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Identifying patients unlikely to benefit from further chemotherapy: A descriptive study of outcome at each relapse in ovarian cancer

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Abstract

Objective. Not all patients with relapsed ovarian cancer (EOC) benefit from further treatment and thus treatment should be selectively applied.

Methods/patients. A retrospective review of survival and response outcomes in 120 women with relapsed EOC, all treated at original diagnosis with surgery and platin plus paclitaxel, who had all their initial and subsequent relapse therapy carried out at the BCCA.

Results. In those patients selected for re-treatment upon relapse, lack of progression rates were 63%, 50%, 45%, 44%, 29%, and 20% respectively for first through sixth relapse. The corresponding median survivals from that relapse were 14, 10, 6, 7, 8, and 5 months. A predictive model based upon the length of the interval between the two preceding relapses (or diagnosis to 2nd relapse) predicted which patients would survive less than 6 months (patient defined "lack of benefit" to chemotherapy criterion): diagnosis to second relapse <12 months; first to third relapse <6 months; second to fourth <6 months; third to fourth <6 months, and fifth to sixth <6 months.

Conclusion. In selected patients, multiple episodes of re-treatment are of value. A time-based statistic identifies those who will not benefit, defined as survival less than 6 months.

Keywords: Re-treatment; Lack of progression; Epithelial ovarian cancer

Introduction

Recurrent epithelial ovarian cancer (EOC) can be regarded as a relatively chronic disease in which repeated rounds of chemotherapy can be useful [1]. Unfortunately, there is little or no information as to the potential outcomes in third or subsequent relapse upon which the patient and physician can make rationale treatment decisions. Outcome data are needed as not all patients will benefit from further chemotherapy (benefit being defined as symptomatic improvement, tumor shrinkage/stabilization, or life extension). However, this lack of benefit does not prevent physicians from treating patients indiscriminately as opposed to selecting those who truly have the potential to benefit. The goal of the physician is to maximize the quality of life while minimizing the toxicity and this mandates not giving unnecessary/ineffective treatment [2–4].

Hence, this is a retrospective review of the outcomes of 120 women with relapsed, advanced ovarian cancer. All were treated at diagnosis with surgical debulking and a platinum analogue plus paclitaxel. Response to treatment, time to next progression, and survival outcomes after each relapse/progression are presented. A survival model that identifies those patients not to re-treat at relapse, based upon the length of the preceding progression-free intervals, is presented.

Methods

All women with stage III, residual positive and stage IV EOC who were diagnosed prior to December 1999 (to allow for a minimum follow up time of 4 years) were identified

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from the British Columbia Cancer Agency (BCCA) computerized patient data base. Only those women who had both their primary treatment and all their subsequent relapse therapies at the BCCA were included in the study cohort. Their primary therapy upon diagnosis had to be a platinum analogue plus paclitaxel (docetaxel was not used at the BCCA in this era). Those not treated at BCCA were excluded as treatment details/response data were often unavailable. There was no algorithm defining which drugs to use upon relapse, in what order, for how long, or who should be treated, but the oncologists involved are all members of the same Gynecology Tumor Group and have similar treatment philosophies/approaches. The number of drugs available to treat relapse increased as the follow-up period progressed. Platins, paclitaxel, and etoposide initially and then, more latterly, gemcitabine, topotecan, liposomal doxorubicin, and vinorelbine. Single agents were usually employed but more latterly carboplatin plus paclitaxel became the standard for the platinum sensitive, first relapse group [5]. The decision whether to re-treat at each relapse, or not, was made by the treating physician with the patients input. No fixed criteria were used, but essentially this revolved around (1) where any other effective drugs available, (2) expectation of response, and (3) desires of the patient. Treatment duration, as with first-line therapy, was usually six cycles unless there was progression or unacceptable toxicity. Occasionally (<5%), it was longer than this if there was ongoing evidence of tumor shrinkage without undue toxicity.

Data were abstracted and entered into a computerized database. For each relapse, information on date of relapse (clinical and serologic), treatment at relapse, outcome, marker level at relapse, performance status, and hematologic parameters were recorded. Patients were not routinely re-staged at each relapse and thus information on sites of disease and size of lesions was not available. Surgical and pathologic data from the time of original diagnosis were also recorded. This retrospective chart review did not require approval by the Institutional Review Board as its conduct was part of ongoing patient management.

Relapse for the purpose of this review was defined clinically, i.e., physical evidence of cancer upon examination or imaging. Serologic relapse alone was not used as our treatment philosophy is not to perform routine marker follow-up post primary chemotherapy. Similarly, routine imaging of the asymptomatic patient was not carried out. Clinical relapse was used so as to be consistent with the literature which uses this end point, not serologic relapse, as the basis for the time-oriented definitions of "sensitive/resistant/refractory" relapse [6,7].

Survival probabilities were estimated according to the method of Kaplan and Meier and compared by the log rank test [8,9]. Overall survival (OS) times were recorded from diagnosis and then from each subsequent clinical relapse or progression. Progression-free survival (PFS) was taken as the time from date of diagnosis to first clinical relapse/progression or from the date of diagnosis of clinical relapse/progression until the subsequent relapse/progression. Multivariable analysis was carried out using Cox regression model using SPSS system. Chi-square test was used for comparisons between treated and non-treated patients.

Response to each treatment was the best ever with no minimum time interval. Complete response (CR) was the disappearance of all disease with normalization of CA 125; partial response (PR) was a 50% or greater shrinkage in the sums of the products of the bidimensional diameters of measurable lesions (or diameters of unidimensionally measurable lesions); progressive disease (PD) was 25% or greater increase in diameter or new lesions or worsening cancer-related symptoms with continuing increase in CA 125. Stable disease (SD) was anything between partial response and progression and had to be maintained for a minimum of three cycles. Non-evaluable disease status (NED) was allocated if the disease was not measurable but did not progress. "Lack of progression rates" are utilized in this report and are the combination of CR plus PR plus SD plus NED, maintained for a minimum of three cycles of chemotherapy. Growing cancer on chemotherapy occurring after three or more cycles of chemotherapy was regarded as relapse not progression. The patient would however be switched to another agent.

Results

Patients

136 patients, of whom 120 subsequently relapsed or progressed, were treated with a platinum analog (either cisplatin or carboplatin) plus paclitaxel as first-line therapy for advanced epithelial ovarian cancer between March 1993 and November 1999 at the Vancouver and Fraser Valley Clinics of the BCCA and had all their subsequent relapse therapy at these clinics. Patients treated with carboplatin or cisplatin alone as their primary therapy were excluded from this analysis. These patients were treated either in the period 1993–1995 when paclitaxel usage was only in the setting of clinical trials (the standard treatment was single agent platinum) or more latterly because their physicians had assessed them as not suitable for initial combination therapy (Table 1).

87 had total abdominal hysterectomy, bilateral salpingo-oophorectomy, and omentectomy as their initial surgery. The remainder had a lesser procedure. Gynecologic oncologists performed 43% of the surgeries, gynecologists 49%, and general surgeons 9%. Gynecologic oncologists and gynecologists did not differ in their type of surgery (69% and 66% rates of total abdominal hysterectomy, bilateral salpingo-oophorectomy/omentectomy). Interval debulking was attempted in 32 (24%) of patients. 76% had papillary serous histology.