Editorial

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Endometrial cancer: a frequent orphan disease

Endometrial cancer is the most frequent invasive cancer of the female genital tract, with an estimated annual incidence of almost 38 000 in the 'old' European Union (before 1 May 2004) and a similar figure in the United States. It is substantially more frequent than ovarian cancer, but can be cured more often by surgery and radiation therapy; this results in about 9000 deaths per year in the EU and 7000 in the United States [1,2]. Epidemiological risk factors for endometrial cancer are well known [3], but the optimal therapy of endometrial cancer has been poorly investigated. While there exists a certain consensus for surgical therapy in so far as a total abdominal hysterectomy and bilateral salpingo-oophorectomy should be performed, the value of pelvic and paraaortic lymphadenectomy remains unproven. Indeed, the frequently cited rationale for retroperitoneal lymphadenectomy, namely the avoidance of adjuvant radiation therapy for node-negative disease, may be wrong in the light of a recently published trial, GOG-99 [4].

The role of adjuvant radiation therapy has been defined much more clearly in recent years, at least for patients with stage I and very early stage II disease. Pelvic radiation therapy dramatically reduced the risk of locoregional recurrence in three randomised controlled trials [4–6], regardless of whether or not retroperitoneal lymphadenectomy was part of the standard surgical procedure. None of these trials revealed a significant beneficial effect of radiotherapy on survival.

The adjuvant medical therapy of endometrial cancer remains poorly investigated. A systematic review and meta-analysis of the Cochrane Collaboration revealed that the adjuvant use of progestational agents may indeed be dangerous. They do not significantly reduce the risk of recurrence and endometrial cancer-related death, but significantly increase the risk of non-cancer-related death [7]. Numerous small trials have investigated the efficacy of adjuvant chemotherapy in endometrial cancer, but were not adequately powered to detect a difference in survival (reviewed in [8]). Adjuvant chemotherapy with doxorubicin and cisplatin has been compared with whole abdominal radiation therapy in stage III and IV disease, and chemotherapy turned out to be superior to radiotherapy with regards to progression-free (hazard ratio 0.81) and overall survival (hazard ratio 0.71; $P < 0.05$) [9].

Similarly, the knowledge base for the therapy of recurrent and metastatic endometrial cancer is small at present. High doses of oral medroxyprogesterone acetate were not found to be more active than lower doses [10]. For cytotoxic chemotherapy, phase I and II trials are abundant, but while they are useful to estimate the efficacy of drugs, they do not contribute to defining the best choice of therapy. A few major randomised controlled trials are nevertheless available (Table 1) in addition to numerous small trials (reviewed in [8]). The combination of doxorubicin and cisplatin is considered standard therapy based upon two trials [11,12] that revealed a very moderate advantage of the combination over single drug doxorubicin, despite the greater toxicity experienced with the combination.

An important trial reported in this issue of *Annals of Oncology* builds upon this foundation and on the promising activity of paclitaxel in phase II trials. The randomised comparison of the standard three-weekly doxorubicin (60 mg/m^2) plus cisplatin (50 mg/m^2) with doxorubicin (50 mg/m^2) plus paclitaxel (150 mg/m^2 as a 24-h infusion) plus filgrastim was performed in an exemplary manner, based upon sound principles of clinical trial design. The randomisation yielded comparable groups of patients, and the selection of patients represented the population of endometrial cancer patients. Despite promising results from preliminary trials and the activity of paclitaxel in a phase III trial [13], the chemotherapy regimens did not differ significantly in terms of activity and toxicity. While this may seem disappointing, at least two points are illustrated: (i) promising observations in phase II trials may be due to patient selection bias and need not be confirmed in randomised trials; and (ii) cisplatin or carboplatin may be essential in the therapy of endometrial cancer. The latter hypothesis is supported by two very recent trials [13,14].

A more general issue, however, also deserves a mention: certain neoplasias that are much rarer than endometrial cancer have been far better investigated. For instance, only 8000 cases of Hodgkin's disease are diagnosed annually in the United States, and a similar number is expected for the European Union; a substantial majority of these patients can be cured by chemotherapy and/or radiotherapy, such that $\sim$1300 patients a year die from Hodgkin's disease in the United States [2]. A long series of trials organised by many collaborative groups in different countries have optimised chemotherapy and radiotherapy to the current state of the art, which allows the majority of patients, even with advanced stage Hodgkin's disease, to be cured. By comparison, endometrial cancer appears to be a poorly investigated orphan disease indeed, despite its frequent occurrence. A substantial decrease in the incidence of endometrial cancer is unlikely in the next few years, and early detection methods have not been proven to have a major impact on mortality [15]. Thus, our efforts should be focused on improving all treatment modalities for endometrial cancer. Such progress will have to begin in the minds of those who care for patients with endometrial cancer. This tumour is neither rarer nor less interesting than other neoplasias that have been studied successfully. In addition to elucidating the molecular events that lead to and characterise endometrial cancer, the oncology community is obliged to set

Table 1. Major randomised controlled trials of chemotherapy for advanced endometrial cancer

Trial	No. of patients	Randomised chemotherapy regimens	Median progression-free survival	Median survival	Comment
Thigpen et al., 1993 [11]	223	Doxorubicin versus doxorubicin + cisplatin	3.9 versus 6.2 months		
van Wijk et al., 2003 [12]	177	Doxorubicin versus doxorubicin + cisplatin	7 versus 8 months	7 versus 9 months	Significant survival benefit for patients with good performance status
Thigpen et al., 1994 [16]	356	Doxorubicin versus doxorubicin + cyclophosphamide	3.2 versus 3.9 months	6.7 versus 7.3 months	
Fleming et al., 2004 [13]	266	Doxorubicin + cisplatin versus doxorubicin + cisplatin + paclitaxel + G-CSF	At 5 months, 50% versus 67%	At 12 months, 50% versus 58%	
Gallion et al., 2003 [17]	342	Standard timed doxorubicin + cisplatin versus circadian timed doxorubicin + cisplatin	6.5 versus 5.9 months	11.2 versus 13.2 months	
Weber et al., 2003 [14]	63	Doxorubicin + cisplatin versus carboplatin + paclitaxel	At 15 months, 24% versus 35%	At 15 months, 27% versus 41%	Randomised phase II trial
Fleming et al., 2004 [18]	317	Doxorubicin + cisplatin versus doxorubicin + paclitaxel + G-CSF	7.2 versus 6.0 months	12.6 versus 13.6 months	

G-CSF, granulocyte colony-stimulating factor.

up and complete clinical trials of endometrial cancer surgery, radiation therapy and medical therapy. At present, the North American Gynecologic Oncology Group is leading the way, but despite regulatory agencies increasingly threatening clinical research, similar contributions will have to be made in Europe.

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