AHFS Final Determination of Medical Acceptance:
Off-label Use of Sequential IV Paclitaxel, Intraperitoneal Cisplatin, and Intraperitoneal Paclitaxel for Initial Adjuvant Treatment of Optimally Debulked Stage III Epithelial Ovarian Cancer

**Drug/Drug Combination:** IV paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel

**Off-label Use:** Initial adjuvant treatment of optimally debulked stage III epithelial ovarian cancer

**Criteria Used in Selection of Off-label Use for Review:**

- Clinical results from a randomized phase 3 trial

**Strength of Evidence:** Level 1 (High strength/quality)

**Strength of Study End Point(s):** Progression-free survival and overall survival

**Grade of Recommendation:** Recommended use (Accepted)

**Narrative Summary:**

**Use:**

Combined IV and intraperitoneal therapy with IV paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel has been used for the treatment of optimally debulked stage III epithelial ovarian cancer.\(^{1000}\)

The National Cancer Institute (NCI) recommends use of a combined IV and intraperitoneal regimen for eligible patients with advanced epithelial ovarian cancer because of a substantial survival benefit.\(^{1000}\) Based on clinical trials, NCI recommends that use of a regimen containing intraperitoneal cisplatin (100 mg/m\(^2\)) and a taxane (either IV only or IV plus intraperitoneal) should be strongly considered following primary surgery in patients with optimally debulked stage III epithelial ovarian cancer.\(^{1000}\) Although an optimal intraperitoneal chemotherapy regimen has not been established,\(^{1000}\) favorable results were observed following sequential administration of IV paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel in the Gynecologic Oncology Group (GOG)-172 study.\(^{1000}\)

In this randomized phase 3 trial (GOG-172), 429 patients with previously untreated stage III epithelial ovarian cancer or primary peritoneal cancer, with no residual mass exceeding 1 cm in diameter following surgery, received either combined IV and intraperitoneal therapy or IV therapy.\(^{1000}\) All patients enrolled in this study had good baseline GOG performance status (0–2) and adequate bone marrow, renal, and hepatic function.\(^{1000}\) Most patients (88%) had ovarian cancer, and serous adenocarcinoma was the most common histologic type (79% of patients).\(^{1000}\) The primary end points of the study were progression-free survival and overall survival.\(^{1000}\) Combined IV and intraperitoneal therapy consisted of IV paclitaxel 135 mg/m\(^2\) by 24-hour infusion on day 1, followed by intraperitoneal cisplatin 100 mg/m\(^2\) on day 2 and intraperitoneal paclitaxel 60 mg/m\(^2\) on day 8.\(^{1000}\) IV therapy consisted of IV paclitaxel 135 mg/m\(^2\) by 24-hour infusion on day 1 followed by IV cisplatin 75 mg/m\(^2\) on day 2.\(^{1000}\) Both regimens were repeated every 21 days for up to 6 cycles.\(^{1000}\) Patients who received combined IV and intraperitoneal therapy had longer median progression-free (23.8 versus 18.3
months) and overall (65.6 versus 49.7 months) survival compared with patients who received IV therapy.10001 Most (83%) of the patients receiving IV therapy completed 6 cycles of their assigned chemotherapy regimen; however, only 42% of patients receiving combined IV and intraperitoneal therapy completed 6 cycles of assigned chemotherapy; patients who could not complete the intraperitoneal regimen received IV therapy for the remaining treatment cycles.10001 The most common reason for discontinuance of intraperitoneal therapy was catheter-related complications.10001 Grade 3 or 4 leukopenia (76 versus 64%), GI effects (46 versus 24%), metabolic effects (27 versus 7%), fatigue (18 versus 4%), neurologic effects (19 versus 9%), infection (16 versus 6%), thrombocytopenia (12 versus 4%), and pain (11 versus 1%) occurred more frequently in patients receiving combined IV and intraperitoneal therapy than in those receiving IV therapy.10001 Although patients receiving combined IV and intraperitoneal therapy reported less improvement in abdominal discomfort before cycle 4, improvement in abdominal discomfort was similar in both treatment groups 1 year after completion of therapy.10002, 10010 Among patients who received combined IV and intraperitoneal therapy, quality of life was worse during and shortly after completion of therapy (before cycle 4 and at 3–6 weeks following therapy) compared with those who received IV therapy.10001,10002 Quality-of-life scores were similar for the groups at 1 year after completion of treatment, except for greater persistence of moderate paresthesias in patients receiving combined IV and intraperitoneal therapy.10001, 10002, 10005

Retrospective review of baseline data (patient and disease characteristics) from two phase 3 clinical trials (including GOG-172) for patients receiving intraperitoneal therapy for optimally debulked stage III epithelial ovarian cancer suggested that extent of residual tumor mass, histology, and age were important predictors of survival in such patients.10004 Patients with clear cell histology appeared to derive less benefit from intraperitoneal therapy compared with those with serous histology (hazard ratio for progression-free and overall survival of 2.66 and 3.88, respectively).10004 In addition, each additional year of age was associated with a 1% increase in the risk of death.10004 Although patients enrolled in the studies had optimally debulked (1 cm or less residual tumor mass) disease, survival was greater in patients with only microscopic residual disease.10004

Retrospective analysis of data from patients receiving a modified IV and intraperitoneal regimen suggests that a reduced dosage of intraperitoneal cisplatin administered in conjunction with a shortened IV paclitaxel infusion time may result in less toxicity and produce a survival benefit similar to that reported in the GOG-172 study (67 months versus 65.6 months reported in GOG-172).10001, 10008 The modified IV and intraperitoneal regimen consisted of IV paclitaxel 135 mg/m² by 3-hour infusion on day 1, followed by intraperitoneal cisplatin 75 mg/m² on day 2 and intraperitoneal paclitaxel 60 mg/m² on day 8 of each 21-day cycle.10008 Most patients (80%) completed 4 or more cycles of therapy and 55% completed 6 cycles.10008 The frequency of grade 3 or 4 neutropenia (12%), GI effects (8%), metabolic effects (5%), neurologic effects (6%), infection (2%), fatigue (2%), and thrombocytopenia (0%) in this series of patients receiving the modified IV and intraperitoneal regimen appeared to be lower than toxicity rates reported in the GOG-172 study.10008 By shortening the infusion time for IV paclitaxel to 3 hours, the modified regimen also may provide an outpatient alternative to inpatient administration over 24 hours.10008 However, randomized controlled trials are needed to establish comparative safety and efficacy of this modified regimen.10008 The modified IV and intraperitoneal schedule containing the lower intraperitoneal cisplatin dosage and the 3-hour IV paclitaxel infusion also has been studied in conjunction with a third cytotoxic drug, but with evidence of excessive toxicity.10013, 10014

Based on current evidence, combined IV and intraperitoneal therapy with IV paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel is recommended (accepted) for use as initial adjuvant treatment of optimally debulked stage III epithelial ovarian cancer in patients with good performance status (GOG performance status of 0–2).

Dosage:

When combined therapy with intraperitoneal cisplatin and IV and intraperitoneal paclitaxel has been used for the initial adjuvant treatment of optimally debulked stage III epithelial ovarian cancer, IV paclitaxel 135 mg/m² by 24-hour infusion on day 1, followed by intraperitoneal cisplatin 100 mg/m² on day 2 and
intraperitoneal paclitaxel 60 mg/m² on day 8, has been administered every 21 days for up to 6 cycles. Modified IV and intraperitoneal regimens are being investigated. (See Use.)

References:


Oncology Expert Committee Voting Results:

Proposed Level of Evidence:

Level 1 (High strength/quality); progression-free survival and overall survival

Concur with rating: 4 votes

Do not concur with rating: 1 vote

Grade of Recommendation:

Recommended use (Accepted): 5 votes

Reasonable choice (Accepted, treatment option): 0 votes
Proposed Consensus Recommendation:

Based on current evidence, combined IV and intraperitoneal therapy with IV paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel is recommended (accepted) for use as initial adjuvant treatment of optimally debulked stage III epithelial ovarian cancer in patients with good performance status (GOG performance status of 0–2).

Concur with recommendation: 4 votes

Do not concur with recommendation: 0 votes

*One Oncology Expert Committee Member was not available during the consensus review.

Oncology Expert Committee Members’ Comments:

Comments in Support of Vote on Level of Evidence and Grade of Recommendation:
Reviewer #1: [Level of evidence] Level 2 (moderate strength/quality). Study was not blinded.

Reviewer #1: [Specific patient population] For good performance status only.

Comments on Draft Narrative Summary:
Reviewer #1: Lower IP completion rate [for IV plus IP regimen versus IV regimen].

Reviewer #1: Use of 24 hour [paclitaxel] is not realistic for outpatient treatment. There is more evidence to support 3 hour paclitaxel due to ease of outpatient use. Suggest looking at results of SWOG trial. I would look at results of SWOG 9912 and SWOG 9619 as options for supporting 3 hour paclitaxel alternatives. Also, JCO Editorial in 2002 by Alberts et al.

Reviewer #1: Marked reference-conversion typographical error.

Reviewer #3: Based on the most recent trial, administration of paclitaxel over 3 not 24 hours, should be considered a suitable alternative option.

Reviewer #3: Marked reference-conversion typographical error.

Comments on Proposed Consensus Recommendation:
None.

Participants:

AHFS Staff Members (writing and editing): Lily Leu, Pharm.D., BCOP; Jane Miller, Pharm.D.

AHFS Oncology Expert Committee Members (reviewing and voting): Marc Earl, Pharm.D., BCOP; LeAnne Kennedy, Pharm.D., BCOP; Robert Mancini, Pharm.D., BCOP; LeAnn Norris, Pharm.D., BCPS, BCOP; Ron Walters, M.D., MBA, MHA, MS

External Consultants: None
Conflict of Interest Disclosures:

Individuals who substantively participated in the development, review, and/or disposition of this off-label oncology determination were screened for direct and indirect conflicts of interests involving themselves, their spouse, and minor children. No conflicts of interest were identified for this determination.

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