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Adjuvant hormone therapy following primary therapy for endometrial cancer

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1. Introduction

Endometrial cancer is the most common malignant disease of the female genital tract. Risk factors for endometrial cancer like early menarche, nulligravidity, late menopause, unovulatory states, unopposed hormone replacement therapy (HRT), tamoxifen therapy demonstrate a hormone dependency for the disease. Although standard therapy for early stage endometrial cancer consists of hysterectomy and bilateral salpingo-oophorectomy combined with radiation, adjuvant endocrine therapy has also been attempted. Several reports have described prognostic factors for the virulence of the disease including tumour stage and grading, histological type, myometrial invasion, lymph node status, age, hormone receptor status and S-phase fraction to predict the patients who are most likely to relapse and who might profit from adjuvant therapy [1].

2. Hormonal treatment for recurrent disease

2.1. Progestins

Studies performed in the last 20 years have reported response rates (RR) between 15 and 25%. A study by Podratz and colleagues in 155 patients reported a lower RR of 11.2% and survival rates of 40% after the first year, 19% after the second year, and 8% after 5 years [2]. Thigpen and colleagues published similar results in 299 patients with a 25% overall response rate (ORR) and an 8% complete response rate (CR) with no difference in the high (1000 mg) or low dose (200 mg) medroxyprogesterone (MPA) groups [3]. The effect was independent of the progestin used, and the dose given, but was significant higher in patients who relapsed more than 3 years after their first diagnoses [4].

2.2. Tamoxifen

Thipgen and colleagues reported on a study conducted by the Gynecological Oncology Group (GOG) involving 68 patients with advanced or recurrent endometrial cancer who had not received systemic therapy. They observed an ORR of 10% and an overall survival rate of 8.8 months [5]. Numerous clinical trials in recurrent disease have demonstrated an ORR following tamoxifen treatment of approximately 22% [6].

3. Adjuvant hormonal treatment for endometrial cancer

3.1. Progestins

Several studies have tried to define the role of the progestins in the adjuvant treatment setting for endometrial cancer [7–10]. One trial involving 205 patients was able to demonstrate a survival benefit for the progestin-treated group. 30% of the patients enrolled had stage II-III disease [11].

3.2. Tamoxifen

Between 1983 and 1989, the South Western Germany Gynaecology Oncology Group (SWGGOG) conducted a randomised trial including 388 patients who received after surgical therapy either MPA ($n=133$) or tamoxifen ($n=121$) orally for 2 years or underwent observation ($n=134$). After a median follow-up of 56 months (range 3–199 months), slightly fewer recurrences and deaths were observed in the tamoxifen group compared with the control or MPA groups [12].

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4. Conclusions

Most trials have failed to demonstrate a survival benefit for patients treated in the adjuvant setting with progestin which demonstrates that such treatment benefits those with well differentiated, PR-positive tumours. However, this is a group which has a 5-year survival of >90%. At present, there seems to be no benefit from progestins or tamoxifen given as adjuvant therapy after primary surgical treatment.

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1997's screening consensus redebated

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There has been keen interest in the effects of tamoxifen on the endometrium since 1985 when reports of the drug's association with endometrial neoplasia were first published [1]. From the perspective of endometrial safety, there is great controversy about what special management, if any, tamoxifen-treated patients should undergo. Some physicians have advocated periodic blind endometrial sampling [2]. Other physicians initially began using transvaginal ultrasound. Because of the problems associated with either of these techniques alone, an approach was developed that utilised transvaginal ultrasound and then proceeded to sonohysterography when the endometrial echo on transvaginal ultrasound was not reliably thin and distinct [3]. Recent studies have confirmed the observation that blind endometrial sampling by itself or unenhanced transvaginal ultrasound by itself are of limited value. The American College of Obstetricians and Gynecologists, in its committee opinions [4,5] has stated that patients receiving tamoxifen therapy should only have an annual pelvic exam with Papanicolaou (Pap) smear if they remain asymptomatic. In women with a hysteroscopically-normal uterus at the start of therapy (i.e. an empty uterus with an atrophic endometrium), atypical endometrial hyperplasia or cancer is unlikely to be found in the first 3 years [6]. Newer data from Europe, however, suggest that there are identifiable high- and low-risk groups of patients relative to their risk of developing atypical hyperplasia on tamoxifen therapy [7]. These two groups were successfully identified by pretreatment screening with transvaginal ultrasound and then hysteroscopy if the endometrial echo on

transvaginal ultrasound was not reliably thin. 17% of patients prior to tamoxifen therapy had polyps. These patients had 18 times the incidence of atypical hyperplasia than those whose uterus was totally negative prior to tamoxifen therapy. Such findings call into question the validity of the only published study of raloxifene where uterine safety was the primary endpoint [8]. In that study, any woman with baseline endometrial findings other than those that were pristinely negative was excluded. Thus, that study was done on what we now must consider a low-risk population. In such a low-risk population, raloxifene, in two doses, did not differ from placebo in its effects on the endometrium. In a real world setting of postmenopausal uteri, however, raloxifene is clearly not tamoxifen-like.

In the Breast Cancer Prevention Trial (BCPT) [9] the relative risk of endometrial carcinoma for women over 50 years taking tamoxifen was 4.01 (Confidence Interval (CI) 1.70–10.90) whereas after three years in the MORE (Multiple Outcomes of Raloxifene Evaluation) trial, the relative risk of endometrial carcinoma with raloxifene was 0.8 (CI = 0.2–2.7) [10]. The existence of potentially high- and low-risk groups relative to the risks of abnormal endometrial changes should be taken into account in any future clinical trials looking at the endometrial safety of selective oestrogen receptor modulators (SERMs) and perhaps even hormone replacement therapy (HRT).

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