Luteinizing Hormone-Releasing Hormone Agonist Triptorelin in Combination with Cytotoxic Chemotherapy in Patients with Advanced Ovarian Carcinoma

A Prospective Double Blind Randomized Trial

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BACKGROUND. Several lines of evidence suggest that the proliferation of ovarian carcinoma might be stimulated by gonadotrophins. A number of Phase I/Phase II clinical trials have reported that the suppression of endogenous luteinizing hormone and follicle-stimulating hormone secretion by luteinizing hormone-releasing hormone (LHRH) analogs induced objective remissions and/or disease stabilization in 10–30% of patients with advanced refractory ovarian carcinoma. The current study was performed to evaluate whether the addition of LHRH agonist treatment to standard platinum-based chemotherapy could prolong survival of patients with surgically treated Stage III or IV epithelial ovarian carcinoma.

METHODS. One hundred and thirty-five patients with Stage III or IV epithelial ovarian carcinoma participated in this prospective randomized double blind trial. After cytoreductive surgery, 69 patients received monthly injections of a depot preparation of the LHRH agonist [D-Trp^6] LHRH (triptorelin, 3.75 mg) and 66 patients received placebo until their deaths or termination of the trial, respectively. All patients were treated with a standard platinum-based chemotherapy, and, if necessary, with second- or third-line cytotoxic regimens.

RESULTS. Endogenous gonadotrophins were reliably suppressed in patients treated with triptorelin. However, their progression free and overall survival were not significantly different from that of patients receiving placebo injections (statistical power $> 80\%$ for a difference between both groups of $\geq 20\%$).

CONCLUSIONS. The results of this trial suggest that the suppression of endogenous gonadotrophins by conventional doses of an LHRH agonist produces no relevant beneficial effects in patients with advanced ovarian carcinoma who receive standard surgical cytoreduction and cytotoxic chemotherapy. ***Cancer* 1996; 78:1452–60.**

KEYWORDS: ovarian cancer, luteinizing hormone-releasing hormone agonist, suppression of gonadotrophins, cytoreductive surgery, cytotoxic chemotherapy.

Cytoreductive surgery in combination with platinum-based chemotherapy has produced a substantial clinical improvement in patients with advanced ovarian carcinoma, yielding high response rates (up to 80%) and increased short and medium term survival.[1–5] How-

The design and brief summaries of interim analyses of this trial were presented at the First International Symposium on GnRH Analogues in Cancer and Human Reproduction, Geneva, Switzerland, February, 18–20, 1988; the Second International Symposium on Hormonal Manipulation of Cancer: Peptides, Growth Factors and New (Anti) Steroidal Agents, Rotterdam, The Netherlands, April 9–11, 1990; the 15th International Cancer Congress, Hamburg, Germany, August 16–22, 1990; the Second International Symposium on GnRH Analogues in

ever, most patients eventually relapse and ultimately die of chemoresistant disease.[1,3–5] Though surgery followed by chemotherapy might increase long term survival in some favorable subgroups,[6] the overall effects on survival have been poor.[1,4] Chemotherapy regimens for ovarian carcinoma patients have shown acute toxicity. In addition, long term sequelae, such as secondary leukemia or myelodysplasia, must be considered.[7–9] Endocrine therapies, based on antiestrogens, progestagens, combinations of estrogens and progestagens, or androgens, have demonstrated either only marginal efficacy against ovarian cancer or none at all.[1,10]

Based on epidemiological and experimental data, it has been suggested that the growth of ovarian carcinoma might be stimulated by endogenous gonadotrophins (for a review, see 11 in References). According to studies by Mortel et al. and Peterson and Zimniski,

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The design and interim results of this trial have been mentioned in the following reviews: Emons G, Pahwa GS, Sturm R, Knuppen R, Oberheuser F. The use of GnRH analogues in ovarian cancer. In: Vickery BH, Lunenfeld B, editors. GnRH analogues in cancer and human reproduction. Volume III. Dordrecht, The Netherlands; Kluwer, 1990: 159–70; Emons G, Pahwa GS, Ortmann O, Knuppen R, Oberheuser F, Schulz K-D. LHRH receptors and LHRH-agonist treatment in ovarian cancer: an overview. *J Steroid Biochem Mol Biol* 1990; 37:1003–6; Emons G, Pahwa GS, Ortmann O, Fassl H, Löhrs U, Schulz K-D, Oberheuser F. GnRH analogues and ovarian cancer. In: Lunenfeld B, editor. GnRH analogues and cancer. Volume 4. Carnforth: Parthenon, 1991:65–8; Emons G, Ortmann, O, Pahwa GS, Oberheuser F, Schulz K-D. LHRH agonists in the treatment of ovarian cancer. In: Höffken K, editor. Peptides in Oncology I, LHRH agonists and antagonists. Berlin: Springer, 1992:55–68; Emons G, Ortmann O, Pahwa GS, Hackenberg R, Oberheuser F, Schulz K-D. Intracellular actions of gonadotropic and peptide hormones and the therapeutic value of GnRH-agonists in ovarian cancer. *Acta Obstet Gynecol Scand* 1992;71 (Suppl 155):31–8; Emons G, Ortmann O, Pahwa GS, Oberheuser F, Schulz K-D. Treatment of ovarian cancer with GnRH-analogues. In: Emons G, Ghraf R, Schulz K-D, editors. GnRH and its analogues in gynecological oncology. Hamburg: Hansischer Medizinischer Verlag, 1992:57–72; Emons G, Schally AV. The use of luteinizing hormone releasing hormone agonists and antagonists in gynecological cancers. *Hum Reprod* 1994;9:1364–79; Emons G, Schulz K-D. New developments in the treatment of endometrial and ovarian cancer. In: Jonat W, Kaufmann M, Munk K, editors. Hormone dependent tumors: basic research and clinical studies. Contrib. Oncol., Basel: Karger, 1995: 272–98; Emons G, Ortmann O, Irmer G, Müller V, Schulz K-D, Schally AV. Treatment of ovarian cancer with LH-RH antagonists. In: Filicori M, Flamigni C, editors. Treatment with GnRH analogs: controversies and perspectives. Carnforth: Parthenon, 1996: 165–72; Emons G, Schulz K-D. Growth regulation of epithelial ovarian cancer by hormones, peptide growth factors, and cytokines. In: Pasqualini JR, Katzenellenbogen BS, editors. Hormone dependent cancer. New York: Marcel Dekker, 1996: 509–40.

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the growth of several human epithelial ovarian cancer cell lines transplanted into nude mice could be reduced by agonists of luteinizing hormone-releasing hormone (LHRH), which induce a suppression of endogenous gonadotrophins.[12,13]

In 1985, Parmar et al. reported on a patient with advanced ovarian carcinoma who relapsed after surgery, chemotherapy, and radiotherapy and was then treated with the LHRH agonist triptorelin. Concomitantly with the suppression of gonadotrophins, there was a marked shrinkage of the tumor mass, which lasted for 12 months.[14] A subsequent series of Phase II trials by several groups showed that LHRH agonist treatment of patients with refractory advanced ovarian carcinoma led to 12% objective remissions (21 of 171 evaluable patients) and stable disease in 19% of patients (32 of 171). The duration of responses varied between 26 and 98 weeks.[15–23]

The objective of the current study was to determine whether the suppression of endogenous gonadotrophins by an LHRH agonist combined with standard platinum-based chemotherapy could prolong survival of patients with surgically treated Stage III or IV ovarian carcinoma who had not received prior chemotherapy.

MATERIALS AND METHODS

Patients and Randomization Procedure

One hundred and thirty-five patients were selected for this trial between October 1987 and March 1994 in the "collaborative trial" institutions listed in the footnotes. To be considered eligible, patients required a histological diagnosis of Stage III or IV ovarian carcinoma (According to stages determined by the International Federation of Gynecology and Obstetrics, or FIGO). Within two weeks before the initiation of systemic treatment, patients received (at the discretion of the clinical investigator) standard debulking surgery aimed at maximal cytoreduction, where feasible. Performance status, hematological, and renal function had to be adequate to allow a first-line chemotherapy containing at least 50 mg/m^2 of cisplatin or an equivalent dose of carboplatin. Exclusion criteria for patients included previous or concomitant malignancy (except carcinoma in situ of the cervix or basal cell carcinoma), additional endocrine and radiotherapy, or prior chemotherapy. Final eligibility was dependent on a central review of pathology materials by the study pathologist (U.L.) and of surgical reports by the central study committee (G.E., O.O., H.F., U.L., S.K., A.K., D.A., F.O.).

Randomization was performed in blocks of 4 for each participating center, allocating 2 patients each to the LHRH agonist (triptorelin) group and the placebo group by using the method of random permutations with fixed block size.

Chemotherapy

All patients received a first-line chemotherapy consisting of at least 50 mg/m^2 of cisplatin or 300 mg/m^2 of carboplatin per cycle, which had to be initiated within 2 weeks after primary surgery (for details, see Table 1). Upon progression, second- or third-line chemotherapies were applied at the discretion of the clinical investigator. For salvage therapy, the following drugs were used either as single agents or in combination chemotherapy: cisplatin, carboplatin, hexamethylmelamine, cyclophosphamide, doxorubicin, epirubicin, mitoxantrone, treosulfane, etoposide, ifosfamide, 5-fluorouracil, methotrexate, and paclitaxel. The different regimens were evenly distributed between the triptorelin and placebo groups.

Treatment with Triptorelin or Placebo

Treatment with triptorelin was started within 14 days after cytoreductive/diagnostic surgery and consisted of 7 daily subcutaneous injections of 500 μg of the peptide (Decapeptyl® 0.5 mg) and an i.m. injection of 3.75 mg of microencapsulated triptorelin (Decapeptyl Depot®) on day 8. The injections of Decapeptyl Depot® were repeated at 28-day intervals until the patients' deaths or the end of the trial. Patients in the placebo group received seven daily subcutaneous injections of saline and thereafter i.m. injections of peptide-free poly (DL lactide-co-glycolide) microcarrier suspension, according to the same time schedule described above. The appearance of placebo formulations was identical to those of the respective triptorelin preparations, and neither the patient nor the clinical investigator were informed as to whether the respective patient belonged to the triptorelin or the placebo group. Disclosure of the double blind code was possible whenever necessary at the discretion of the clinical investigator, who could open a sealed envelope and thereby terminate the trial for a particular patient. The study protocol was approved by the Ethics Committee of the Medical University of Lübeck, Germany, and, when necessary, by the local ethics committees of the participating centers. Each patient was thoroughly informed about the trial, including randomization and double blind design. Consent was obtained from each patient before entry into the study, according to the institutional guidelines and national regulations of the centers participating in the study.

Patient Follow-Up

Patients reported at 28-day intervals for injections of Decapeptyl Depot® or placebo. Before each injection,

TABLE 1
Patient Characteristics

Parameters	No. of patients		
	Triptorelin	Placebo	Total
FIGO Stage III	57	54	111
FIGO Stage IV	12	12	24
Histology			
Serous	59	57	116
Endometrioid	2	2	4
Mucinous	4	4	8
Clear cell	1	0	1
Undifferentiated unclassified	3	3	6
Tumor grade			
1	8	9	17
2	17	15	32
3	44	42	86
Residual tumor after primary surgery			
No residual tumor	11	8	19
≤2 cm (including patients without residual tumor)	37	41	78
>2 cm	32	25	57
Age			
≤44 years	5	7	12
45-54 years	17	13	30
55-64 years	23	24	47
65-74 years	22	18	40
>75 years	2	4	6
Menopausal status			
Premenopausal	12	8	20
Postmenopausal	57	58	115
Karnofski Index ($\bar{x}$ ± SE)	8.6 ± 1.3	8.8 ± 1.3	
First line CHT			
Cisplatin/ cyclophosphamide	43	34	77
Cisplatin/epirubicin	6	9	15
Cisplatin/melphalan	9	8	17
Cisplatin/treosulfan	4	4	8
Cisplatin/epirubicin/ cyclophosphamide	3	5	8
Carboplatin/ cyclophosphamide	4	6	10
Mean dose per patient of first line CHT [mg] ($\bar{x}$ ± SE)			
Cisplatin	714 ± 129; n = 65	794 ± 191; n = 60	
Cyclophosphamide	6426 ± 640; n = 47	7097 ± 668; n = 41	
Epirubicin	743 ± 73; n = 9	587 ± 72; n = 13	
Melphalan	135 ± 18; n = 9	128 ± 32; n = 8	
Treosulfan	7500 ± 2250; n = 4	26162 ± 4367; n = 4	
Carboplatin	5690 ± 2090; n = 4	2138 ± 838; n = 6	

FIGO: International Federation of Gynecology and Obstetrics; SE: standard error; n: no. of patients.

a blood sample was drawn for the determination of luteinizing hormone (LH), follicle-stimulating hormone (FSH), CA 125, and standard toxicology parameters (hemogram, renal, and liver function tests). A physical examination that included a pelvic examination was performed at 4-week intervals during the first year of treatment, and every 3 months during the following years. Additional diagnostic procedures (abdominal and pelvic sonography, chest X-ray, and CT-scans of abdomen and pelvis) were performed every 3 months (sonography) or every 6 months (CT) during the first year and every 6 months thereafter, or ad hoc if a relapse was suspected clinically. Second-look procedures were not part of the protocol. In case they were performed, their results were registered. In addition to the tests mentioned above, standard assessments of toxicity of chemotherapy (audiograms, neurological status, and cardiac function) were performed according to the institutional guidelines of the participating centers.

Radioimmunoassays

In order to keep the double blind design of the trial, determinations of LH and FSH serum levels were performed centrally (from 1987 to 1989 at the Endocrine Laboratory of the Department of Obstetrics and Gynecology, University of Lübeck, under the supervision of G.E. and thereafter at the Endocrine Laboratory of the Department of Obstetrics and Gynecology, Philipps University, under the supervision of G. Sturm). The results for individual patients were not reported to their respective clinical investigators. In addition, CA 125 levels were centrally determined in the serum samples at the above institutions. LH was measured with the LH-MAIA-clone system (Serono, Freiburg, Germany), using the first IRP 68/40 standard (lower limit of detection 0.2 mIU/ml, intraassay CV $< 5\%$, interassay CV $< 9\%$). FSH levels were determined with the FSH-MAIA clone system (Serono) using the first IRP 78/549 standard (lower limit of detection 0.3 mIU/ml, intraassay CV $< 5\%$, interassay CV $< 8\%$). CA 125 concentrations were measured with the Centocor CA-125 II radioimmunoassay (ID-CIS-Isotopendiagnostik, Dreieich, Germany) (lower limit of detection 2 U/ml, intraassay CV $< 9\%$, interassay CV $< 12\%$).

Statistics

The duration of patients' survival and the time to disease progression were calculated from the start of triptorelin/placebo treatment. All eligible patients who received at least one injection of either Decapeptyl Depot® or placebo were included in the analyses. Progression was defined as a 25% or greater increase of measurable tumor size or the appearance of new le-

sions. As response rates were not the subject of the current study trial, they were not analyzed. The definition and assessment of complete or partial remissions and of stable disease were therefore left at the discretion of the participating clinical investigators. Only progressive disease was explicitly defined, as described above. Curves for progression-free and overall survival were calculated using life table analyses.[24] Survival experiences were compared using the Lee-Desu statistics.[25] For all calculations, SPSS statistical software (SPSS Inc., Chicago, IL) was used.

RESULTS

Sixty-nine patients were randomized for treatment with triptorelin, and 66 received placebo. As detailed in Table 1, our randomization procedure resulted in a homogenous distribution of patients within parameters that might have been relevant to prognosis, including FIGO stage, histological type and grade of tumor, extent of surgery, age, menopausal status, performance status, and type and dose of first-line chemotherapy. As previously stated, a wide variety of salvage chemotherapies were used, but their distribution between the triptorelin and placebo groups was also balanced. No toxicity was reported that might have been related to triptorelin or placebo treatment. No differences in toxicities related to standard chemotherapies were observed between the two groups of patients. Nine patients from the triptorelin group and 16 patients from the placebo group could not be followed until the completion of the trial, due to their unwillingness to report at monthly intervals. Most of these patients had already undergone long observation periods ($\bar{X} \pm$ standard error = 15.4 ± 2.2 months in the placebo group and 16 ± 2.8 months in the triptorelin group). These patients were censored on the date of their last follow-up visit.

In patients receiving the LHRH analog, LH and FSH levels were reliably suppressed, whereas patients receiving placebo injections had elevated serum gonadotrophin concentrations characteristic for the postmenopausal/postovariectomy situation (Fig. 1).

No significant difference in overall survival could be observed between the patients receiving triptorelin and those receiving placebo (Fig. 2). The statistical likelihood for the detection of a difference in overall survival between the two groups of >20% after two years, calculated according to Lachin,[26] was greater than 80%. Interim analyses performed at 6-month intervals during the trial had never shown a trend for longer overall survival in the triptorelin group but had always anticipated the final results shown in Figure 2. No significant differences in overall survival could be established when treatment modalities were analyzed

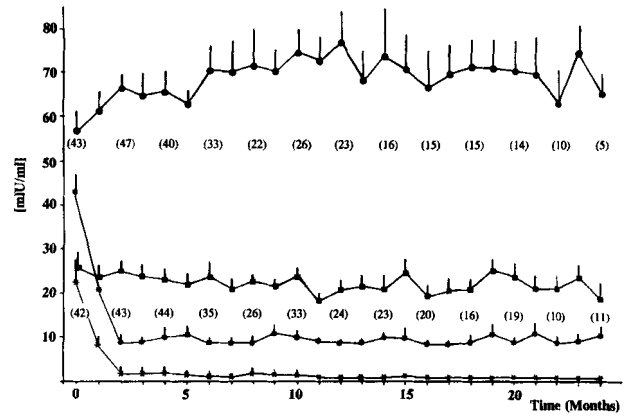


FIGURE 1. Serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations are shown for the patients in the trial (from whom serum samples were available) treated with either triptorelin or placebo. ■, LH placebo; *, LH triptorelin; ●, FSH placebo; ★, FSH triptorelin. Numbers in parentheses indicate the number of samples per time point.

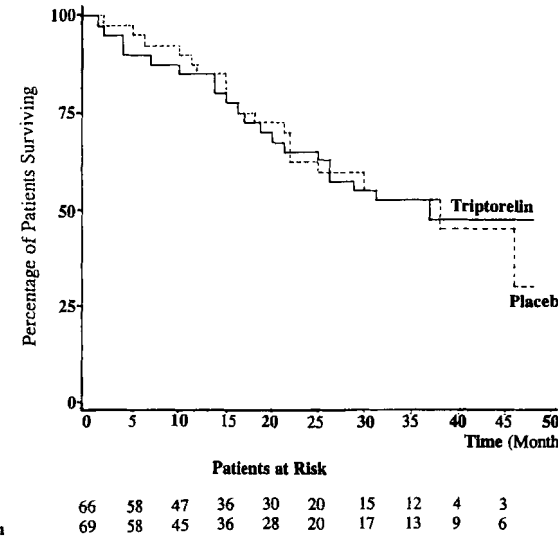
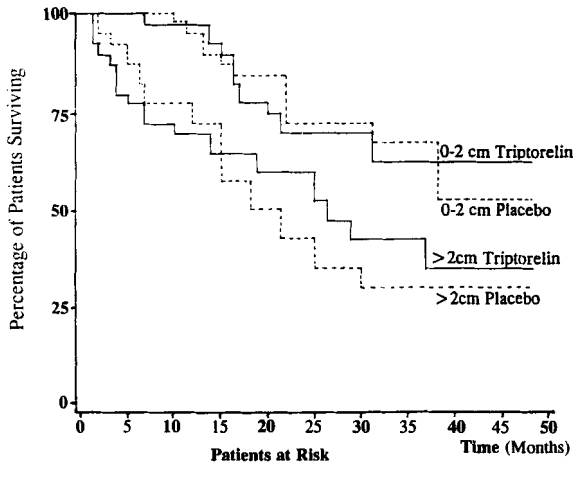


FIGURE 2. Overall survival of patients receiving either triptorelin or placebo is shown.

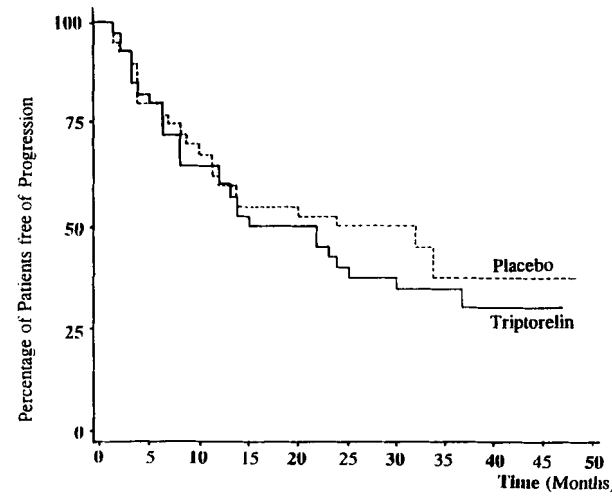
separately either by volume of residual disease left at the initial operation (Fig. 3) or by FIGO stage (data not shown). Survival advantage was significant ($P < 0.01$) when the analyses were based on the residual disease (≤2 cm versus >2 cm) unrelated to triptorelin therapy (Fig. 3). A similar observation was apparent for a comparison between FIGO Stages III and IV, although the number of patients with FIGO Stage IV disease was too small to allow a statistical comparison (data not shown).



Patients at Risk

0-2 cm Placebo	41	38	33	28	23	15	11	8	3	2
Triptorelin	37	35	29	24	18	11	10	7	4	2
>2 cm Placebo	25	20	14	8	7	5	4	4	1	1
Triptorelin	32	23	16	12	10	9	7	6	5	4

FIGURE 3. Overall survival curves, according to residual disease extent before chemotherapy, are shown.



Patients at Risk

Placebo	66	49	35	28	25	18	12	8	3	2
Triptorelin	69	50	33	25	22	15	12	10	6	3

FIGURE 4. Progression-free survival of patients receiving either triptorelin or placebo is shown.

When progression-free survival was analyzed, again no significant differences could be established between the triptorelin group and the placebo group (Fig. 4). Again, when treatment modalities were analyzed separately by volume of residual disease left at the initial operation (≤2 cm versus >2cm), no significant differences in progression-free survival could be found between the triptorelin group and the placebo group. Progression-free survival was significantly increased ($P < 0.05$) in patients with residual disease ≤ 2 cm, as compared with those with tumor residues of >2 cm unrelated to triptorelin treatment (data not shown).

Because there were only 20 premenopausal patients in the trial, a separate statistical analysis of their survival data could not be performed. Regarding overall survival, a separate analysis of the survival data of the postmenopausal patients gave the same results as for the whole patient population. No significant difference in overall survival could be observed between postmenopausal patients receiving triptorelin and those receiving placebo. Survival advantage was significant ($P < 0.05$) when the analyses were based on the residual disease (≤2 cm versus >2cm) unrelated to triptorelin therapy (data not shown). When progression-free survival was analyzed separately in the postmenopausal group, no difference could be established between the triptorelin and placebo groups. Progression-free survival was increased in postmenopausal patients with residual disease ≤ 2 cm unrelated to triptorelin treatment, though these differences were no longer statistically significant in some cases ($0.05 < P < 0.2$) due to the smaller number of patients analyzed.

Serum CA 125 levels correlated with the course of disease in individual patients, and no systematic differences could be observed between the triptorelin and placebo groups.

DISCUSSION

The purpose of this study was to evaluate the possible efficacy of the suppression of endogenous gonadotrophins through an LHRH agonist in the treatment of epithelial ovarian cancer in a prospective double blind randomized trial. From a theoretical point of view, an ideal design for such a trial would have been the application of single agent LHRH agonist versus placebo in patients with FIGO Stage III or IV disease who had just undergone primary surgery. However, since platinum-based chemotherapy, which has an established efficacy at least with regard to short and medium term survival, is available,[1,3–6] such a strategy would have been unethical. Similarly, a comparison of single agent LHRH agonist versus the established first-line chemotherapy, i.e. platinum-based regimens, could not be considered because the expected responses to LHRH agonists were clearly lower than responses to standard polychemotherapy. The approach of testing the LHRH analog versus placebo in patients with advanced disease, who were refractory to chemotherapy or would not tolerate it, was abandoned due to the extreme heterogeneity of such a patient popula-

tion with regard to previous treatments and actual disease status. In addition, all members of the trial group considered such a strategy unethical, because it would have meant the elimination of a specific treatment for the patients allocated to the placebo group. Finally, tumors in such heavily pretreated patients might have become refractory to endocrine manipulations.

A good approach would have been to test the LHRH agonist versus the placebo as a consolidation therapy in these patients, who had a complete remission of their disease after first-line chemotherapy assessed by second-look laparatomy. At the time, however, when the trial was planned, almost all participating centers had abandoned routine second-look operations for diagnostic purposes and considered it unethical to reinstall this procedure only for scientific purposes. In addition, because the percentage of histopathologically proven complete responders to first line chemotherapy is low,[27] the time needed for the selection of a sufficient number of patients for such a trial would have been too long.

Therefore, the current design for the trial seemed to be the best feasible compromise. By starting LHRH analog treatment immediately after initial surgery, the problem of heavily pretreated tumors, possibly resistant to endocrine manipulations, was avoided. In addition, in those patients who were responding to chemotherapy, it was to be expected that there would be relevant time periods in the absence of chemotherapy during which only the LHRH agonist or placebo would be applied. Finally, this study design created no relevant ethical problems, because the patients were to receive the standard first-line chemotherapy and, if necessary, salvage regimens as well. Some concern remained about possible negative interference of LHRH agonist treatment with the efficacy of chemotherapy. For this reason, interim analyses were performed at 6-month intervals, and the trial was to be stopped immediately if any evidence appeared for a loss of efficacy of standard chemotherapy in patients receiving triptorelin as compared to patients receiving placebo.

Despite the clear and consistent suppression of endogenous gonadotrophins induced by triptorelin, this treatment had no measurable effect on progression-free or overall survival. When these parameters were analyzed according to the extent of residual disease ($\leq$2 cm or >2 cm) before chemotherapy, again no differences were found between the triptorelin and placebo groups. However, patients with residual disease > 2 cm had significantly lower progression-free and overall survival rates, regardless of triptorelin or placebo treatment. This difference confirms that our patient population represented a valid sample for advanced ovarian carcinoma, because the extent of residual disease before chemotherapy ($\leq$2 cm versus >2 cm) was significantly related to progression-free and overall survival, as described in many other trials (for a review, see 2 in References). In addition, the clear relations between the extent of residual disease and prognosis in our patient population that existed regardless of triptorelin or placebo treatment confirm the validity of our randomization procedure.

The results of this prospective double blind randomized trial fail to support a role for the suppression of gonadotrophins by LHRH agonist in combination with cytotoxic chemotherapy in the management of Stage III and IV ovarian carcinoma. One conclusion from this negative result might be that endogenous gonadotrophins, even at the high levels observed in the placebo group, have no relevant effect on the progression of ovarian carcinoma, and so their suppression by LHRH agonists does not alter the course of the disease. However, it could also be argued that although LH levels were clearly suppressed below the range of cycling women, FSH serum concentrations, though markedly reduced, were still approximately 10 mIU/ml, and this degree of FSH activity might be sufficient to stimulate proliferation of the cancer cells. A trial aimed at a complete suppression of FSH levels, either through higher doses of an LHRH agonist or by a combination of an LHRH analog and an oral contraceptive, might test this speculation.

In addition, it has to be admitted that the concomitant application of LHRH agonist and chemotherapy might conceal marginal beneficial effects of LHRH agonist treatment. When the trial was planned in 1986, we were expecting effects greater than 20% based on the first reports on the efficacy of LHRH agonists in the salvage situation.[15,18-20] However, subsequent Phase II trials in refractory patients resulted in much lower response rates, so the overall efficacy of LHRH agonists in the salvage situation is probably only in the range of 12% of objective responses.[15-23] Such a low efficacy might have been missed in the setting of the current study. It might also be speculated that the efficacy of chemotherapy could have been slightly reduced by the concomitant LHRH agonist treatment, thus neutralizing the marginal antitumor effects of the LHRH analog. Similar hypotheses have been advanced to explain the apparent lack of efficacy of tamoxifen in combination with cytotoxic chemotherapy in Stage III or IV epithelial ovarian cancer[28] which contrasted with the marginal activity of this antiestrogen in the salvage situation found in Phase II trials.[29,30]

Likewise, for progestin treatment of ovarian carcinoma, marginal activity was found in Phase II trials in the salvage situation, which could not be confirmed

in controlled trials where progestins were combined with chemotherapy (for a review, see 10 in References). Thus it is unclear whether or not putative beneficial effects of endocrine manipulations of epithelial ovarian cancer are lost by combination with chemotherapy, or whether or not the marginal efficacy (at best around 15–20% of objective responses in Phase II trials) of endocrine therapies can be substantiated in controlled trials. As discussed above, controlled trials that evaluate the value of single agent hormonal therapies are difficult to perform in ovarian carcinoma.

It is noteworthy that progression-free and overall survival were quite good in our patient population, as compared with trials discussed in the literature.[1,3,28,31] This phenomenon might be due to the high proportion (58%) of patients with residual disease ≤ 2 cm before the initiation of systemic treatment in our population. When survival of our patients was analyzed according to the extent of residual disease, the respective curves were more in line with those of historical controls.[1,3,28,31] It is important to note, however, that the special characteristics of our trial (intensive follow-up, monthly visits of the patients to their clinical investigator, and expectations as to the efficacy of the novel endocrine therapy) might also have contributed to the rather favourable outlook for our patients. This phenomenon stresses the importance of using a double blind trial design whenever feasible.

Erickson et al.[32] recently reported a Phase II trial of cyclophosphamide, cisplatin, and the LHRH agonist leuprolide acetate after the debulking of Stage III or IV epithelial ovarian cancer in 33 patients. They found that FSH levels were consistently suppressed to less than 20 mIU/ml by LHRH agonist treatment. Leuprolide acetate did not alter the toxicity profile or the effectiveness of chemotherapy when comparisons were made with historical controls. Though this trial was based on a small number of patients and was not controlled, its results are in agreement with our findings.

Our trial suggests that the use of LHRH agonists aimed at the suppression of endogenous gonadotrophins has no measurable efficacy in patients with advanced ovarian carcinoma. However, we consider it premature to exclude the application of LHRH analogs in this disease. Recently, we and others have demonstrated the expression of LHRH and of LHRH receptors by human ovarian carcinoma cell lines as well as by the majority of ovarian carcinoma specimens obtained by surgery.[33–37] The proliferation of several human ovarian carcinoma cell lines was reduced by treatment with both agonistic and antagonistic analogs of LHRH.[33,37,38] These findings suggest the existence of a local regulatory system in ovarian carcinoma based on LHRH and its receptors, which might be a target for direct antitumor effects of LHRH analogs. However, the concentrations of LHRH analogs necessary to induce direct antitumor activity in vitro probably cannot be achieved in humans by the application of usual doses of LHRH agonists.[1] The development of new LHRH analogs such as potent antagonists[39] or of LHRH analogs containing cytotoxic radicals[40] might permit a better exploitation of direct antitumor effects in the treatment of ovarian carcinoma.[11]

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