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Chemotherapy for Primary and Recurrent Epithelial Ovarian Cancer

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Abstract

Epithelial ovarian cancer is the second most common gynecological cancer. It causes more deaths despite advances in treatment over the last few decades. Following explorative surgery and after histological assessment, the tumor can be formally “staged” according to the size, extent and location of the cancer. Staging during surgery determines the appropriate treatment regimen and the long-term outcome (prognosis). Recommendations for treatment after surgery are dependent on the stage of the cancer. Chemotherapy is recommended after surgery for stage III or IV ovarian cancer; certain tumor factors determine its use in stage I or II disease.

Keywords: chemotherapy, ovarian cancer, recurrence

1. Introduction

Epithelial ovarian cancer is the second most common gynecological cancer. It causes more deaths despite advances in treatment over the last few decades.

Epithelial ovarian cancer is the most common histological subtype diagnosed, accounting for 80% of cases [1]. It arises from the coelomic epithelium, 75% are serous cystadenocarcinoma, other types are less frequent and include endometrioid, mucinous, Brenner transitional cell, clear cell and unclassified carcinomas. Germ cell and sex cord-stromal tumors represent the other 20% [1].

2. Staging

Following explorative surgery and after histological assessment, the tumor can be formally “staged” according to the size, extent and location of the cancer. Staging during surgery determines the appropriate treatment regimen and the long-term outcome (prognosis).

Recommendations for treatment after surgery are dependent on the stage of the cancer. Chemotherapy is recommended after surgery for stage III or IV ovarian cancer; certain tumor factors determine its use in stage I or II disease.

3. Chemotherapy in advanced and metastatic ovarian cancer

3.1. History of chemotherapy

Twenty years ago, patients with advanced ovarian cancer were treated most commonly with the alkylating agents such as cyclophosphamide, chlorambucil, thiotepa and melphalan, all as monotherapy. These drugs have resulted in overall objective response rates between 33 and 65% and complete clinical responses in nearly 20% of patients [2].

In 1970, cisplatin was established by Wiltshaw and Kroner [3] as one of the most active agents for ovarian cancer, with a reported overall response rate of 26.5% in 34 patients who were resistant to alkylating agents. Moreover, Young et al. [2] obtained objective responses (one was complete) in 29% of 25 patients refractory to alkylating agents.

The North Thames Cooperative Group reported in 1985 the results of the first randomized comparison of first-line cisplatin and an alkylating agent cyclophosphamide in women with advanced ovarian cancer, it demonstrated significantly longer survival and response duration rates in patients receiving platinum therapy [4].

3.2. Which platinum: carboplatin or cisplatin?

The meta-analysis of the advanced ovarian cancer trialists group and two trials comparing cisplatin with cyclophosphamide and carboplatin + cyclophosphamide showed that cisplatin and carboplatin have the same activity in ovarian cancer [1].

3.3. What is the effective dose of platinum?

A retrospective review reported a significant correlation between the dose intensity of cisplatin and response rates and survival [4]. Data from 10 trials focusing on platinum agents in approximately 2000 patients showed improvements in outcomes with doses up to 25 mg/m²/week [5]. When the dose is increased above this there is increasing toxicity but without any clinical benefit observed [5]. In respect to carboplatin, clinicians use AUC from 5 to 7.5 [1].

3.4. What drug should be combined with platinum (the role of taxane)?

3.4.1. Anthracycline

Five meta-analyses from 10 trials in 1702 patients compared cyclophosphamide plus cisplatin with cyclophosphamide, cisplatin and doxorubicine (C A P), a modest but significant improvement in survival was seen for the regimen using doxorubicine (overall hazard ratio 0.85, P 1/4 0.003) [5]. Most investigators in the United States abandoned the use of anthracycline in 1986 due to cardiotoxicity that may outweigh the clinical benefit [5].

3.4.2. Paclitaxel

A significant development in the treatment of ovarian cancer was the discovery of the taxane class of cytotoxics. Two randomized controlled trials of first-line cisplatin based dual therapy showed additional clinical benefit when cyclophosphamide was replaced by paclitaxel [6, 7].

The Gynecological Oncology Group (GOG) 111 trial studied 386 women with stage III suboptimally debulked or stage IV disease [6]. Whereas the intergroup OV10 trial had wider selection criteria and assessed 675 women with FIGO stage IIb, IIc, III or IV disease with or without successful debulking surgery [7].

In GOG 111, patients received paclitaxel at 135 mg/m² over 24 h with cisplatin at 75 mg/m² or cyclophosphamide at 750 mg/m² every 3 weeks for a total of 6 courses. The same drugs were studied in OV10 and paclitaxel was given at 175 mg/m² over 3 h. The median follow-up intervals were 38.5 and 37 months in the OV10 and GOG 111 studies, respectively; the combination of platinum and paclitaxel is more effective with respect to OS and PFS. Hence the chemotherapy regimen is based on this combination.

3.5. Carboplatin as a substitute for cisplatin

Regimens containing carboplatin and paclitaxel were generally better tolerated than cisplatin plus paclitaxel in three major studies in which the two doublets showed similar efficacy.

The Dutch/Danish study [8], treated 208 patients and Arbeitsgemeinschaft Gyneco-oncology (AGO) study [9] examined 798 patients (3 weekly paclitaxel at 175 or 185 mg/m² given over 3 h plus cisplatin at 75 mg/m² with carboplatin AUC 5 or 6 plus the same dose of paclitaxel). Patients in both studies had stage IIb, IV and were followed up for a median of 37 months [8]. The GOG 158 trial compared 792 eligible patients with optimal stage III disease given paclitaxel 135 mg/m² over 24 h added to cisplatin at 75 mg/m² with paclitaxel 175 mg/m² over 3 hrs added to carboplatin AUC 7.5 [10].

The final results from AGO, GOG 158 and Dutch/Danish study noted little difference between treatments in the median PFS (the median overall survival was similar between treatment arms in each study), toxicities were mainly as expected, paclitaxel plus carboplatin were better tolerated [8–10].

4. Neoadjuvant chemotherapy

Neoadjuvant chemotherapy (NAC) followed by interval debulking surgery (IDS) has been proposed in the management of advanced Epithelial ovarian cancer in order to increase the rate of complete optimal surgery with less surgical morbidity [11–13]. Reserved initially for unresectable disease or for patients in bad and poor general condition, the use of NAC and IDS has increased over the past two decades and frequently the first debulking is now realized only after several cycles of chemotherapy [11, 13]. Vergote et al. [11] in a large phase III randomized trial including patients with advanced stages IIIc-IV reported the non-inferiority of interval surgery after 3 cycles of NAC compared to upfront surgery [11]. The hazard ratio for death (intention-to-treat analysis) in the group assigned to neoadjuvant chemotherapy followed by interval debulking was 0.98 (90% confidence interval [CI], 0.84–1.13; $P = 0.01$ for non-inferiority) [11].

However, in clinical practice, optimal surgical timing and selection criteria for neoadjuvant chemotherapy and interval surgery remain controversial. Retrospective studies and meta-analyses observed a large survival advantage for patients receiving initial and complete removal of all macroscopic tumors prior to chemotherapy [14]. Moreover, the quality of surgery was heterogeneous in the EORTC trial among participating centres with variations in surgical aggressiveness and rates of complete resection, residual tumor of 1 cm or less was achieved in 42% of patients in the primary cytoreduction arm and in 81% of patients in the NACT arm. In the intent to treat analysis, the NACT arm was non inferior to the primary surgery arm with respect to the primary outcome of overall survival [14]. This argument explains the comparatively low survival observed for those treated with upfront surgery in this study. Furthermore, retrospective data have also suggested that NAC and IDS compared to primary surgery may increase the risk of developing platinum-resistant disease and less sensitive recurrent disease [15]. A minimum of 6 cycles of treatment is recommended including at least 3 cycles of adjuvant therapy after interval debulking surgery [16].

5. Targeted therapy

The addition of bevacizumab (a humanized monoclonal antibody to VEGF) to first-line chemotherapy based on platinum-taxane in advanced ovarian cancer demonstrated a significant improvement of PFS. This was evaluated in GOG-218 [17] a phase 3 trial in which they randomly assigned patients with newly diagnosed stage III (incompletely resectable) or stage IV epithelial ovarian cancer who had debulking surgery to receive one of these three treatments:

1. Cycles 1–6: carboplatin, AUC 6 Paclitaxel, 175 mg/m² Placebo (starting in cycle 2) every 3 wk. Cycles 7–22: placebo every 3 weeks.
2. Cycles 1–6: carboplatin, AUC 6 Paclitaxel, 175 mg/m² Bevacizumab, 15 mg/kg (starting in cycle 2) every 3 weeks the Cycles from 7 to 22 patients received Placebo every 3 weeks.
3. Cycles 1–6: carboplatin, AUC 6 Paclitaxel, 175 mg/m² Bevacizumab, 15 mg/kg (starting in cycle 2) every 3 weeks the Cycles from 7 to 22 patients received Bevacizumab at 15 mg/kg every 3 weeks.

The median progression-free survival was 10.3 months in the control group, 11.2 in the bevacizumab-initiation group, and 14.1 in the bevacizumab-throughout group [18].

The administration of bevacizumab during and up to 10 months after paclitaxel and carboplatin chemotherapy prolongs the median progression-free survival by about 4 months in patients with advanced epithelial ovarian cancer [18].

Similar results were obtained in the ICON-7 trial [19] where a total of 1528 women from 11 countries were studied, 70% had stage IIIC or IV ovarian cancer. In this study patients were randomly assigned to carboplatin and paclitaxel (175 mg/m²) every 3 weeks for 6 cycles, or to this regimen plus bevacizumab (7.5 mg/Kg), given every 3 weeks for 5 or 6 cycles and continued for 12 more cycles or until disease progression. The PFS at 36 months was 20.3 months with chemotherapy alone, as compared with 21.8 months with chemotherapy plus bevacizumab. In the updated analyses, PFS at 42 months was 22.4 months without bevacizumab versus 24.1 months with bevacizumab ($P = 0.04$); in patients at high risk for disease progression, the benefit was greater with bevacizumab than without it, with PFS at 42 months of 18.1 months with bevacizumab, versus 14.5 months with standard chemotherapy, with median overall survival of 36.6 and 28.8 months, respectively [19].

These observations suggest that effectiveness of anti-angiogenic therapy may be greater in more advanced disease. However this was not supported by other studies testing the impact of different anti-angiogenesis factors added to chemotherapy in advanced ovarian cancer [18]. Both pazopanib [20] and nintedanib [18] showed a significant increase in PFS in patients with small tumors. The PFS benefit of the addition of nintedanib to first-line chemotherapy resulted in a more pronounced effect in the non-high-risk subgroup (stage II or stage III and residual ≤ 1 cm) with 27.1 vs. 20.8 months. In contrast, there was no significant benefit noted for high risk patients (FIGO IV or stage III with residual tumors). Pazopanib as maintenance therapy after first line chemotherapy showed a significant advantage with respect to PFS compared to the control group 17.9 vs. 12.3 months, HR 0.77, $P = 0.0021$) [18].

6. Intraperitoneal chemotherapy

The peritoneal cavity is the most common route of ovarian cancer spread.

The rationale for giving chemotherapy directly into the peritoneal cavity is supported by pre-clinical, pharmacodynamics and pharmacokinetic data [21]. Compared with intravenous (IV) treatment, intraperitoneal (IP) administration allows an increase in drug concentration inside the abdominal cavity.

In the majority of patients, epithelial ovarian cancer is confined to the peritoneal cavity at initial diagnosis and in recurrence [22]. As a result ovarian cancer is a good target for intraperitoneal therapy.

The hypothesis of improved effectiveness is explained by the increasing concentration of the cytotoxic agent in the tumor microenvironment. Analysis of intratumoral drug concentrations demonstrates that higher drug exposure is observed for lesions 2–3 mm or smaller

when intraperitoneal administration is performed compared with intravenous infusion [23]. Moreover, avascular tumors are more exposed to higher drug concentrations with intraperitoneal rather than intravenous administration [24].

A meta-analysis of five clinical trials confirmed a benefit in OS for intraperitoneal chemotherapy [25]. This led to a National Cancer Institute alert in 1996 recommending that intraperitoneal chemotherapy should be considered in patients with small volume (<1 cm) or no residual disease after surgery [16]. However, this has not been adopted as a standard care of in the majority of institutions and countries due to its great toxicity [16].

7. Adjuvant chemotherapy in early stage disease

After surgery, there is still a risk that cancer cells remain and may return or spread to other organs of the body. Adjuvant chemotherapy is administered after surgery to destroy these cells and improve the chance of curing ovarian cancer and to decrease the risk of the death due to ovarian cancer.

A recent Cochrane meta-analyses of five prospective clinical trials (4 of 10 with platinum-based chemotherapy) demonstrated that chemotherapy is more beneficial than observation in patients with adequately staged early-stage ovarian cancer [26]. Patients who received adjuvant chemotherapy had better OS [hazard ratio (HR) 0.71; 95% confidence interval (CI) 0.53–0.93] and PFS (HR 0.67; 95% CI 0.53–0.84) than patients who did not receive adjuvant treatment [26].

Two-thirds of the patients included in the two major studies were suboptimally staged, in optimally staged patients, benefit for chemotherapy cannot be excluded, Long-term follow-up of the ICON 1 trial confirms the benefit of adjuvant chemotherapy, particularly in those patients at higher risk of recurrence (stage 1B/C grade 2/3, any grade 3 or clear-cell histology) [26].

Therefore, adjuvant chemotherapy should be recommended not only to suboptimally staged patients but also to those optimally staged at higher risk of recurrence [16].

8. Recurrent ovarian cancer

Recurrent ovarian cancer can be diagnosed by the appearance of new symptoms, radiologic evidence of recurrent disease or a rising CA-125 level in an asymptomatic patient.

In the past, treatment for recurrent ovarian cancer was given based on rising levels of tumor markers alone even without symptoms. However, a phase III randomized study (OV05-EORTC 55955) demonstrated no survival benefit of starting chemotherapy based on the increasing level of CA-125 alone and that quality of life may be improved by awaiting the appearance of symptoms or signs of ovarian cancer recurrence.

In this study treatment was delayed by a median of 4.8 months with no benefice on OS (HR 1.01; 95% CI 0.82–1.25; $P = 0.91$) [27]. Similarly, third-line treatment was started 4.6 months

earlier in the patients who had regular CA 125 monitoring. Quality of life was lower in the early treatment group [27].

The choice of chemotherapy agents in recurrent disease is based on the response to first line treatment, the current symptoms; the time elapsed from last chemotherapy and the side effects of previous drugs administered.

The prognosis and the response to second-line therapy and subsequent lines depends in great part on the progression-free interval after the last dose of the preceding line of chemotherapy.

We define:

- Platinum-refractory disease when the progression occurs during treatment or within 4 weeks after the last dose.
- Platinum-resistant disease as a progression within 6 months of platinum-based therapy;
- Partially platinum-sensitive disease when the progression occurs between 6 and 12 months;
- Platinum-sensitive patients progressing with an interval of more than 12 months (GCIG Consensus) [28].
- For patients with platinum-sensitive recurrent ovarian cancer: carboplatin-doublet should be the treatment of choice [16].

A meta-analysis including four randomized trials confirmed an improvement in PFS with a HR of 0.68 (95% CI 0.57–0.81) and OS with a HR of 0.8 (95% CI 0.64–1.0) [29]. The phase III Calypso [30] trial compared two doublets, taxol and carboplatin vs. carboplatin with pegylated liposomal doxorubicin (PLD). The PFS with the second regimen (11.3 months) was not inferior to the taxane-carboplatin (9.4 months, $P < 0.001$, HR = 0.82) [3]. However the PLD regimen was better tolerated because of the minimal incidence of neuropathy, alopecia, and arthralgia and with less hypersensitivity reactions [3].

Again, the selection between the different options of platinum-based doublets should be based on the previous toxicity profile and convenience of administration [16].

Bevacizumab (Avastin) has also been studied as a treatment option in patients with recurrent ovarian cancer. The phase III OCEANS [31], study performed in women with platinum-sensitive recurrent ovarian cancer compared gemcitabine plus carboplatin with or without bevacizumab for 10 cycles followed by bevacizumab alone until disease progression or toxicity as compared to placebo. Chemotherapy with bevacizumab improved PFS, 12 months with bevacizumab vs. 8 months in the placebo group, as well as the response rate (79 vs. 57%, $P < 0.001$) [31].

Regimens based on non-platinum combinations are another option for patients with platinum-sensitive disease. In a phase III randomized trial OVA 301 [32], PLD alone was compared with PLD combined with the Mariane-derived alkaloid trabectedin (Yondelis), this combination regimen improved the PFS [32], Median PFS was 7.3 months with trabectedin/PLD vs. 5.8 months with PLD (hazard ratio, 0.79; 95% CI, 0.65–0.96; $P = 0.0190$). Overall response rate (ORR) was 27.6% for trabectedin/PLD vs. 18.8% for PLD ($P = 0.0080$) [32].

It has been hypothesized that this benefit is due to the restoration of 'platinum-sensitivity' by prolonging the platinum-free interval. This is now being explored in two prospective randomized trials [16].

8.1. Maintenance therapy in platinum-sensitive recurrent ovarian cancer

Many clinical trials have evaluated the role of drugs aimed at prolonging the second remission. One of these is the OCEANS trial that demonstrated the role of bevacizumab as noted above in combination with chemotherapy and as maintenance therapy [31]. Chemotherapy with bevacizumab improved PFS, 12 months with bevacizumab vs. 8 months in the placebo group, as well as the response rate (79 vs. 57%, $P < 0.001$) [31].

In women with the BRCA mutation, the Poly-ADP ribose polymerase (PARP) inhibitor: rucaparib, olaparib is an active drug; a trial assessed olaparib in women with recurrent advanced ovarian cancer; the overall response rate was 34% (complete response, 2% and partial response, 32%) [33].

The FDA approved olaparib for patients with advanced ovarian cancer who have received treatment with 3 or more lines of chemotherapy and have germline BRCA mutation [34].

8.2. Platinum-resistant recurrent ovarian cancer

8.2.1. Treatment selection

In platinum-resistant recurrent cancer, patients should be treated with non-platinum based chemotherapy. The treatment aims to palliate symptoms, optimizing quality of life and prolonging life. In general in this case, response rates are low and the prognosis is poor.

We should use non cross-resistant agents and avoid toxicities based on side effects that have developed from previous therapies, in general higher response rates and PFS rates longer than 2–3 months are obtained with the use of combination regimens. But combination drugs is associated with higher toxicity without any improvement in OS compared with the use of single agent therapy [16]. In fact, for the platinum-resistant cancer, a treatment based on single agent is preferable since it may offer a balance between efficacy and toxicity.

8.2.1.1. Taxane

Many drugs have documented activity in platinum-resistant disease. In phase II and III trials, the use of single agent paclitaxel has permitted objective responses in 22–30% of patients [35].

8.2.1.2. Pegylated liposomal doxorubicin

A phase III trial compared PLD with topotecan [36] in women with recurrent ovarian cancer, patients were stratified prior to being randomized according to the platinum sensitivity of their tumor. Similar results were obtained for each of these regimens with respect to the overall RR (20 vs. 17%), time to progression (22 vs. 20 weeks) and median OS (60 vs. 56.7 weeks) [36]. PLD has resulted in a significant OS benefit with longer follow up, mainly for patients

with platinum-sensitive disease, and PLD was found to be significantly superior to topotecan ($P = 0.008$) [36].

Compared with topotecan, PLD caused lower rates of neutropenia, thrombocytopenia and was associated with higher rates of hand foot syndrome and stomatitis [36].

8.2.1.3. Topotecan

Topotecan has similar efficacy to paclitaxel and PLD in the treatment of platinum-resistant recurrent ovarian cancer [36, 37]. Its use is usually associated with some degree of myelosuppression especially neutropenia.

Monochemotherapy is therefore the standard of early “platinum-resistant” relapse of ovarian cancers [16].

The use of bevacizumab was demonstrated in the AURELIA trial that showed an improved PFS in patients with platinum-resistant ovarian cancer treated with bevacizumab in combination with single agent chemotherapy when compared to treatment with chemotherapy alone (5.7 vs. 4 months) [38].

9. Summary

Chemotherapy is the first systemic treatment of epithelial ovarian cancer at all disease stages. It is based on platinum with paclitaxel in the adjuvant and neoadjuvant setting. In advanced stage cases chemotherapy with bevacizumab improved the response.

Most cases of newly diagnosed ovarian cancer will respond to initial therapy, but 80% or more will ultimately relapse and further chemotherapy may be indicated. Newer strategies involving gene testing such as BRCA has proven to be an important addition to the treatment strategy. The choice of treatment for recurrent disease is based on the duration of response to prior therapy, previous treatment toxicity and quality of life.

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