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.[10001]

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.[10005] 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.[10001, 10005] Although an optimal intraperitoneal chemotherapy regimen has not been established,[10005] favorable results were observed following sequential administration of IV paclitaxel, intraperitoneal cisplatin, and intraperitoneal paclitaxel in the Gynecologic Oncology Group (GOG)-172 study.[10001]

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.[10001] All patients enrolled in this study had good baseline GOG performance status (0–2) and adequate bone marrow, renal, and hepatic function.[10001] Most patients (88%) had ovarian cancer, and serous adenocarcinoma was the most common histologic type (79% of patients).[10001] The primary end points of the study were progression-free survival and overall survival.[10001] Combined IV and intraperitoneal therapy consisted of IV paclitaxel 135 mg/m² by 24-hour infusion on day 1, followed by intraperitoneal cisplatin 100 mg/m^2 on day 2 and intraperitoneal paclitaxel 60 mg/m² on day 8.[10001] IV therapy consisted of IV paclitaxel 135 mg/m² by 24-hour infusion on day 1 followed by IV cisplatin 75 mg/m^2 on day 2.[10001] Both regimens were repeated every 21 days for up to 6 cycles.[10001] 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/m^2 by 3-hour infusion on day 1, followed by intraperitoneal cisplatin 75 mg/m^2 on day 2 and intraperitoneal paclitaxel 60 mg/m^2 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/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, has been administered every 21 days for up to 6 cycles.[10001] Modified IV and intraperitoneal regimens are being investigated.[10008, 10013, 10014] (See Use.)

References:

10001. Armstrong DK, Bundy B, Wenzel L et al. Intraperitoneal cisplatin and paclitaxel in ovarian cancer. *N Engl J Med*. 2006; 354:34-43.

10002. Wenzel LB, Huang HQ, Armstrong DK et al. Health-related quality of life during and after intraperitoneal versus intravenous chemotherapy for optimally debulked ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol*. 2007; 25:437-43.

10004. Landrum LM, Java J, Mathews CA et al. Prognostic factors for stage III epithelial ovarian cancer treated with intraperitoneal chemotherapy: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2013; 130:12-8.

10005. National Cancer Institute (NCI). NCI clinical announcement on intraperitoneal chemotherapy for ovarian cancer (January 5, 2006). From NCI web site (http://ctep.cancer.gov/highlights/20060105_ovarian.htm).

10008. Barlin JN, Dao F, Bou Zgheib N et al. Progression-free and overall survival of a modified outpatient regimen of primary intravenous/intraperitoneal paclitaxel and intraperitoneal cisplatin in ovarian, fallopian tube, and primary peritoneal cancer. *Gynecol Oncol*. 2012; 125:621-4.

10010. Wenzel L, Huang HQ, Cella D et al. Validation of FACT/GOG-AD subscale for ovarian cancer-related abdominal discomfort: a Gynecologic Oncology Group study. *Gynecol Oncol*. 2008; 110:60-4.

10013. Smith HO, Moon J, Wilczynski SP et al. Southwest Oncology Group Trial S9912: intraperitoneal cisplatin and paclitaxel plus intravenous paclitaxel and pegylated liposomal doxorubicin as primary chemotherapy of small-volume residual stage III ovarian cancer. *Gynecol Oncol*. 2009; 114:206-9.

10014. Alberts DS, Markman M, Armstrong D et al. Intraperitoneal therapy for stage III ovarian cancer: a therapy whose time has come! *J Clin Oncol*. 2002; 20:3944-6. Editorial.

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

Not fully established (Unclear risk/benefit or equivocal): 0 votes

Not recommended (Unaccepted): 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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