; Kreuser *et al.*, 1990). Therefore, we have carefully compared the study and the control groups for each of these parameters. Neither the age, nor the dosages of the various cytotoxic drugs were significantly different between the two groups (Tables I, II, Figures 1, 2). The only significant difference was the incidence of POF and hypergonadotrophic amenorrhoea between the two groups (61 versus 6.3%; $P < 0.01$). However, one should be very cautious about drawing long term conclusions from these promising yet preliminary data, since the follow up in the study group was only 4 years as compared to up to 8 years in some of the patients in the control group. This difference is attributed to the nature of the control group (retrospective historical control) whereas the study protocol was a prospective one. Even though the follow-up in the control group is longer than in the study group, the observations within 4 years in both groups suggest that longer follow up will not significantly affect these results. Future prospective randomized studies will be needed unequivocally to resolve this problem, and we are currently starting such a prospective randomized protocol.

Two of our young patients, one in the study group, and one in the control group, out of three who have undergone high dose chemotherapy and autologous bone marrow transplantation, have turned subsequently menopausal. This is in keeping with recent experience that such intensification regimens carry a high risk of permanent infertility and POF (Nademanee *et al.*, 1992; Muller and Stahel, 1993). It has been well established that chemotherapy with total body irradiation followed by allogeneic or autologous bone marrow transplantation causes permanent elevation of gonadotrophin levels, hypo-oestrogenism, and amenorrhoea in 92–100% of female patients (Nademanee *et al.*, 1992; Muller and Stahel, 1993). Future endeavours are obviously needed to challenge the long term infertility problem of young women treated with chemotherapy.

If the protective effect observed in our preliminary study of GnRHa and chemotherapy on future ovarian function is persistent in larger and prospective randomized studies, it may become mandatory in the future to use this co-treatment protocol in every woman undergoing chemotherapy. Thus, ovarian protection may enable future fertility to survivors and prevent the bone demineralization and osteoporosis associated

with hypo-oestrogenism and ovarian failure (Kreuser *et al.*, 1992).

Adjuvant chemotherapy has been shown to significantly increase disease-free and overall survival of premenopausal women with operable breast cancer (Bianco *et al.*, 1991). However, Collichio and Pandya (1994) reviewed the literature and concluded that no benefits in terms of breast cancer disease-free survival were found in amenorrhoeic patients. Thus, the long term benefits of adjuvant chemotherapy in preventing recurrences in young women must be carefully weighed against the risk of premature menopause and the morbidity in terms of osteoporosis, heart disease, urogenital distrophy, vasomotor symptoms (hot flushes) and in general diminished quality of life due to chronic hypo-oestrogenism and premature ovarian failure in young survivors of breast carcinoma. Goldhirsch *et al* (1990) concluded that although cytotoxic-induced amenorrhoea is associated with a better outcome, it is unlikely that the endocrine manipulation is the main mechanism of response to adjuvant systemic chemotherapy. The future combination of GnRHa and adjuvant chemotherapy may possibly provide an answer to the above raised question. Moreover, this co-treatment may possibly combine the advantage of increased survival associated with adjuvant therapy, and the possibility of a return of ovarian function after a temporary and reversible pituitary–ovarian desensitization, thus preventing the long term morbidity of premature ovarian failure. Further experience is obviously needed to resolve these practical unanswered questions. Another practical problem in the therapeutic modalities of young women with breast cancer is their possible hyper-response to tamoxifen by supraphysiological doses of oestrogen and ovarian cysts formation (Shulman *et al*, 1994). Tamoxifen is being increasingly used among women with positive oestrogen receptors, but the ovarian hyper-response may limit its practice. The combination of tamoxifen and GnRHa in such premenopausal women may offer a practical resolution as preliminary shown by Shulman *et al.* (1994) in a preliminary study.

Future endeavours may use GnRH antagonists instead of agonists for achievement of more rapid pituitary–ovarian desensitization, eliminating the waiting period of 7–14 days needed by the GnRHa to achieve down-regulation (Linde *et al.*, 1981). Moreover, since almost one quarter of young women with systemic lupus erythematosus in the reproductive age may develop premature ovarian failure after cyclophosphamide pulses (Langevitz *et al.*, 1992), the GnRHa co-treatment may possibly be offered to these young women in parallel to the cytotoxic treatment.

Acknowledgement

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