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# A Multicenter Phase II Study with Triptorelin (Sustained-Release LHRH Agonist) in Advanced or Recurrent Endometrial Carcinoma: A French Anticancer Federation Study

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**The objective of this phase II multicenter study was to assess the efficacy and tolerance of triptorelin (a sustained-release LHRH agonist) in advanced or recurrent endometrial cancer. A total of 101 monthly intramuscular injections were administered to 24 eligible patients (median number/patient = 3; range 1–12). Mainly due to progression, only 16 patients received 3 or more injections. Among the 23 evaluable patients, 1 complete and 1 partial response (response rate of 8.7%) and 5 disease stabilizations were observed, often of long duration, but never in an irradiated area or after progestogens treatment failure. Median survival for eligible patients was 7.2 months (range: 1–36 months). Only grade 1 toxicities possibly related to the treatment were observed in 4 patients. In conclusion, triptorelin was safe, well tolerated, and easily manageable, and the very low toxicity did not impair the quality of life in these patients with a very poor prognosis. Although the response rate was disappointing, several patients showed early evidence of efficacy which may be of long duration. Response rates range between 0 and 45% in different published studies. Additional studies with stricter inclusion criteria and a larger sample size are necessary to better evaluate the role of LHRH agonists in endometrial adenocarcinomas.** 

## INTRODUCTION

Endometrial adenocarcinoma is the most frequent cancer of the female genital tract [1]. Local recurrence, metastatic disease, and locally advanced forms, which are often inoperable, are associated with a very poor prognosis (5-year survival rates of 30% for stage III and 10% for stage IV disease) [2]. Chemotherapy has given disappointing results, with at best a 30% objective response rate for single-agent therapy and 40% with a multiple drug regimen. Responses are usually partial and the median survival averages only 10 months [3, 4]. Chemotherapy is further hindered by the relatively advanced age of the patients (median incidence between 65 and 70) and the frequently associated diseases such as arterial hypertension or diabetes.

Progestins have led to objective response rates on the order of 15 to 20% in disseminated or recurrent forms [5], and the median survival is 12 months. Moreover, this therapy is generally beneficial only in histologically well-differentiated tumors and/or estrogen or progestin-receptor-positive tumors [6] and can induce thromboembolic or cardiovascular side effects.

LHRH (luteinizing hormone–releasing hormone) agonist analogs by continuous administration, after an initial transient increase, induce the suppression of gonatropin secretion (LH and FSH), by a mechanism of pituitary desensitization. The resulting inhibition of ovarian estradiol secretion explains their well-established efficacy in premenopausal women [7, 8] in certain hormone-dependent benign gynecological diseases such as endometriosis [9] and uterine fibroma [10] and in the treatment of metastatic breast cancer [7, 8].

In menopausal women the mechanism of action of LHRH agonists is unclear. They have shown very modest activity in ovarian cancer [8]. Specific LHRH [11] and triptorelin (Decapeptyl SR 3.75 mg) [12] receptors have been detected in endometrial adenocarcinoma tissue, suggesting that triptorelin might have a direct effect on the tumor in these menopausal women. When our study was initiated, only one phase II study of the efficacy of other LHRH agonists, leuproline or goserelin, in patients with recurrent endometrial adenocarcinoma had been published (Gallagher study, [13]). In this study the objective response rate was 35% with a mean duration of 20 months. Unlike chemotherapy [3, 4], which gave similar objective response rates, no notable toxicities were described in these patients.

The present study aimed to evaluate the antitumor response and the tolerance of a treatment with triptorelin, marketed under the brand name Decapeptyl SR 3.75 mg, in women with advanced or recurrent endometrial cancer.



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## PATIENTS AND METHODS

Patients with histologically documented endometrial adenocarcinoma at primary diagnosis (FIGO stage III or IV) [14] with cytologically or histologically proven persistent and progressive disease after surgery and/or radiotherapy or with locoregional recurrent disease or secondary metastases were eligible for this study.

At least one clinically and/or radiologically measurable (two dimensions) or evaluable (one dimension) progressive disease, inside or outside the irradiated area, was required. Patients could have received prior first-line chemotherapy or progestin therapy. A minimum of 3 months following radiotherapy for a single target located in irradiated area, a minimum of 4 weeks following chemotherapy or 6 weeks if it included mitomycin, and a minimum of 4 weeks following progestin therapy were also required before inclusion in this study. Exclusion criteria were WHO performance status greater than 2; life expectancy less than 3 months; cerebral or leptomeningeal metastasis; history or a concomitant second cancer (excepting *in situ* cervical cancer or basal cell skin cancer); bone metastasis, pleural effusion or ascites as a unique target.

This protocol was approved by the local Ethics Committee and all patients signed an informed consent form. The inclusion evaluation consisted of a complete gynecological and physical examination, laboratory tests (general blood assessment: hematology, creatininemia, ionogram, hepatic tests), plasma hormone levels (FSH, LH, estradiol), assay of serum tumor markers (CEA, CA 19-9, CA 125), and a radiological evaluation (abdominopelvic ultrasound and/or abdominopelvic CT scan). All patients had a chest X ray. A thoracic CT scan was only performed in case of pulmonary metastasis.

One month after inclusion a physical examination and hormone assays identical to those in the inclusion evaluation were carried out. All elements of the inclusion evaluation were repeated every 3 months. Radiological examinations only concerned the target lesions and the same radiological technique had to be used throughout the study.

The objective response rate for any measurable or evaluable target was chosen as the main criterion and was evaluated according to WHO criteria [15]. Progression-free intervals (responses and stabilization) and durations of survival (all included patients) were calculated from the start of triptorelin treatment to either disease progression or date of last contact. Tolerance of the treatment was also analyzed.

### *Treatment*

Treatment was given as an every-4-weeks intramuscular depot injection of 3.75 mg of triptorelin. Except in cases of early progression, at least three injections had to be administered for a patient to be evaluable for efficacy. All patients who have received at least one injection were evaluable for tolerance of triptorelin. Treatment was discontinued in case of documented progression, occurrence of a serious adverse event, or on request of the patient.

If a complete response was achieved, triptorelin could be continued for 12 months starting from the time of complete response, after which the decision to stop or continue treatment was made by the investigating physician and the patient. In case of partial response or stabilization, treatment was continued until documented disease progression.

The protocol authorized any concomitant treatments that did not interfere with the hormone therapy. Patients were withdrawn from the study if they required chemotherapy or radiotherapy for purposes other than pain relief on an isolated bone lesion not taken for the target or if another hormone therapy was necessary.

### *Statistics*

The required sample size was determined in two steps: in the first step, 14 patients were included. If no responses were observed, the study would be terminated. If one or more responses were observed, the minimum sample size to include in the second step was determined by the Gehan table [16] according to the number of responses, with a $\beta$ risk of 5% of wrongly rejecting a 20% response rate.

Survival duration was calculated by an actuarial method using 1-month intervals. Patients lost to follow-up during a given interval were considered as being present for half of this interval.

## RESULTS

Twenty-five patients were included between July 1992 and January 1994. Table 1 describes patient and disease characteristics at the initial diagnosis. In 9 patients the histological grade of the initial tumor could not be determined. Four patients had previously received systemic therapy. The first had metastatic disease which progressed under chemotherapy. The second had initially positive peritoneal cytology. Chemotherapy followed by external radiation was performed. Clinical and radiological tests were normal after this initial treatment. The third patient had a stage IVb tumor at diagnosis. Following chemotherapy, progestin therapy was initiated (protocol violation). A partial response was obtained at the end of each therapeutic regimen. The fourth patient had received progestins alone as adjuvant treatment.

Between the end of the initial treatment and inclusion, three patients had complete resection of a metastasis followed in two cases by chemotherapy and in one case by chemotherapy and radiotherapy.

Table 2 describes patient and disease characteristics at inclusion. Among the five progressions or locoregional recurrences, four either received radiation ($n = 2$) or occurred in an area irradiated during the initial treatment ($n = 2$).

One patient was wrongly included: the only evaluable target

**TABLE 1**
**Initial Patient and Disease Characteristics and Treatment**

| | |
|---|---|
| Number of patients | 25 |
| Median age (years) (range) | 62 (36–82) |
| Initial diagnosis | |
| Histology (number and %) | |
| Endometrioid | 14 (44%) |
| Clear cell | 3 (12%) |
| Serous papillary | 4 (16%) |
| Adenosquamous | 4 (16%) |
| Grade [FIGO 17] | |
| G1 | 6 |
| G2 | 6 |
| G3 | 4 |
| Unknown | 9 |
| FIGO stage [14] | |
| I | 13 (52%) |
| II | 8 (32%) |
| III | 2 (8%) |
| IVb | 2 (8%) |
| Treatment (*n*) | |
| Hysterectomy + BSO | 23 |
| Hysterectomy + USO | 1 |
| External radiotherapy[a] | 14 |
| Brachytherapy[a] | 20 |
| Chemotherapy[b] | 3 |
| Hormone therapy[b] | 2 |

*Note.* BSO, bilateral salpingo-oophorectomy; USO, unilateral salpingo-oophorectomy.
[a] Thirteen patients received brachy- and external radiotherapy.
[b] One patient received chemotherapy and progestins.

was in bone and the patient had received two lines of chemotherapy as initial treatment. Efficacy and survival data for this patient will be presented separately.

### *Efficacy*

A total of 101 injections were administered in 24 eligible patients, with a median of 3 injections per patient (range: 1–12). One patient was lost to follow-up and another died of unknown causes after receiving one injection. The efficacy analysis concerns 23 patients and the survival analysis concerns all included patients.

In 6 patients, disease progression led to treatment discontinuation after two injections. Among the 16 patients who received at least three injections, there were 9 progressions, 5 stabilizations, 1 partial response, and 1 complete response (for an overall response rate of 8.7%). Table 3 reports the characteristics of patients with response or stable disease ($n = 7$). In 6 cases the tumor was endometrioid. No responses or stabilizations were observed in poorly differentiated tumors (grade 3), in targets previously irradiated or localized in an irradiated area, or after progestin treatment failure.

The mean progression-free interval for the 24 patients was 4.2 months ($\pm$4.8 months). Complete response on an evaluable lymph node target was maintained throughout the study (12 months). Although at 3 months there was 1 partial response and 5 stabilizations (12.5%), at 6 and 9 months there were, respectively, 3 and 1 stabilizations. Two patients with stable disease after three injections died 1 month later. The first, a 74-year-old patient, died of cerebral hemorrhage unrelated to the treatment or the disease. The second 70-year-old patient died of bilateral infectious pneumonia.

The course was especially unfavorable in the presence of hepatic metastasis (survival less than 7 months), with a single 4-month stabilization in the six patients with liver involvement. Median survival differed between patients without progression (21.7 months; 4.3–35.5) and those with progressive disease (6.6 months; 3.2–24.5) on triptorelin.

Inhibition of the gonadotropin axis and compliance with treatment were checked by plasma assays of estradiol, FSH, and LH before treatment and then at 1, 3, and 6 months of treatment in 20, 18, 13, and 5 patients, respectively. The results confirmed that triptorelin induced pituitary desensitization in all these patients. Plasma assays after 1 month showed a sharp decrease in LH and FSH levels with estradiol levels similar to

**TABLE 2**
**Disease at Inclusion**

| | |
|---|---|
| Number of patients | 25 |
| Median age (years) (range) | 64.7 (46–85) |
| Time from initial diagnosis to inclusion | |
| Median (months) (range) | 29 (3–144) |
| 3 months (*n*) | 4 |
| >3–18 months | 7 |
| >18–36 months | 4 |
| >36 months | 10 |
| Disease localization | |
| *n* (time from initial diagnosis to inclusion) (months) | |
| LRD alone | 3 (16,20,45) |
| LRD + metastasis | 2 (3,45) |
| Metastasis alone | 20 (3–144) |
| Site of metastases[a] | |
| Lomboaortic lymph nodes | 2 |
| Subclavicular lymph nodes | 5 |
| Liver | 6 |
| Lung | 10 |
| Bone | 4 |
| Others[b] | 7 |
| Previous treatment for the target (recurrence and/or metastasis) (time from initial diagnosis to inclusion—months) | |
| *n* | 25 |
| None | 17 |
| Radiotherapy[c,d] | 3 (3,13,45) |
| Chemotherapy[d] | 4 (49,45,81,144) |
| Hormone therapy | 2 (12,32) |

*Note.* LRD, locoregional disease.
[a] Association of several sites in some patients.
[b] Skin, peritoneum, abdomen, kidneys, adrenals.
[c] Lomboaortic lymph nodes. (1 pt), pelvis (2 pts).
[d] One patient received radiotherapy and chemotherapy.

**TABLE 3**
**Characteristics of Patients with Response or Stable Disease**

| Age | Histology | Grade | Stage | Initial treatment | Initial diagnosis/ inclusion (months) | Prior treatment of target | Target | Duration (months) triptorelin | Status | Survival (months) | Response |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 78 | End | 2 | II | S + B | 18 | 0 | Subclav.[a] | 12 | Alive | 35 | CR |
| 74 | End | 1 | IB | S + R + B | 59 | 0 | Px | 7 | Alive | 22 | PR |
| 68 | CC | ? | II | R + B | 144 | 0 | LAo Px, skin | 7 | Died | 16 | SD |
| 76 | End | ? | IA | S | 40 | 0 | Liver, peritoneum | 5 | Died | 4 | SD |
| 56 | End | 2 | II | S | 81 | C(PR)[a] | Px Mediastinal | 9 | Alive | 30 | SD |
| 63 | End | 1 | IB | S + R + B | 29 | 0 | Mammary chain LN, peritoneum | 9 | Alive | 21 | SD |
| 70 | End | ? | IA | S + B | 20 | 0 | Peritoneum | 4 | Died | 4 | SD |

*Note.* End, endometrioid; CC, clear cell; S, surgery; R, external radiotherapy; B, brachytherapy; C, chemotherapy; ?, unknown; CR, complete response; PR, partial response; SD, stable disease; LAo, lomboaortic; Px, pulmonary; LN, lymph node; Subclav, subclavicular LN.
[a] Clinical evaluation.

those observed before treatment. LH and FSH levels sharply decreased in all patients at 3 and 6 months to below the threshold of pituitary desensitization. Plasma estradiol levels also decreased. Estradiol levels before starting treatment with Decapeptyl were 25 and 7 pg/ml in the 2 patients who did not have bilateral salpingo-oophorectomy.

CEA was assayed at least twice in 22 eligible patients. Among the 17 patients in which the initial value was normal (<7 ng/ml), there was no notable increase during disease progression. Initial values were moderately elevated (<30 ng/ml) in 3 patients while 2 others had levels of 56 and 229 ng/ml. Among these 5 patients, a close correlation with clinical status was observed in 4 cases and a progressive increase in CEA levels despite clinical disease stabilization was noted in the fifth patient.

CA 19-9 was initially assayed in 22 patients, among which 13 had high levels (>33 ng/ml). Eighteen patients had several assays done: of the 8 patients with normal values, no subsequent increases were observed. There was a good correlation with clinical status in 8 of the 10 patients with initially high levels.

CA 125 was initially assayed in 23 patients with a mean value of 218 ± 311 IU/ml. In 2 of 8 patients with an initial normal assay (<35 IU/ml), subsequent increase occurred during disease progression. Among the 12 patients with elevated initial levels who had several assays, there was no correlation with clinical status in 5 cases.

The survival analysis was performed on December 31, 1995. Median survival for eligible patients was 7.2 months (range: 1–36 months). Among the 18 recorded deaths, 15 were related to disease progression, including 10 (55.5%) which occurred in the 6 months following inclusion. Median survival duration for all included patients was 13 months as of the date of last contact.

The ineligible patient received six injections. The bone target was stable at 6 months. Only CEA was assayed and the levels normalized (from 13 to 7) after 6 months of treatment. This patient was alive (23+ months of follow-up) at the cutoff date.

### *Safety*

There were no treatment discontinuations due to toxicity or patient refusal. Four adverse events (all grade 1) were considered possibly related to triptorelin: headache (one patient), asthenia (one patient), altered liver function (one patient), and pruritus (one patient). There were no reports of local injection site reactions.

## DISCUSSION

The prognosis of endometrial adenocarcinoma is especially poor in advanced disease (10% of patients) [2] or recurrent forms. Systemic treatments have only moderate, transient efficacy and are often complicated by the fact that these older patients usually present with other chronic diseases (renal, venous, or cardiovascular disease or diabetes) [18].

The presence of GnRH receptors in endometrial adenocarcinoma tumor tissue and the low toxicity of GnRH analogs has led them to be proposed as an interesting alternative to other hormone therapies in this disease. In 1986 Perl *et al.* [19] were the first to report a tumor response to a GnRH agonist. Further encouraging results reported by Gallagher *et al.* in 1991 [13] in 17 patients showing an objective response rate of 35% and a median remission of 20 months prompted us to continue our clinical research along these lines. The conclusions of this study were taken into account in our choice of inclusion criteria. Thus, patients with progestin-resistant tumor or with a target located in an irradiated zone were eligible.

Among the 23 evaluable patients in our study, 1 complete

response, 1 partial response (response rate of 8.7%), and 5 stabilizations were obtained. These results are markedly lower than that previously described with GnRH agonists. Thus, initially, three groups (Perl *et al.* [19], Gallagher *et al.* [13], De Vriese and Bonte [20]) have reported detailed results obtained with GnRH agonists in progressive or recurrent adenocarcinoma. The combined results of these three studies in 25 patients give an overall response rate of 45%. More recently, Gallagher *et al.* updated their study with another 15 patients (with a lower dose of leuproreline) [21] and Covens *et al.* [22] reported no response in 25 patients treated with leuprolide. Combining all these results, the response rate is 21% in 65 patients.

Our response rate is also lower than those described with other hormone therapies. Recent, well-designed studies have reported response rates of 15 to 20% with progestins [18, 23, 24] and 0 to 53% with tamoxifen, with an average value of about 20% [18, 24].

The efficacy of hormone therapy in endometrial adenocarcinoma is related to various clinical and/or histological factors. The highest response rates are observed for well-differentiated tumors and for tumor cells containing cytosolic hormone receptors (mainly for progesterone), although the assay of such receptors is neither standardized nor common clinical practice. The highest response rates are also observed for lesions located outside previously irradiated zones, for small tumor volumes, and for late recurrence (disease-free interval over 3 years) [23].

Steroid or LHRH receptors status were not determined in our study and are not described in the studies of Gallagher *et al.* or Covens *et al.*

In the 9 patients in our study in which the initial histological grade could not be determined, there were no responses and 3 stabilizations. In the 16 patients with a defined histological grade tumor, no responses or stabilizations were observed for poorly differentiated tumors (grade 3). In the Gallagher *et al.* study [21], there was no significant difference in response rate according to the histological grade of tumors. In Coven's study, 24% of tumors were well differentiated and no response was observed. So, the impact of grade of the endometrial adenocarcinoma on the efficacy of LHRH agonists is unclear. For further studies concerning hormone therapy in endometrial adenocarcinoma we believe that grading should be an eligibility criterion.

Usual criteria for hormone therapy failure in endometrial adenocarcinoma were observed in our study. So, contrary to Jeyarajah *et al.* [21], no responses were obtained on irradiated targets or targets in the irradiated area (6 patients); in patients included less than 18 months after the initial diagnosis (11 patients); or in case of prior progestin therapy failure (4 patients). This latter observation parallels what has been observed with tamoxifen: neither Slavik *et al.* [25] nor Edmonson *et al.* [26] observed with tamoxifen a response after progestin treatment failure. Like Jeyarajah *et al.* [21], we also observed failure of LHRH agonists on hepatic targets but this might be a reflection of widespread dissemination and large tumor volume.

Six tumors progressed after two injections. This is probably due to an inherent lack of efficacy of the treatment and not to a flare-up effect in these ovariectomized patients. Plasma assays after 1 month showed a sharp decrease in LH and FSH levels with estradiol levels similar to those observed before treatment.

The response rate is low in our study. The complete and partial responses lasted, respectively, for 7 and 12+ months, shorter than in the Jeyarajah *et al.* study [21] and similar to the report of Covens *et al.* [22]. In five other patients, stabilization lasted for a median of 7 months (range: 4–9). Four of our patients were still alive as of Dec. 31, 1995, with 21, 22, 30, and 35 months of follow-up. We observed a difference in median duration of survival between patients who did not progress (21.7 months) and those who did (6.6 months; similar to the study of Covens *et al.* [22]). Among the seven patients who did not progress under triptorelin, only one died from progression of disease (at 16 months). It is difficult to determine the respective roles of the progressive nature of the disease (well- or moderately differentiated endometrioid tumors, time to relapse between 18 and 144 months in the seven patients who did not progress) and the inherent efficacy of the treatment itself. The two responses obtained and the fact that these patients had progressive (and not simply persistent) disease at inclusion argue in favor of a beneficial impact of treatment, including in case of disease stabilization. Same or similar response durations have been reported with progestins (16 to 28 months) [27].

The mechanism of action of LHRH agonists in menopausal patients has not yet been elucidated. It could occur at two levels: pituitary and tumoral.

The predisposing role of hyperestradiolemia (absolute or relative) in the genesis of endometrial adenocarcinoma is well established [28–30]. In postmenopausal women, circulating estrogens arise mainly from conversion in adipose tissue of androgens originating in the adrenals or ovarian stroma. In most cases the initial treatment of endometrial adenocarcinoma includes salpingo-oophorectomy. In our study, only 2 of 25 patients did not have bilateral salpingo-oophorectomy and estradiol levels before triptorelin treatment were low.

Circulating estradiol levels tended to decrease during treatment (even within castrate ranges). It should, however, be noted that the initial levels were not very high and the interpretation of assays under 10 pg/ml is difficult. Gallagher *et al.* [13] did not detect modifications of serum levels of estradiol, progesterone, testosterone, or sex hormone binding globulins. So, this minimal and unexplained decrease in plasma estradiol during LHRH agonist treatment in women with bilateral salpingo-oophorectomy might play a role in the mechanism of action of LHRH agonists. However, if it exists, it is not essential. Pituitary desensitization does not therefore appear to

be a sufficient explanation for the mechanism of action of LHRH agonists in this indication.

Specific, biologically active receptors for LHRH [11, 31] and for triptorelin [12, 32] have been detected at the surface of endometrial adenocarcinoma tumor cells. The percentage of these receptors is higher in adenocarcinoma (77%) than in normal endometrium (23%) [12], suggesting a possible direct action of LHRH agonists on tumor cells. *In vitro*, both high-affinity [12, 31, 32] and low-affinity [11, 32] binding sites have been described. In contrast to what has been described for progestins [23, 33], LHRH receptors are found in over 90% of tumors, regardless of their histological grade [31]. Direct *in vitro* inhibition of tumor cell proliferation by LHRH agonists was subsequently demonstrated. This inhibition depends on the dose and duration of exposure and is probably mediated by the high-affinity binding sites [31, 32]. A direct antiproliferative action via autocrine–paracrine regulation of cell function was therefore hypothesized [34]. Unfortunately, more recent work by Bax *et al.* [35, 36] raised doubts about these hypotheses because high-affinity receptors were not found in endometrial adenocarcinoma tumor cells and LHRH agonists did not inhibit tumor growth. In this last study, receptor expression varied according to the culture conditions. Furthermore, Kleinman *et al.* [37] didn't observe a significant sensitivity of endometrial cancer cells lines on agonist buserelin. On the whole, Bax *et al.* [35] were unable to provide any convincing arguments for a direct extrapituitary effect of LHRH agonists mediated by LHRH receptors. Finally, we must stress that the presence of receptors does not necessarily implicate a role of such receptors in the mechanism of action. Thus, in ovarian adenocarcinoma, GnRH receptors have been detected in a large proportion of tumors and *in vitro* inhibition of tumor growth has been demonstrated [8]. Despite these *in vitro* data, published response rates with LHRH agonists are only 11% (14/121 patients). This low response rate alone does not bring into question the effect of a direct action on the tumor (by another mechanism of action), but the intensity of this action may be too low compared to the tumor volume and the existence of poorly vascularized targets in the irradiated zone to have a clinical effect.

The previously cited studies used LHRH agonists other than triptorelin: leuproreline (56 patients) and gosereline (8 patients) [20–22]. It is difficult to bear in mind that the observed differences in activity are due to the drug used, as efficacy is similar in the other pathologies [38, 39] and *in vitro* results are identical with gosereline and triptorelin [35]. Furthermore, Jeyarajah *et al.* [21] and Covens *et al.* [22] both used leuprolide.

Tolerance of the treatment was excellent. In our study only four grade 1 adverse events were observed for 101 injections. None of the patients requested that treatment be stopped. The absence of alopecia and gastrointestinal upset, together with the monthly treatment schedule, promotes good compliance with the treatment and, in particular, allows it to be administered at home, thereby avoiding frequent trips to the hospital. Similar results have been reported in other studies [20–22]. We did not undertake quality of life measurement, but the absence of toxicity of treatment avoided impairment of the quality of life of these patients.

Chemotherapy and hormone therapy give similar response rates in endometrial cancers. Responses are usually brief (several months) and median survival is identical (about 10 months) [3, 4, 23]. They must therefore be considered palliative treatments. It is essential to choose the most effective therapy possible which is suited to the physiological condition of the patient and which does not impair quality of life. Hormone therapy has fewer associated toxicities than chemotherapy, although progestins are not devoid of side effects, particularly on the veins. Tamoxifen has few associated toxicities but its use will be possibly limited (at least psychologically) in this indication because it has been linked to the development of endometrial cancer in patients treated for breast cancer [40].

In conclusion, we cannot explain differences observed between the published studies in terms of response rates. In some cases LHRH agonists may give long-lasting responses. Their ease of administration, absence of contraindications, and low toxicity make them a candidate among the different hormone therapies. We believe that such a treatment can be proposed mainly for well- or moderately differentiated endometrioid tumors without liver metastases, which did not progress under progestin therapy and which did not recur in a previously irradiated area. Additional studies with stricter inclusion criteria and a larger sample size are necessary to better evaluate the efficacy of LHRH agonists in order to more precisely define their indications. Now, two multicenter phase II studies are ongoing, one in Germany and one in the United States [22].

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