Hormone therapy in epithelial ovarian cancer

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Abstract

Although epidemiologic studies, animal experiments and receptor studies have shown that not only normal ovaries but also many malignant ovarian tumors can be considered as endocrine related and hormone dependent, the place of hormonal therapy in the management of patients with ovarian cancer remains unsettled. Most trials of hormonal treatment in ovarian cancer have been retrospective, involved only limited numbers of patients, and lacked important patient-related data and information pertaining to tumor characteristics. In addition, a variety of hormonal preparations with different degrees of potency and in different dosages were included in these studies. A literature review shows that response to hormonal therapy even in a preterminal setting, is modest, with about 8% objective response but almost no side effects. In a similar patient setting, more toxic therapeutic agents do not yield a better response. The place of hormonal therapy in the management of patients with epithelial ovarian cancer needs more thorough evaluation in well-designed randomized trials.

Introduction

Ovarian cancer is the leading cause of death from all gynecologic malignancies. The disease affects elderly or middle aged women and the greatest incidence rates are reported in North America and Northern Europe, particularly in Scandinavia (Parkin 1989, Adami et al. 1990, Trope & Makar 1991, Pettersson 1994). The incidence rate in Norway was 19.3 per 100 000 in 1989. The incidence of ovarian cancer increases with age: it is relatively rare in women younger than 30 years, with only 1.5 new cancers/100 000 women per year in the 20–29 years age group, but beyond this age the incidence increases rapidly to a rate of 49/100 000 in women in the 60–69 years age group (Mant & Vessey 1995).

Ovarian cancer is characterized by its insidious onset and lack of early specific symptoms. About two-thirds of patients with ovarian cancer will present in International Federation of Gynecology and Obstetrics (FIGO) stages III and IV, having widespread tumor dissemination in the abdominal cavity, with or without varying degrees of pleural effusion. The prognosis of these patients remains poor, with 5-year actuarial survival of 23% and 14% for FIGO stages III and IV, respectively (Pettersson 1994, Makar et al. 1995). Management of these patients consists mainly of primary debulking surgery followed by platinum-based chemotherapy (Makar 1995, Makar et al. 1995).

Over the past several years, combinations of platinum and taxol became standard in the primary management of advanced ovarian cancer (Caldas & McGuire 1993). Despite a primary response rate of up to 70%, the majority of patients suffer relapse (Neijt 1995). The probability of response to second-line chemotherapy depends mostly on the relapse-free interval. Patients with disease relapse during a regimen of platinum-based chemotherapy or within 6 months after its discontinuation are considered to be platinum resistant. Unfortunately, regimens used as second-line therapy in such situations have a low response rate and are associated with severe side effects that negatively influence the quality of life and necessitate long stays in hospital and intensive palliative care. It is therefore important to explore alternative treatment modalities that have cost–benefit ratios favorable in terms of toxicity. Hormonal therapy perhaps best fulfils these requirements.

Epidemiologic studies

Several case–control studies have found a decrease in risk of the epithelial ovarian cancer associated with pregnancy, breast feeding and use of oral contraceptives (OCs). This prompted the hypothesis of incessant ovulation, which holds that factors that suppress ovulation may reduce the risk of developing ovarian cancer (Fathalla 1971, Wu et al. 1988,
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Franceschi 1989). Gwin et al. (1989) showed, in a multicenter population-based, case–control study, that the estimated relative risks of epithelial ovarian cancer were 0.6 (95% confidence interval 0.5 to 0.8) for women who have ever been pregnant, 0.6 (95% confidence interval 0.5 to 0.8) for women who have ever had breast feed, and 0.5 (95% confidence interval 0.5 to 0.7) for women who have ever used oral contraceptives. The risk of ovarian cancer seemed to decrease with increasing duration of use of OCs and the protective effect of OCs was even noticed in ex-users (at least 15 years). The findings of Van Leeuwen & Rookus (1989) were in agreement. The study by Wu et al. (1988) also showed that the risk of ovarian cancer tends to decrease with increasing age at menarche. Similarly, the risk of ovarian cancer was significantly decreased in women reporting life-long menstrual irregularities (Parazzini et al. 1989). Smith & Oi (1984) concluded that a group to be regarded at high risk should comprise women aged 45 years and older who are nulliparous, or whose first pregnancy occurred after the age of 30, who experienced menopause after age 55 years, or who had 40 years or more of ‘ovulatory age’. However, the case–control study of Risch et al. (1983) was able only partly to confirm the theory of incessant or extravagant ovulation as a possible mechanism in the pathogenesis of ovarian cancer. These workers used a logistic regression method to test the hypothesis that equal periods of anovulation, regardless of cause, produced the same reduction in ovarian cancer risk. They found that the amounts of anovulatory time attributable to different exposures did not completely account for their protective effects. They suggested that the explanation of such a correlation cannot be based merely on hormonal suppression (Risch et al. 1983).

During the past decades, with new advances in fertility treatment, many questions have arisen regarding the effect of fertility drugs on the pathogenesis of ovarian cancer. The answer remains unclear. Clomiphene does not seem to be associated with any increased risk of ovarian cancer when used for fewer than 12 cycles. The relationship between gonadotropin use and ovarian cancer risk is less clear because of the small numbers of women exposed in the studies and short follow-up times. Prospective cohort studies are necessary, including more women exposed to clomiphene and gonadotropin and with correction for all the necessary confounding factors such as parity and with longer follow-up times. The putative risks must, however, be discussed with all patients before fertility treatment is commenced (Whittemore et al. 1992, Whittemore 1993, Mosgaard et al. 1997, Parazzini et al. 1997).

**Experimental studies**

The results of receptor and in vitro studies have also shown that ovarian cancer is an endocrine-related cancer (Amin et al. 1987, Galtier-Dereure et al. 1992, Langdon et al. 1994a, b, Hua et al. 1995, Miller & Langdon 1997).

Slotman & Rao (1988), in a comprehensive analysis of 52 studies, reported the presence of estrogen (ER) and androgen receptors (AR) in the majority of primary ovarian cancers (63% and 69% respectively). Progesterone receptors (PgR) were also found in about 50% of tumors. Similarly, 88% of ovarian cancers were found to express glucocorticoid receptors (Galli et al. 1981). There has been inconsistency regarding the presence of greater levels of hormonal receptors, particularly PgR, in ovarian adenocarcinomas of the endometrioid type and in postmenopausal women (Sutton et al. 1986).

Binding sites for gonadotropic hormones and gonadotropic releasing hormone have also been detected in ovarian tumors. The receptors for luteinizing hormone-releasing hormone (LHRH) were found in nearly 80% of human ovarian cancers (Simons et al. 1983).

Estrogen-stimulated growth has been demonstrated in several cell lines characterized by an ER content greater than 23–30 fmol/mg protein (Nash et al. 1989b, Langdon et al. 1994b, Miller & Langdon 1997). Cell lines with lower ER concentrations appear unresponsive (Langdon et al. 1994b). As in ER-positive breast cancer models, 17-β estradiol (E2) regulates expression of the number of proteins associated with growth and invasion. On exposure to E2, the ER content of ER-positive cell lines is downregulated and the PgR receptor content is increased, both in culture and in vivo (Hamilton et al. 1984, Geisenger et al. 1989, Nash et al. 1989b, Miller & Langdon 1997). Expression of transforming growth factor (TGF)-α is also increased and, consistent with the action of this growth factor, there is eventual downregulation of the epidermal growth factor (EGF) receptor (Simpson et al. 1996, Miller & Langdon 1997). Other growth factor-mediated events include increased expression of TGF-β and modulation of several insulin-like growth factor (IGF) binding proteins (Nash et al. 1989a, Kyrwicki et al. 1993, Miller & Langdon 1997). Estrogen also activates the early growth response genes c-myc and c-fos (Hua et al. 1995, Miller & Langdon 1997). Mutations in the putative tumor suppressor gene BRCA1 are strongly associated with familial ovarian cancer and expression of this gene was found to be regulated by estrogen in an ovarian cancer cell line (Miller & Langdon 1997, Romagnolo et al. 1996). E2 also upregulates expression of procathepsin D, a protease likely to be involved in invasion and metastases. Overexpression of c-erbB-2 and cathepsin D in cancer cell lines is found to override estrogen control, leading to estrogen resistance (Hua et al. 1995, Miller & Langdon 1997).

Antiestrogens, including tamoxifen, have been found to inhibit estrogen-stimulated growth in ER-positive cell lines and xenografts. However, as in the case of endometrial cancer, tamoxifen also showed a growth-stimulating effect
under certain circumstances (Langdon et al. 1994a, Miller & Langdon 1997). Tamoxifen and ICI 182,780 (steroidal pure antiestrogen) also had a significant apoptotic effect even on ER-negative ovarian cancer cell lines, and this was found to have a dose–response relationship (Ercoli et al. 1998).

Kikuchi et al. (1993) showed that the presence of tamoxifen or clomiphene potentiated the antiproliferative effect of cis-diaminedichloroplatinum (CDDP) in ER-negative CDDP-resistant cancer cells by enhancing CDDP uptake in ovarian cancer cells by 30–80%. Similar results were obtained by McClay et al. (1994), who showed that tamoxifen delays the development of resistance to cisplatin in human melanoma and ovarian cancer cell lines.

Animal experiments have also shown LHRH agonists to have an antiproliferative effect on ovarian cancer cells (Peterson & Zimniski 1990). Peterson et al. (1994) showed this response to be latent and transient. A study by Yano et al. (1994) showed that chronic exposure to LHRH antagonists reduced the concentration of receptors for EGF and IGF-I in tumor cell membrane. This phenomenon is related to tumor growth inhibition, suggesting a direct antitumoral effect, rather than exclusively one of inhibition of the pituitary–gonadal axis.

A study by Miyazaki et al. (1997) compared the antiproliferative effect of LHRH (AN-152) with that of doxorubicin, in nude mice bearing LHRH-receptor-positive and -receptor-negative ovarian cancer cell lines. They showed a significant antiproliferative effect on LHRH-positive ovarian tumors in nude mice even with the lowest tested dose of AN-152. An equivalent dose of doxorubicin caused substantial mortality.

Although the data regarding effects of androgens and progesterins are less extensive, Rose & Barnea (1996) reported the antiprogestin mifepristone to downregulate progesterone expression on human ovarian cancer cell lines. Mifepristone blocked cells in a G_0/G_1 phase and thus reduced the number of cells in the S phase. The efficacy of mifepristone was compared with that of taxol and tamoxifen in the same ovarian cancer cell line. Continuous exposure to tamoxifen resulted in a varied cytostatic response and in a transient change in the cell cycle. Taxol inhibited growth of some but not all cancer cell lines.

The data regarding glucocorticosteroids are controversial. Both dexamethasone and cortisol increase expression of c-erbB-2 by a post-transcriptional mechanism and inhibit production of the tumor marker CA 125 (Karlan 1988, Hua et al. 1995, Miller & Langdon 1997).

The postmenopausal ovary and steroid hormone production

The cortex of the postmenopausal ovary is thin. The remaining follicles are few and atretic. Granulosa cells have disappeared and are replaced by fibrocytes, and theca cells seem to differentiate towards interstitial cells of the stroma. These cells are still capable of hypertrophy and of steroid production in response to LH or human chorionic gonadotrophin. In contrast to the premenopausal situation, no cyclic variation in steroid hormone production by the ovary occurs after the menopause (Greenblatt et al. 1976).

Although production of progesterone ceases after menopause, lower levels of progesterone were observed in oophorectomized women than in postmenopausal controls (Bakstrom et al. 1983). The postmenopausal concentrations of androstenedione are roughly comparable to those in the early follicular phase (smallest premenopausal plasma values) (Abraham et al. 1969, Mahlick 1989). Concentrations are also lowest in oophorectomized women.

Testosterone concentrations do not decrease after the menopause, possibly because of an increase in postmenopausal gonadotropin. Another reason could be the unchanged binding capacity of sex hormone binding globulin after menopause, as metabolism acts only on the unbound fraction (Judd et al. 1974a,b, Mahlick 1989).

Ovarian estrogen production ceases after the menopause, but some aromatase activity remains. The main origin of the postmenopausal circulating estrogen, essentially estrone, is found in the extraovarian aromatization of androstenedione in the skin and adipose tissue (Grodin et al. 1973).

Mahlick (1989) showed that, in postmenopausal patients with epithelial ovarian cancer, plasma concentrations of progesterone, androstenedione, estradiol and testosterone were directly correlated with tumor volume and FIGO stage. Positivity for PgRs and the preoperative plasma concentration of progesterone were found to be independent prognostic factors for survival (Mahlick 1989, Sevelda et al. 1990 Harding et al. 1990). As in the case of CA 125 serum measurements (Makar 1995), changes in hormonal concentrations (with the exception of testosterone) reflected the response of ovarian cancer to therapy. The combined measurement of progesterone and androstenedione also allowed detection of disease relapse earlier than did clinical means, in the majority of patients (Mahlick 1989).

Contrary to these findings, in other studies no consistent correlation between the presence of steroid receptors and response to hormonal therapy was observed (From et al. 1991, Slotman & Rao 1988). However, more sensitive and specific assays of hormone receptors are needed, as defective processing mechanisms and heterogeneity of the receptors within the tumor may influence the results (O’Brien et al. 1981). Burger et al. (1999) showed a weak correlation between immunohistochemical and biochemical analyses of hormone receptors in ovarian tumors. This discrepancy was explained by heterogeneity of the receptor within the tumor and the presence of progesterone and androgen in the stromal section of the tumor. The study also showed that ERs are mostly present in the epithelial component (Burger et al. 1999).
Patient trials

Hormonal therapy for epithelial ovarian cancer has resulted in uneven but consistent responses. Unfortunately, most trials of hormonal treatment of ovarian cancer have included only limited numbers of patients and were retrospective. In addition, important patient characteristics, including histologic type and tumor grade, type and extent in addition to the response to previous treatments, were not critically defined in the majority of cases. Furthermore, most reports implied the use of hormonal therapy in a setting in which almost every line of standard chemotherapy had failed. This last observation is important, as the clinical efficiency of salvage chemotherapy in ovarian cancer is strongly influenced by the presence of platinum resistance, indexed as previous response to platinum-containing chemotherapy and a treatment-free interval between the last cytotoxic drug and the initiation of second line chemotherapy. It is therefore essential in considering any salvage program to know how effective this treatment is in patients considered clinically to be platinum refractory.

The earliest suggestion that ovarian cancer might be hormone sensitive was from a study published by Long & Evans in 1963. Using diethylstilbestrol in 14 patients with advanced ovarian cancer, four (28%) achieved a partial response. Estrogen might also decrease serum gonadotropin concentrations by a mechanism of negative feedback inhibition. This is in agreement with findings of epidemiologic studies suggesting a reduction in the death rate from ovarian cancer among women younger than 55 years to be consistent with a protective effect of the oral contraceptive pill (Mant & Vessey 1995). Estrogen replacement therapy was equally found to have no adverse effects in patients with ovarian cancer (Guidozi & Papone 1999).

Progestational agents have been the most extensively studied, although there has been inconsistency regarding doses and routes of administration (Bergquist et al. 1981, Rendina et al. 1982, Geisler 1983, 1985, Trope et al. 1982, Thigpen et al. 1984, Van Der Vange et al. 1995). The response rate in a series with adequate numbers of patients and response criteria was about 7% (Van Der Vange et al. 1995). No dose–response relationship was consistently found and the trial by Geisler (1983), using high doses of megestrol acetate (800 mg/day for 30 days, then 400 mg/day) and showing an objective response of 43%, could not be confirmed by others (Silic et al. 1986, Ahlgren et al. 1993, Wilailak et al. 1999). Although most of the reported series found no correlation between response and histologic types or grades, some overviews suggest more response in cases of serous and endometrioid adenocarcinomas of the ovary when given as first-line agents or after only a single alkylating agent (Bergquist et al. 1981, Rendina et al. 1982, Thigpen et al. 1984, Geisler 1985). Estrogen has the ability to induce PgRs, and was used in two different doses to enhance treatment by progestational agents (Jolles et al. 1983). The results showed no difference between the two dosages, and the overall response rate was 14% (9/65). A similar regimen was used by From et al. (1991), who observed a partial response in 17% of their patients.

Perhaps the first report of clinical activity of antiestrogens in ovarian cancer was that by Myers et al. (1981). Tamoxifen has been the most used antiestrogen: the literature contains reports of more than 500 patients with advanced ovarian cancer who were treated with this drug (Schwartz et al. 1982, 1989, Shirley et al. 1985, Slevin et al. 1986, Beecham et al. 1987, Weiner et al. 1987, Markman et al. 1996, Marth et al. 1997). The reported rates of response to tamoxifen varied between 0 and 28% and the overall response rate was of the order of 8%. However, a significant percentage of patients (20–75%) benefited from disease stabilization for some time. As in the case of trials with progestational therapy, most of the patients in these trials also were at a ‘pre’ terminal stage of disease and were refractory to different lines of treatment.

Markman, in 1996, updated a Gynecologic Oncology Group study evaluating tamoxifen in patients with advanced ovarian cancer after stratifying patients according to whether or not they were refractory to platinum. In 77 patients in the platinum-refractory group, a clinical response rate of 13% was described. The response rate in patients who were platinum sensitive did not differ markedly (15%). Stable disease was also found in more than 35% of patients with a median disease duration of 3 months. Van Der Velden et al. (1995) obtained a mean duration of stable disease of 11.5 months (4–30 months) when tamoxifen was started on the basis of increasing CA 125 serum concentrations without a clinically or radiologically detectable mass.

Although a Norwegian report (Marth et al. 1995) suggested a better response in endometrioid adenocarcinomas of the ovary, literature review reveals no apparent difference in histologic subtype, grade of tumor or hormone receptor values between responders and non-responders, and no correlation between response rate and tumor ER and PgR content was evident (Schwartz et al. 1982, 1989, Shirley et al. 1985, Slevin et al. 1986, Beecham et al. 1987, Weiner et al. 1987). Endometrioid tumors are known to have the best prognosis among all ovarian adenocarcinomas (Makar 1995, Makar et al. 1995). It remains an open question whether the better response observed with these tumors represents a therapeutic gain or merely reflects the behavior of biologically less aggressive tumors.

Only a few trials showed better responses with high doses of tamoxifen up to 80 mg (Ahlgren et al. 1993), and there is no convincing evidence that sequential use of tamoxifen and progestational agents improves response rates (Belinson et al. 1987, Jakobson et al. 1987).
The place of LHRH agonists in the management of ovarian cancer has also been evaluated, and the response rate observed in cases of chemotherapy-refractory ovarian cancer seems to be modest (Adelson & Reece 1993, Parmar et al. 1988, Bruckner & Motwani 1989, Kavanagh et al. 1989). Among the problems in evaluating the efficacy of such treatment is the enrolment of patients with expected poor outcome and the use of several different gonadotropin-releasing hormone (GnRH) analogs. It is unclear whether the various GnRH analogs possess similar antitumor potency in vivo, as marked differences in potency were observed in in vitro studies (Adelson & Reece 1993). In a review of the literature, Adelson & Reece (1993) reported statistically significant differences in the number of responders among patients treated with leuprolide as compared with those receiving goserelin.

In two reports including 59 patients, an objective response rate of 15% was observed in patients with advanced-stage disease (Parmar et al. 1988, Kavanagh et al. 1989); stable disease was reported in 12%. The study by Parmar et al. (1988), showed a mean duration of response of 10 months, and the median duration of response reported by Kavanagh’s group was 52 weeks. The findings of Kavanagh et al. (1989) also suggested a greater response rate among patients with highly differentiated tumors. Van Der Vange et al. (1995), reported a complete response using LHRH agonists for 38 months in patients with highly differentiated ovarian tumors. Furthermore, a prospective analysis reported 12% partial responses (clinical or radiological) in 32 patients with advanced refractory ovarian cancer who were treated with leuprolide acetate (Marinaccio et al. 1996). The mean duration of response was 8.7 weeks and all responders showed a significant decrease in CA 125 concentrations. In addition, 15% of patients had stable disease for a mean time of 5.2 months. A significant difference in survival was observed between responders and non-responders (P<0.05). All patients included in this study had either moderately or poorly differentiated tumors.

At least two studies with a total of 87 patients with advanced ovarian cancer, however, revealed no objective response to LHRH analogs (Scambia et al. 1990, Jager et al. 1995). The majority of patients in the report by Scambia’s group had poorly differentiated tumors; the paper by Jager et al. (1995) did not report tumor grade. Furthermore, the addition of GnRH analogs to first-line platinum-based chemotherapy did not seem to improve the outcome of patients with advanced ovarian cancer in the prospective randomized double-blind study including 135 patients with FIGO stages III and IV published by Emons et al. (1996). Similar results were reported by Erickson et al. (1994) and Falkson et al. (1996).

Alternative endocrine approaches in the hormonal treatment of ovarian cancer include the use of androgens, antiandrogens, and aminoglutethimide. Androgens have been used unsuccessfully (Kavanagh et al. 1987); negative results were also reported with aminoglutethimide (Rothschild et al. 1987, Ahlgren et al. 1993). From the theoretical point of view, antiandrogen therapy seems to be helpful. Decreased activity of aromatase enzyme in ovarian tumors leads to a local accumulation of androgens, as they are not converted to estrogen. As ovarian carcinomas without aromatase activity are AR-positive, androgen may influence the tumor cells through this receptor (Van Der Vange et al. 1995). This said, the literature contains few results suggesting beneficial effects with antiandrogen therapy (Slotman & Rao 1988, Van Der Vange et al. 1995).

Summary

Ovarian cancer is an endocrine-related cancer as shown by epidemiological, receptor and in vitro studies. In postmenopausal patients with epithelial ovarian cancer, the concentration of plasma progesterone has an independent prognostic significance and correlates with tumor volume, FIGO stage and response to chemotherapy. Furthermore, combined determination of progesterone and androstenedione concentrations allows early detection of disease relapse.

In contrast to findings in breast and endometrial cancers, receptor status in ovarian cancer was not predictive of hormonal response. Wide variations in the level of receptors in different cells from the same ovarian cancer have been observed, and the level of receptors in metastases appears to be lower than that in the primary tumor. The average magnitude of receptor concentration in ovarian cancer cells is lower than in breast or endometrial cancer cells, and ER concentrations of more than 100 fmol/mg – which are relatively common in breast cancer and have the greatest probability of response – are relatively uncommon in ovarian cancer (Miller & Langdon 1997). Although experimental studies have shown manifest antiproliferative activity in response to hormonal therapy that is comparable to that achieved with platinum, antracycline or taxol, even in the presence of ER-negative cell lines, response rates in patient trials remain modest. Also, the addition of hormonal therapy to standard first-line chemotherapy failed to improve either response or progression-free survival in a limited number of trials. However, it is unclear whether the marginal efficiency of endocrine therapies (at best around 10% of objective responses in phase II trials) can be substantiated in controlled trials. For ethical reasons controlled trials that evaluate the value of single agent hormonal therapy as first-line treatment are difficult to perform in ovarian carcinoma.

A large number of trials have evaluated the place of hormonal therapy in cases of disease relapse (mostly in patients at a preterminal stage of disease). The inconsistency in defining patients and tumor characteristics included in these trials, the wide variations in the dosages of drugs used
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(partially in case of progesterational agents) and the variety of preparations used that had different potency (particularly in case of GnRH analogues), are all factors that explain why the correct place of hormonal therapy in the management of ovarian cancer remains poorly evaluated, notwithstanding an objective response of around 8% and stable disease in a significant number of patients. In addition to the critical need to identify new drugs that are active in combattting ovarian cancer, it is also important to develop rational therapeutic strategies for the relapsed/refractory setting that focus on optimizing quality of life. The 8% objective response rate of tamoxifen in platinum-refractory ovarian cancer establishes this agent as equaling the demonstrated antitumor effectiveness of more toxic regimens such as hexamethylmelamine and ifosfamide. In view of the favorable toxicity profile of tamoxifen, certainly as compared with alternative cytotoxic chemotherapeutic drugs, it is not difficult to justify treating an individual with advanced ovarian cancer with this agent despite being unable to ‘prove’ that the ‘stable disease state’ is the direct result of treatment with this antihormone agent. Finally, future studies are needed to evaluate the place of tamoxifen or other hormonal therapy in different settings in ovarian cancer such as:

1. Consolidation therapy for patients with pathological complete response after first-line chemotherapy. Hormonal therapy can be randomized with placebo.
2. Therapy for asymptomatic patients with an increasing CA 125 antigen concentration after first- or second-line chemotherapy.
3. Activity in patients previously treated with paclitaxel.
4. Identification of subsets of patients with less aggressive tumors who might derive maximum benefit from hormonal therapy, such as those with highly differentiated tumors, diploid tumors, tumors with c-erbB-2 expression, or tumors with high steroid receptor content (Iversen 1988, Berchuck et al. 1990, Kaern et al. 1990, Makar et al. 1994, Van Der Vange et al. 1995, Miller & Langdon 1997).

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