Effect of a Luteinizing Hormone Releasing Hormone Agonist Given During Combination Chemotherapy on Posttherapy Fertility in Male Patients With Lymphoma: Preliminary Observations

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Six men undergoing potentially curative chemotherapy for advanced lymphomas received daily injections (50 μg) of an analogue of luteinizing hormone releasing hormone (LH-RHa) in an attempt to protect posttreatment gonadal function. The median duration of combined LH-RHa–chemotherapy administration was 25 weeks (range, 14 to 31 weeks). During the simultaneous administration of LH-RHAs and chemotherapy, plasma testosterone levels decreased to subnormal levels, while both follicle-stimulating hormone (FSH) and luteinizing hormone levels declined to the lower limit of normal. All subjects became oligospermic or azoospermic within eight weeks of starting treatment. Following discontinuation of chemotherapy and LH-RHAs, both plasma testosterone and LH promptly increased to a level well above the normal range. FSH progressively increased to a level well above the normal range. Only one patient has recovered evidence of active spermatogenesis at 84 weeks postcessation of chemotherapy. No untoward side effects due to LH-RHAs were experienced. Although LH-RHAs can be administered safely during combination chemotherapy, no improvement in posttreatment fertility has yet been demonstrated.

INFERTILITY represents one of the main long-term consequences of combination chemotherapy given for Hodgkin's disease. The impairment of gonadal function is much more frequent in men than in women, occurring in up to 90% of postpubertal males. 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 thereby render the germinal epithelium less susceptible to the effects of chemotherapy. Glode et al tested this hypothesis using a murine model and concluded that an analogue of luteinizing hormone releasing hormone (LH-RH), D-Leu₄-des-Gly-NH₂-pro-ethylamide GnRH, appeared to protect male mice from the gonadal damage normally produced by cyclophosphamide. Recently, Linde et al demonstrated that another LH-RH analogue, D-Trp⁵-Pro⁸-N-ethylamide-LHRH (LH-RHa), could safely and reversibly inhibit spermogenesis in normal adult males. Based on these reports, we undertook a prospective evaluation to determine if LH-RHa could preserve posttreatment fertility in men. Our preliminary results are reported here.

MATERIALS AND METHODS

Six men with advanced-stage lymphomas (five with Hodgkin's disease, one with a lymphoblastic lymphoma) agreed to participate in this study. Patient characteristics, treatment regimens, and response to treatment are given in Table I. All six men had experienced normal sexual development and were known to be sexually active prior to chemotherapy. No patient had fathered a child. Each patient considered his libido and frequency of sexual intercourse to be normal.

Patients were seen within 48 hours of diagnosis, at which time baseline levels of testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were obtained. All blood samples were collected in the morning; three specimens were obtained from each patient at 20-minute intervals and pooled for hormone determinations. Semen samples were collected via masturbation into sterile plastic cups and transported promptly to the laboratory for evaluation. At least two baseline semen samples were obtained from each patient at 48-hour intervals. Sperm motility ranged from 40% to 80% (median, 75%), and all but one patient had fewer than 5% abnormal forms.

Following collection of semen samples, patients were started on LH-RHa 50 μg/d subcutaneously for as long before the institution of chemotherapy as was considered safe by each patient's attending physician (median, five days; range, three to ten days). This dose was previously shown to reversibly inhibit spermatogenesis. LH-RHa was continued throughout the course of chemotherapy (and radiotherapy, when given) and for at least one week following the completion of treatment. Median duration of LH-RHa administration was 25 weeks (range, 14 to 31 weeks). During chemotherapy, blood samples for hormone determinations were obtained at least at every other clinic visit (ie, every four to eight weeks). An attempt was made to obtain semen samples at each clinic visit; however, due to LH-RHa–induced impotency, some patients were unable to provide semen samples at each visit. All patients with Hodgkin's disease received mechlorethamine/Oncovin/procarbazine/prednisone (MOPP) chemotherapy with or without radiotherapy. No patient received a toxic gonadal dose of irradiation. The Hodgkin's patients received the following mean (± SD) cumulative doses of...
cytotoxic agents: nitrogen mustard, 79.6 ± 26.9 mg (range, 55.0 to 112.5 mg); procarbazine, 7.6 ± 1.4 g (range, 6.3 to 10.0 g); vincristine, 17.4 ± 6.5 mg (range, 12.0 to 24.9 mg); and prednisone, 1,484.0 ± 573.8 mg (range, 980 to 2,240 mg). One patient with a lymphoblastic lymphoma received two cycles of an investigational chemotherapy regimen, consisting of high-dose cyclophosphamide (3 g/m²), cycosine arabinoside (100 mg/m²), methotrexate (200 mg/m²), and prednisone (40 mg/m²) followed by four cycles of cyclophosphamide, doxorubicin, Oncovin, and prednisone (CHOP) chemotherapy.

Total cumulative doses of these agents included one, 4.7 determinations. Mean hormone values for these men were: testosterone, 1.5 ng/mL; FSH, 5.7 ± 3.7 mIU/mL; LH, 10.6 ± 4.4 mIU/mL (mean ± SD).

The protocol was reviewed and approved by the Committee for the Protection of Human Subjects of Vanderbilt University. All study participants gave their written informed consent. LH-RHa was obtained.

RESULTS

Pretreatment Plasma Hormones and Semen Analyses

All six subjects had a normal pretreatment plasma testosterone level (mean, 3.9 ± 2.2 ng/mL; range, 1.8 to 7.5 ng/mL) (P > .5), although two men had values at the lower limit of normal. Likewise, pretreatment FSH levels were normal in all six patients (mean, 5.5 ± 1.3 mIU/mL; range, 4.5 to 8.0 mIU/mL) (P > .5). Three men had an elevated pretreatment LH level; the remaining three subjects had values within the normal range (mean, 16.3 ± 10.3 mIU/mL; range, 5.5 to 35.0 mIU/mL) (P > .5). Pretreatment sperm counts varied considerably with one patient (No. 5) having counts consistently in the subfertile range (ie, <20.0 × 10⁶ sperm/mL seminal fluid). The mean pretreatment sperm count was 185.6 ± 119.6 × 10⁶/mL (range, 1.5 × 10⁶ to 322.0 × 10⁶/mL) (Table 2).
mean FSH level has subsequently declined but remains above the normal range even one year after stopping LH-RHa (mean, 15.7 ± 2.9 mIU/mL; Fig 2) \( (P < .05) \).

Five of six patients (83%) are azoospermic at a median follow-up of 52.5 weeks (range, 35 to 84 weeks) after LH-RHa. One patient (No. 2) has recently regained evidence of active spermatogenesis 84 weeks after stopping treatment (Table 3), although both his FSH and LH levels remain elevated (14.0 mIU/mL and 19.0 mIU/mL, respectively) with normal plasma testosterone (5.3 ng/mL).

Side effects attributable to LH-RHa were minimal. Five men (83%) complained of impotence usually within eight weeks of starting LH-RHa. However, all had recovered normal libido and sexual function within four weeks of completing LH-RHa treatment. Only one patient (17%) complained of local irritation at the site of LH-RHa injection. Giode et al.9 conjectured that the concomitant administration of LH-RHa with chemotherapy might increase myelosuppression. However, none of our patients required hospitalization for leukopenia and fever or hemorrhage due to thrombocytopenia. Only one patient (No. 5) required any chemotherapy dose reductions and all achieved a complete remission.

**DISCUSSION**

Because a substantial percentage of patients with advanced Hodgkin’s disease can be expected to be cured with chemotherapy and since a majority of such

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Numbers in parentheses represent the week after completing LH-RHa and time of most recent evaluation.
patients are young, concern about posttreatment fecundity has increased.6,15 Despite recent optimistic reports regarding preservation of fertility in women with Hodgkin's disease,16 the outlook for male patients remains dismal.2,7 Several investigators have suggested that inhibition of spermatogenesis during exposure to cytotoxic drugs might reduce or even eliminate treatment-induced gonadal injury in men.3,8,17 Although the initial work of Glode et al appeared to support this hypothesis, a follow-up report indicated that there was no ultimate difference in the fertility between the LH-RH protected and unprotected groups of mice,8 presumably because neither gonadotropins nor testicular steroids are lowered in the mouse with chronic LH-RH administration.19 Nevertheless, because previous work at our institution had indicated that LH-RHa would safely and reversibly inhibit spermatogenesis (and steroidogenesis) in normal males, we attempted to protect gonadal function in male lymphoma patients undergoing potentially curative chemotherapy by administering this LH-RHa analogue before and during treatment. Although LH-RHa is a potent agonist of acute gonadotropin secretion, its biologic effects in humans10 and beagle dogs20 change with continued administration. Stimulation of LH and FSH secretion with an initial treatment dose is rapidly lost with continued use, a process termed pituitary “down-regulation” or “desensitization.” Chronic intermittent agonist administration to normal men results in a dramatic decline in testosterone production within one month and in sperm production within seven to 18 weeks.10 Chronic continuous therapy provides similar results.21 Since long-term treatment results in impotence, testosterone has been added to LH-RHa therapy with a delayed decrease in spermatogenesis but with preservation of normal sexual function.21,22

Consistent with earlier reports,10,23 the continuous administration of LH-RHa produced a prompt and persistent decline of plasma testosterone levels. Chapman et al.5 previously found that plasma testosterone levels usually remain unaffected by chemotherapy given for Hodgkin's disease. Both FSH and LH levels declined during LH-RHa administration, whereas the levels usually increase rapidly with the institution of chemotherapy alone.5 These alterations in plasma testosterone and gonadotropins closely resemble the hormonal changes seen in normal men given LH-RHa.10

All patients became oligospermic or azoospermic following institution of combined treatment with LH-RHa plus chemotherapy, usually within eight weeks. Normal men given LH-RHa experienced sperm count nadirs between the seventh and 18th week of treatment.10 The rapidity of development of low sperm counts in our patients compared with normal subjects suggests that chemotherapy plays a significant role in the onset of oligospermia.

Although these data indicate that our patients received an effective dose of LH-RHa, only one patient (17%) has recovered evidence of active spermatogenesis. This is in stark contrast to previous findings in normal men who usually recovered active spermatogenesis within ten weeks of stopping LH-RHa.10 Also, the single patient with evidence of return of spermatogenesis has been off chemotherapy longer than any other subject (84 weeks). Perhaps even more importantly, the changes in plasma testosterone and gonadotropin levels noted in our patients following discontinuation of LH-RHa closely resemble the changes in hormone levels seen in chemotherapy-treated male Hodgkin’s disease patients3,4,6,7 as opposed to LH-RHa-treated normal men.10 Thus, our data suggest that although LH-RHa administration can effectively suppress the pituitary-gonadal axis during chemotherapy, gonadal injury is not prevented when administered as outlined in our study.

Several reasons might be given for the failure of LH-RHa administration to preserve postchemotherapy fertility. The dose of LH-RHa administered may have been insufficient to completely inhibit spermatogenesis, and studies using substantially larger doses would be valuable. However, doubling the dose of LH-RHa has not resulted in a more complete inhibition of spermatogenesis in normal men24 nor has adding testosterone to various LH-RH analogues in rhesus monkeys,25 beagle dogs,20 or normal men22 improved the completeness of gonadal suppression. More importantly, the length of LH-RHa administration prior to beginning chemotherapy was insufficient to allow for complete arrest of spermatogenesis. A longer duration of LH-RHa treatment prior to institution of cytotoxic therapy might affect greater protection of gonadal function. However, return of normal spermatogenesis has not occurred in dogs adequately pretreated with an LH-RH agonist and subsequently given combined chemotherapy and agonist.26 Also, due to the nature of the illness, it is unlikely that longer postponement of potentially curative therapy would be endured by patients (or their physicians) whose primary concern remains eradication of disease and not preservation of fertility. Treatment with an LH-RH antagonist might conceivably provide a greater protective effect since this class of agents has a more rapid onset of action and more potent gonadal suppression. Because plasma testosterone levels remained depressed throughout therapy in all patients with a single exception (patient No. 1, week 10 LH-RHa), we do not believe patient noncompliance contributed to the failure, although
this remains a possibility. Last, the potency of LH-RHa could have been inadequate, although the rapid and persistent fall in testosterone levels in all our patients makes this improbable.

Based on these findings it is not yet evident that the concurrent administration of LH-RHa during combination chemotherapy for advanced lymphomas (at least as outlined above) will affect a substantial improvement in recovery of posttreatment fertility. However, due to the small number of patients studied thus far, we cannot exclude the possibility that a small but significant benefit might be realized if a larger patient population were evaluated. Also, longer follow-up of these patients may reveal an increased although delayed recovery of posttreatment spermatogenesis. Future trials should include an evaluation of LH-RH antagonists.

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REFERENCES

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