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Treatment Issues in Clear Cell Carcinoma of the Ovary: A Different Entity?

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Learning Objectives

After completing this course, the reader will be able to:

1. Discuss the clinical features of OCCC.
2. Discuss the current data regarding treatment strategies and outcome of patients with OCCC.
3. Explain the rationale for using alternative treatment approaches (i.e., clinical trials) in patients with OCCC.

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Abstract

Background. **Ovarian clear cell carcinoma (OCCC) is a distinct histopathologic subtype of epithelial ovarian cancer (EOC) with an incidence of <5% of all ovarian malignancies. Our goal was to review the clinical features and management of patients with OCCC.**

Methods and Results. **We performed a PubMed search using the phrase "clear cell ovarian cancer." We reviewed 54 articles referring to OCCC. OCCC patients have a high incidence of stage I disease and frequently present with a large pelvic mass. Recurrences are more frequent with this entity than with other types of EOC. The clinical management of advanced EOC includes maximal cytoreduction and platinum plus paclitaxel–based chemotherapy. The survival rates of patients with advanced OCCC are lower than those of patients with advanced serous EOC (serous subtype). The poor response rate to platinum-based regimens may be related to the intrinsic chemoresistance of these tumors. Despite their aggressive clinical course, OCCCs are still treated similarly to the other EOCs at the present time, because the rarity of these tumors prevents the conduction of randomized studies.**

Conclusion. **Novel treatment approaches should be adopted in OCCC. Molecular-targeted therapies and effective new agents without cross-resistance to platinum compounds should be evaluated in a prospective clinical trial in OCCC.** ***The Oncologist*** *2006;11:1089–1094*

Introduction

Ovarian cancer is more lethal than all gynecological malignancies combined in Western society [1]. The current standard treatment of epithelial ovarian cancer (EOC) of all histological subtypes involves primary optimal debulking surgery followed by cisplatin/paclitaxel-based chemotherapy. Despite, however, the significant advances in surgery and chemotherapy achieved over the past decades, the resulting overall 5-year survival rate in patients presenting with advanced-stage disease remains quite low, approximately 40%, probably as a result of the lack of effective therapies [2–5].

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In 1973, the World Health Organization (WHO) strictly defined ovarian clear cell carcinomas (OCCCs) as lesions characterized by clear cells growing in solid/tubular or grandular patterns as well as hobnail cells lining tubules and cysts [6]. Generally, it consists of <5% of all ovarian malignancies and its incidence is in the range of 3.7%–12.1% of all EOCs [7–11]. Since 1973, a growing body of reports has recognized these tumors as a distinct pathologic subtype in contrast to other histologic types of EOC [8, 9, 11–15]. These tumors have a high incidence of stage I disease [8, 12], frequently present as a large pelvic mass [8, 12, 16, 17], rarely occur bilaterally, and are often associated with endometriosis [8, 12, 16], thromboembolic vascular complications [12, 18], and hypercalcemia [8, 18].

Staging

Data from the literature support the tendency of OCCC to present at earlier stages [14]. Behbakht et al. [14], in a series of 45 OCCC patients, found 27 (60%) stage I and five (11%) stage II cases for an overall rate of 71%, while Nishino et al. [19] reported that, in a series of 20 patients, the majority (90%) were in stage I/II (12 patients Ic, one patient IIa, five patients IIc). Similarly, Kennedy et al. [20] reported an incidence of 60% for early stages (stage I and II). In other studies, the proportion of stage I/II OCCC is in the range of 59%–66% [8, 11, 12, 15, 17, 21, 22]. Skirnisdottir et al. [22] reported that OCCCs were frequently found (64%) in International Federation of Gynecology and Obstetrics (FIGO) stages Ic and IIc, and that this was more common than with non-OCCC. In a comparative study by Jenison et al. [12] of OCCC versus the serous subtype, 59% of OCCCs were early stage, compared with 40% of the serous subtype. The reason for the presentation at early stages of OCCC is the earlier diagnosis because of the frequent presentation of these tumors as a pelvic mass, often large [14].

Tumor Size

Several studies have reported that OCCCs present predominantly as a large pelvic mass. Behbakht et al. [14] reported that OCCCs were in the range of 3–20 cm and all these tumors were detected before surgery, either by clinical examination or by preoperative imaging techniques. Similarly, other investigators [8, 23, 24] described tumors in the range of 5–30 cm in diameter. While serous and mucinous primary peritoneal cancers have been described, none of these studies reported a primary peritoneal variant of OCCC.

Because the screening of ovarian cancer relies on the presence of an ovarian mass as a marker of early cancer, the in-depth study of cancers that frequently present at an early stage as a pelvic mass may shed some light on the pathophysiology of cyst formation. In vitro data support a different behavior for clear cell tumors than for epithelial tumors. In an in vitro model of ovarian cancer, cells originating from clear cell tumors remained attached to the mesothelial cells without invading for >18 hours, whereas cells from serous tumors invaded rapidly into the mesothelial cell layer. This behavior in vivo may explain the propensity for clear cell tumors to remain localized until they cause the formation of a pelvic cyst. This may be related to a specific genetic prevalence in this particular histological type of ovarian cancer [25]. It is possible that OCCCs are also associated with a distinct portfolio. Further investigation into the in vitro behavior and genetics of OCCC is warranted.

Recurrence of Early and Advanced Stages

Recurrences are more frequent than expected based on series of early-stage EOC (Table 1). Sugiyama et al. [15] reported recurrence in 27% of stage I patients, 37% of stage Ic patients, and 30% of stage II patients. The median time to recurrence was 12.2 months in patients with stage I/II OCCC. Behbakht et al. [14] reported recurrence rates of 37% in stage I and 54% in stage Ic patients, with a median time to recurrence of 35 months. Similarly, Kennedy et al. [8] reported recurrence in all six patients with stage Ic disease, whereas Pather and Quinn [21] reported that one in three patients with stage I disease developed recurrence despite adjuvant chemotherapy. In contrast, Hreshchyshyn et al. [26] reported a 6% recurrence rate in stage I EOC patients treated with adjuvant chemotherapy and Nishino et al. [19] reported only one recurrence among 18 patients with stage I/II disease treated with an adjuvant combination of irinotecan and mitomycin-C. That patient developed recurrence in the para-aortic lymph nodes 18 months after the initial chemotherapy. She was alive and free of disease 58 months after surgery and combination chemotherapy with carboplatin and docetaxel.

In the series of Behbakht et al. [14], 29% of patients had stage I/II disease. Six of these patients with measurable residual disease were treated with paclitaxel and either cisplatin or carboplatin. There were four partial responses. Of these, three were alive after 10, 13, and 18 months of follow-up and one died 21 months after diagnosis. One stage IV patient died during treatment. All the remaining six patients recurred, with a median time to recurrence of 4 months. In the series of Kennedy et al. [8], there were 17 patients with stage III and eight patients with stage IV disease. The median progression-free survival times were 0.9 and 0.4 months for stage III and IV, respectively, and the median survival times were 1.7 and 0.7 months, respectively. Survival decreased with increasing stage, and no patient with stage IV disease survived for 5 years. Sugiyama et al. [15] reported recurrences in 62% of stage III and 73% of stage

Table 1. Retrospective studies on OCCC compared with other EOCs

Study	Number of patients with OCCC	Comparison group	Chemosensitivity of OCCC	Survival of OCCC compared with other types
Kennedy et al. [8]	29	305 patients with non-OCCC	Few objective responses to adjuvant chemotherapy	Early stages had survival similar to the other EOCs, whereas advanced stages had a dismal prognosis
Omura et al. [10]	24 patients with stages III and IV	702 women with stages III and IV non-OCCC	Disease progression on chemotherapy	Patients with advanced stages had more dismal outcome than all other histologies except mucinous
Sugiyama et al. [15]	101	235 patients with serous subtype	Resistance to platinum	Dismal outcome
Pectasides et al. [30]	35 patients with stages III and IV	70 serous subtype	Resistance to platinum	Survival times did not differ significantly
Goff et al. [13]	24 patients with stage III	34 papillary serous tumors	Poor response to platinum-based therapy	Patients with stage III OCCC had shorter median survival
Kennedy et al. [20]	64	High-grade epithelial ovarian cancer patients		Matched for grade and stage, the overall survival in OCCC is identical to that of other high-grade EOCs
Recio et al. [18]	111	109 patients with EOC non-OCCC	Poor response to platinum-based chemotherapy; no difference in outcome between platinum and nonplatinum regimens in OCCC	

IV patients. The recurrence rate increased as the clinical stage advanced from stage Ic to stage IV ($p = .12$). Similarly, Pather and Quinn [21] reported 11 tumor recurrences and 10 deaths among 18 patients with locally advanced and advanced disease (IIc, IIIc, and IV).

Prognosis and Management

Recent trends in the clinical management of advanced EOC include increased attention to maximal cytoreduction and a general acceptance of platinum plus paclitaxel–based chemotherapy. Clinical studies using this regimen [27] have included only a small percentage (2%) of patients with OCCC, and thus the effects of this regimen applied to OCCC are as yet undetermined.

Many investigators have studied the prognosis of patients with OCCC compared with that of patients with serous EOC. However, no clear agreement has been documented. Some reports published since 1970 have indicated no difference in outcome between patients with OCCC and their stage-matched, serous-subtype counterparts [7, 28]. In addition, Kennedy et al. [8] reported that stage I and II patients with OCCC had survival that was similar to that of patients with other EOCs, while stage III and IV OCCC patients had a more dismal outcome. Contrary to the aforementioned reports, several recent studies indicated that advanced-stage OCCC has a poor prognosis [8, 10, 12, 15, 29]. The Gynecological Oncology Group (GOG), evaluating cisplatin plus cyclophosphamide with or without doxorubicin in stage III, optimally cytoreduced patients, showed that the group of OCCC patients had a poor outcome in response to platinum-based chemotherapy. Of the 24 advanced OCCC patients, 52% progressed on primary chemotherapy and an additional 16% had progressive disease at re-exploration [13]. Recently, Sugiyama et al. [15] reported a very low response rate of 11.1% and a high incidence of progressive disease (81.5%) with platinum-based chemotherapy in patients with OCCC, whereas patients with the serous subtype had a high response rate of 72.5% and a low incidence of progressive disease. The results in our study confirmed that advanced stages of OCCC have a low response rate of 45%, compared with 81% for the serous subtype [30].

We recently reported that the survival rates of patients with advanced OCCC were lower than those of patients with advanced serous subtype. However, this difference in survival between patients with OCCC and those with the serous subtype was not statistically significant [30]. These findings are in line with the results of the majority of the previous studies. Goff et al. [13] reported that patients with stage III OCCC, compared with serous histology patients, had a shorter median survival duration. Also, Kennedy et al. [20] showed that stage III OCCC patients experienced a 5-year survival rate of only 26%, while stage IV patients had a 0% chance of survival at 5 years. However, they reported that the 5-year survival rate (17%) of patients with stage III/IV OCCC was not significantly different from that (22%) of patients with other high-grade, stage III/IV EOCs. In addition, Omura et al. [10] reported that OCCC conferred the worst prognosis in stage III and IV EOC of all types, except mucinous histology. Sugiyama et al. [15] reported that the survival rate for stage III OCCC patients was significantly

lower than that of stage III serous subtype patients. The median survival duration of patients with advanced stage III disease was 12.7 months, compared with 26.8 months for patients with serous histology. However, Recio et al. [18] demonstrated that platinum-based chemotherapy did not appear to improve the 5-year survival rate of patients administered nonplatinum-based chemotherapy (36% versus 32%). They suggested that OCCCs generally lack sensitivity to conventional platinum-based chemotherapy such as cisplatin and cyclophosphamide (CP) with or without doxorubicin (CAP). In support of this, an in vitro study by Gorai et al. [31] demonstrated that OCCC cells exhibited resistance to cisplatin. Our findings are in line with those reported by other investigators [8, 10–12, 15, 29]. The low response rate contributed to poor survival in our study. At any rate, the retrospective nature of our study, as well as similar studies, does not permit firm conclusions. Our patients received various platinum-based regimens (CP, CAP, platinum plus 5-day continuous infusion 5-fluorouracil [5-FU], platinum-based monotherapy, or platinum or carboplatin plus paclitaxel), and therefore definitive conclusions cannot be drawn. It is also clear that optimal cytoreduction improves outcome in advanced EOC patients [32]. In our study, although the percentage of patients surgically cytoreduced to <2 cm residual tumor in OCCC was similar to that of patients with the serous subtype, the lower response rate translated to a worse prognosis for patients with OCCC.

Recently, combination chemotherapy with platinum plus paclitaxel–based chemotherapy has been accepted as the standard regimen for EOC. Ho et al. [33] demonstrated the potential benefit of a carboplatin and paclitaxel regimen for stage I OCCC. Few papers have specifically addressed the efficacy of cisplatin plus paclitaxel–based chemotherapy for advanced OCCC. Ho et al. [34] treated 23 patients with advanced OCCC (16 pure [using WHO criteria], defined as typically clear cells or hobnail cells present in papillary, solid, or tubulocystic patterns, and seven with mixed-type histology, defined as the presence of other epithelial cell types and clear cell carcinoma, where each epithelial component is not <10%) with cisplatin plus paclitaxel and 22 (15 pure and 7 mixed type) with conventional cisplatin-based chemotherapy. Overall, for patients with pure OCCC, 58% had progression, compared with only 22% in those with mixed-type histology ($p = .127$). The median survival time of patients with pure OCCC was 11 months, compared with >48 months (the median survival had not been reached) for those with mixed-type histology ($p = .003$). The estimated 5-year survival rate for patients with pure OCCC was 12%, compared with 61.4% for those with mixed-type histology. The tumor behavior of mixed-type OCCC seemed similar to that of serous histology.

The poor response rate to platinum-based regimens may be related to chemoresistance. In support of that conclusion, an in vitro study indicated that OCCC cells exhibited resistance to platinum [31]. The mechanisms underlying OCCC resistance to platinum-based chemotherapy is not yet understood. Several mechanisms that may be involved in drug resistance have been proposed, including a decrease in the accumulation of the drug and an increase in detoxification of the drug within the cell and an increase in DNA repair [35–37]. Multidrug resistance is an important and well-defined mechanism of drug resistance. The low proliferation rate of OCCC may also contribute to its resistance to chemotherapy [38, 39]. Currently, no antineoplastic agent is definitively effective for OCCC based on large-scale clinical studies, and the mechanism of resistance to chemotherapy in OCCC is not well understood. The in vitro chemosensitivity of 23 antineoplastic drugs using four established cell lines has been studied. Irinotecan was found to be effective for OCCC [40]. Ohta et al. [41] evaluated the cytotoxicity of chemotherapeutic agents in four OCCC and two serous subtype lines. Paclitaxel was more effective in clear than in serous cell lines. The intensification of cytotoxicity was observed in the combinations of cisplatin plus paclitaxel and cisplatin plus cyclophosphamide or 5-FU irrespective of histopathological features, indicating individualized regimens may improve survival in ovarian cancer patients. Reed et al. [42] found higher mRNA levels of ERCC1 and XPB (two key genes in the nucleotide excision repair pathway) in OCCC, indicating de novo drug resistance against DNA-damaging agents. Some promising results have been reported with the combination of cisplatin plus irinotecan [43]. Shimizu et al. [44] suggested that irinotecan and mitomycin-C may have activity in OCCC. Based on in vitro chemosensitivity data [45], they conducted a phase II trial of combined irinotecan and mitomycin-C in 25 patients with cisplatin-refractory clear cell and mucinous EOC. They reported an overall response rate of 52% and a median survival time of 15.3 months. Similarly, Tanaka et al. [46] reported encouraging results with the combination of mitomycin-C and irinotecan. The combination of a fixed dose (80 mg/m^2) of nedaplatin and a rising dose (from 60 mg/m^2 to 80 mg/m^2) of irinotecan was administered to patients with advanced OCCC based on the results of chemosensitivity tests. With this combination, a pathologic complete response was achieved in a patient with advanced OCCC [47].

Recent molecular studies support the hypothesis that OCCC represents a biologically distinct entity. Some investigators [48–50] found a mutation in the tumor suppressor gene *p53* more often in the serous subtype than in OCCC. Patients with tumors overexpressing *p53* have a response to chemotherapy that is significantly inferior to that of patients with *p53*-negative tumors [48, 50]. In contrast, K-*ras* onco-

gene activation is more often found in mucinous EOC than in nonmucinous EOC [47]. Tsuda et al. [51] examined the DNA, mRNA, and protein levels of cyclin E and the protein level of P53 in 44 OCCCs and 39 serous subtype EOCs using microdissected tissues. Relative cyclin E mRNA expression was significantly higher in the OCCCs (3.62; 95% confidence interval [CI], 2.24–4.99) than in serous subtype EOCs (1.75; 95% CI, 1.05–2.45; $p = .0098$). The percentage of positive nuclear staining of cyclin E was significantly higher in OCCC (48.3%; 95% CI, 40.4%–56.1%) than in the serous subtype (25.3%; 95% CI, 17.4%–33.3%; $p = .0001$). The percentage of positive nuclear staining of cyclin E was significantly higher in *p53*-positive cases (51.8%; 95% CI, 40.0%–63.5%) than in *p53*-negative cases (36.2%; 95% CI, 28.2%–44.2%; $p = .028$). Cyclin E expression was significantly related to *p53* positivity. They concluded that cyclin E expression is significantly higher in OCCC than in the serous subtype. Tanabe et al. [52] found no difference in the overexpression rate of HER-2/*neu* among ovarian histologic subtypes. This overexpression was not a risk factor for outcome in OCCC. The role and incidence of microsatellite instability (MSI) in OCCC remain unknown. Cai et al. [53] conducted a trial to evaluate the frequency of MSI in OCCC and to evaluate the sensitivity and specificity of immunohistochemistry in predicting mismatch-repair gene deficiency. Forty-two OCCCs were analyzed for MSI using a panel of five microsatellite markers (BAT25, BAT26, D5S346, D2S123, and D17S250). Alterations in the expression of hMLH1 and hMSH2 proteins in these tumors were examined. Of the 42 OCCCs analyzed, six demonstrated a high level of MSI (MSI-H), three demonstrated a low level of MSI (MSI-L), and the remaining 33 exhibited microsatellite stability (MSS). Loss of expression of either hMLH1 or hMSH2 was observed in four of the six (66.7%) MSI-H tumors, whereas 34 of the 36 (94.4%) MSI-L or MSS tumors expressed both the *hMLH1* and *hMSH2* gene products. They concluded that MSI-H is involved in the development of a subset of OCCC. A strong correlation exists between alterations in the expression of *hMLH1* and *hMSH2* and the presence of MSI-H in these tumors. Tsuchiya et al. [54] investigated the oligonucleotide array technique to identify genes generally involved in OCCC. All examined OCCC specimens had nuclear staining for hepatocyte nuclear factor (HNF)-1β, compared with non-OCCC specimens, which showed no immunostaining or focal and faint staining in the nucleus. They suggested that HNF-1β could be a molecular target for therapy of OCCC.

OCCC is still treated in the same manner as other EOCs at the current time, without any particular consideration, because of its low rate of incidence among EOCs. The current data are provocative and suggest that a new strategy for chemotherapy in OCCC should possibly be adopted, one that focuses on new agents without cross-resistance to platinum compounds. Additionally, in vitro studies using OCCC cell lines and evaluation of patients with this disease may help define the pathophysiological role of chemoresistance in these tumors. Effective new agents should be evaluated in a prospective clinical trial in the treatment of OCCC as soon as possible.

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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