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Review

Hormonal therapy of endometrial cancer

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Abstract

Hormonal therapy of advanced or recurrent endometrial cancer is a well-established therapeutic option. Patients most likely to respond have lower grade tumours and possess progesterone receptors on the surface of their cancer cells.

Keywords: Endometrial cancer; Hormonal therapy; Progesterone

Endometrial cancer is a highly curable malignancy, with an overall 5-year survival rate for all stages combined of >80% [1]. Unfortunately, for the relatively small population of women presenting with distant spread of this cancer, or who develop metastatic disease, treatment options are limited [2], and include judicious use of surgery and local radiation therapy, as well as systemic anti-neoplastic pharmaceutical agents.

It has long been recognised that the development of endometrial cancer is strongly associated with excess oestrogen production, either from endogenous sources (e.g., obesity), or exogenous exposure (e.g., unopposed oestrogen use in post-menopausal women) [3–6]. This knowledge led to initial efforts in the 1950s to employ the hormone, progesterone, as an anti-cancer therapy for women with endometrial cancer, with the first formal report of the clinical utility of this strategy in 1961 [7].

Subsequent experience suggested that as many as one-third of women with metastatic or recurrent endometrial cancer will achieve an objective response when treated with one of several available progesterone preparations [8], although more recently reported trials with rigorously-defined endpoints have noted the response rate is somewhat lower (20–25%) [9–11]. While most remissions are partial in extent and relatively brief in duration, occasionally patients remain without progression of the disease process for extended periods of time (>2 years). For example, for the 145 patients with advanced or recurrent endometrial cancer who received medroxyprogesterone at a dose of 200 mg/day in a Gynecologic Oncology Group (GOG) trial, the median progression-free and overall survival figures were 3 months and 11 months, respectively [9].

While the precise mechanisms for the anti-cancer effects of progesterone are unknown, this class of agents has been shown to control cellular proliferation, induce differentiation and interfere with the invasive potential of endometrial cells [12].

A number of clinical features associated with endometrial cancer have been demonstrated in both retrospective laboratory studies, and prospective clinical trials, to be useful in the selection of patients who may be predicted to have a greater opportunity to achieve objective and subjective (improvement in cancer-related symptoms) benefit from the administration of a hormonal-based management strategy (Table 1) [2,9,10].

The presence of progesterone receptors on endometrial cancer cells has been shown to be strongly associated with the potential for a tumour to decrease in size following such therapy. In the previously noted GOG trial, the objective response rate was 37% in the patient

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Table 1
Clinical features predictive of a favourable response to hormonal therapy in endometrial cancer

Presence of high levels of progesterone receptors on cancer cells
Grade 1 cancers
Extended treatment-free interval between initial diagnosis and subsequent development of metastatic cancer

population defined as having progesterone receptor-positive disease (16 of 46 patients), while only 8% of women responded (7 of 86 patients) if the cancer was progesterone receptor-negative [9].

Tumour grade also influences response, with only 9% of 127 patients with grade 3 cancers responding in the GOG study, compared with 37% of 59 individuals with grade 1 cancers [9]. Cancers histologically classified as being grade 2 experienced an intermediate response rate (23% of 113 patients). An earlier study performed by the GOG reached similar conclusions, with 37% of 30 patients with grade 1–2 endometrial cancers achieving an objective response, but only 8% of grade 3 tumours (2 of 24 patients) responded [10].

Patients whose cancers are of lower tumour grade and possess progesterone receptors experience superior survival, compared with those individuals with higher-grade cancers that lack hormonal receptors [9,13]. In the GOG study, the median survival for patients with grade 1 cancers was 18.8 months, compared with only 6.9 months for grade 3 tumours [9]. Of note, these data make it more difficult to assess the direct impact of hormonal therapy on survival in advanced endometrial cancer, since it is not possible to know if patients live longer because of a response to treatment, or if responses occur in individuals who would have already been predicted to experience a superior outcome.

With the demonstrated strong association between the presence, or absence, of progesterone receptors in defining the opportunity for a patient to achieve a favourable therapeutic outcome following hormonal therapy, it is interesting to inquire why some tumours which possess receptors fail to respond, while a limited number of cancers which appear to not express receptors on their cell surface will exhibit regression. Investigators have demonstrated substantial heterogeneity in the distribution of the progesterone receptor within an individual tumour specimen [14,15]. Thus, a small biopsy containing limited tumour tissue may not be highly representative of the receptor status in the entire cancer. In addition, normal endometrial tissue, which possesses receptors, may contaminate the sample and result in a "false-positive" determination for the presence of progesterone receptors in the tumour itself. Heterogeneity for the presence of progesterone receptors between cancer cells in the primary endometrial specimen and metastatic sites has also been noted, with a demonstrated substantial reduction in the percentage of tumours that would be classified as being receptor-positive if only the metastatic sites were evaluated [16].

Progesterone preparations are available for both oral and parenteral administration. Currently available data indicate either method of delivery is acceptable in clinical practice as treatment of metastatic endometrial cancer. A direct comparison of serum levels following oral or intramuscular administration of progesterone revealed higher medroxyprogesterone concentrations following use of the oral route, although the clinical implications of this finding are uncertain [17].

High-dose progesterone therapy (e.g., medroxyprogesterone acetate 1000 mg/day) has been investigated as a method to improve the effectiveness of hormonal treatment of endometrial cancer. Both phase 2 experience [10], and the results of a randomised phase 3 trial [9], have failed to demonstrate the superiority of this approach, compared with delivery of lower dose (e.g., medroxyprogesterone acetate 200 mg/day) regimens.

The major toxic effects of progesterone when employed at dose levels routinely used in the treatment of endometrial cancer include the development of thrombophlebitis, pulmonary emboli, weight gain and oedema [9,10]. With high-dose regimens, clinically relevant hyperglycaemia has been noted [10].

The hormone, tamoxifen, widely used as a strategy to both treat and prevent breast cancer, has been demonstrated to increase the risk of endometrial cancer [18–20]. Paradoxically, tamoxifen has also been shown to be an effective agent in the management of metastatic endometrial cancer [21]. While there have been no direct comparisons of tamoxifen to progesterone when employed in this clinical setting, the phase 2 response rate to tamoxifen (10%) observed in a GOG trial was approximately one-half that seen by the cooperative group when progesterone was employed in a similar patient population [9,10,21]. Further, tamoxifen is inactive in patients whose tumours have been shown to be resistant to a progestational agent or chemotherapy [22]. As with progesterone therapy, low-grade endometrial cancers are far more likely to respond to treatment with tamoxifen, compared with high-grade tumours [21]. One advantage of tamoxifen over progesterone preparations is the lack of significant weight gain. For a patient who would be an appropriate candidate for treatment with a hormonal agent, but where this potential side-effect is an important consideration, tamoxifen may be a reasonable therapeutic option.

Provocative data have suggested that treatment with tamoxifen can increase the percentage of endometrial cancer cells that contain progesterone receptors, as well as the concentration of surface receptors [23]. This experience would argue that combination hormonal therapy, with tamoxifen followed by a progesterone preparation, may be more effective therapy than either agent alone.

Unfortunately, a GOG trial evaluating this provocative concept has failed to demonstrate any improvement in the objective response rate compared with single agent hormonal treatment [11].

Other hormonal agents have been explored for a role in the management of metastatic or recurrent endometrial cancer. Of potential interest, it has been shown that a high percentage of endometrial cancer cells possess receptors for gonadotropin-releasing hormone, including high-grade cancers [24]. While one study involving treatment of endometrial cancer with a gonadotropin-releasing hormone analogue observed a 28% objective response rate [25], another trial failed to reveal any meaningful activity [26]. Further study of this class of agents is required before any conclusions can be drawn regarding their utility in this clinical setting.

Combination therapy employing a cytotoxic drug and a hormonal agent has been investigated in the treatment of endometrial cancer in several very small clinical trials. There is currently no evidence for the superiority of this approach, compared with either management strategy alone. Further, delivering a hormone with a cytotoxic agent negates one of the major advantages associated with use of hormone therapies, i.e., elimination of the side-effects associated with cytotoxic drugs (e.g., emesis, fatigue, alopecia, neutropenia, neuropathy). Therefore, it is appropriate to conclude that currently there is no role for this management approach outside of the investigative setting.

Conflict of interest statement

None declared.

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