Adjuvant Treatment in Ovarian Cancer

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Adjuvant therapy of early stage (stage I and II) epithelial ovarian

• 25 percent of women
• (IA or IB) and/or well-differentiated (grade 1) tumors,
• Excellent Prognosis with survival of at least 90 % with surgery alone
• For all others, adjuvant chemotherapy is recommended.

• High Risk EOC
  • ●Stage IC or stage II
  • ●Clear cell histology (any stage)
  • ●High tumor grade (grade 3)
Benefit of adjuvant Therapy

• Two meta-analyses:
• 13 trials conducted between 1965 and 2004 were included
• only eight of these studies exclusively in stage I ovarian cancer
• The pooled results for chemotherapy
  • benefit in recurrence-free survival (Relative Risk [RR] 0.70, 95% CI 0.58-0.86)
  • Overall survival (RR 0.74, 95% CI 0.58-0.94).
• Five-year overall survival was improved with the use of adjuvant platinum-based therapy (HR 0.67, 95% CI 0.50-0.90).

• In the second,
• five randomized trials conducted between 1990 and 2003 involving 1277 women were included in the analysis
• adjuvant chemotherapy
• PFS (HR 0.67, 95% CI 0.52-0.84)
• overall survival (HR 0.71, 95% CI 0.53-0.93).

• No gross residual following surgery, chemotherapy did not improve overall survival when compared with observation (HR 1.22, 95% CI 0.63-2.37).
• In comparison, for women who had incompletely resected disease, chemotherapy resulted in superior survival when compared with observation (HR 0.63, 95% CI 0.46-0.85).
• Women with high-risk tumors had a survival advantage with the use of adjuvant chemotherapy over observation (HR 0.48, 95% CI 0.32-0.72). Those with low-risk tumors did not derive a benefit from chemotherapy (HR 0.95, 95% CI 0.54-1.66).

Cochrane Database Syst Rev. 2012;
CHOICE OF ADJUVANT TREATMENT

• Platinum-based doublet (ie, paclitaxel plus carboplatin) largely based upon indirect evidence that it improves outcomes when administered as adjuvant therapy for more advanced disease

• No. of Cycles
  • 3 vs 6

• Gynecologic Oncology Group Trial 157 (GOG 157),
  • A nonsignificant trend towards lower risk of recurrence (20 versus 25 percent)
  • Similar five-year survival rate (83 versus 81 percent)
  • More toxicity (neurotoxicity, granulocytopenia, and anemia)
Clear cell histology

• A significantly lower response rate to platinum-based therapy (11 versus 72.5 percent).

• Lower duration of overall survival
  • Stage I/II (31.8 versus 42.3 months)
  • Stage III disease (12.7 versus 26.8 months), although it was only significant for patients with stage III disease.

• However, overall survival similar among patients who presented with stage IV disease (17.8 versus 19.4 months).
Unstaged patients

• Occasionally made during surgery for an emergent (eg, torsion) or benign (ie, ovarian cystectomy) indication

• Women will not have undergone surgical staging and technically speaking would be considered to have apparent early but unstaged ovarian cancer

• Some evidence suggests that surgery may not be required if adjuvant chemotherapy is administered.
Adjuvant Chemotherapy in Ovarian Neoplasm (ACTION) trial

- adjuvant chemotherapy versus observation
- For the 297 women who were not completely staged,

- adjuvant chemotherapy was associated with significant improvement in recurrence-free survival (Hazard Ratio [HR] 1.78, 95% CI 1.15-2.77) and overall survival (HR 1.75, 95% CI 1.04-2.95) compared with observation.

- For the 224 women enrolled in to the observation arm, complete staging was associated with a significant improvement in recurrence-free (HR 1.82, 95% CI 1.02-3.24) and overall survival (HR 2.31, 95% CI 1.08-4.96) over incomplete staging.
• For the 151 women who were completely staged, chemotherapy was not associated with a recurrence-free or overall survival advantage over observation.
• In a retrospective study of 88 patients
• Early stage ovarian cancer (36 unstaged),
• Patients who given adjuvant chemotherapy,
• No difference in outcomes among women who underwent staging after a diagnosis of EOC and those who did not undergo a second surgery for staging.
• The estimated rates of five-year progression free survival were 85 and 80 percent, respectively, with corresponding rates of overall survival of 85 and 88 percent.

• While these underpowered studies suggest that it might be safe to omit formal surgical staging.

• Prospective studies are needed to confirm this finding before incorporating this into standard practice.

• For women who choose not to undergo formal surgical staging, we recommend adjuvant chemotherapy.

• With grade 3 or clear cell tumors, where chemotherapy will be administered regardless of staging outcome, there may be less impetus for a secondary procedure.
Intraperitoneal chemotherapy

• The use of adjuvant intraperitoneal (IP) chemotherapy for patients with early stage disease is experimental and is being evaluated in clinical trials.

• Risk of catheter-related complications and serious gastrointestinal toxicity.
Maintenance therapy

• Studies have investigated the use of maintenance therapy for early stage EOC.
• three courses of paclitaxel (175 mg/m²) and carboplatin (AUC 6) followed by either 24 weeks of paclitaxel (40 mg/m²) or observation
• not associated with improvements in the five-year risk of recurrence (HR 0.807, 95% CI 0.565-1.15) or estimated rate of survival at five years (85 versus 86 percent, respectively)
• Grade 2 or greater adverse events

Gynecol Oncol. 2011;122(1):89
First-line chemotherapy for advanced (stage III or IV) epithelial ovarian, fallopian tubal, and peritoneal cancer
Background

• Primary surgical cytoreduction followed by systemic chemotherapy is the preferred initial management for women with stage III or IV EOC.

• Patients who are not good candidates for surgery due to the location and volume of disease involvement or medical co morbidities at the time of diagnosis may be considered for neoadjuvant chemotherapy.
**TIMING OF TREATMENT INITIATION**

- usually within two to four weeks from surgery

- limited data suggest that a delay of greater than approximately one month in instituting chemotherapy may be associated with a poorer outcome

- However, it is not clear whether it is the delay itself, or the clinical factors that are frequently associated with delay (such as medical comorbidities, surgical complications, delayed healing, malnourishment) that are responsible for the worse outcome.
TREATMENT SELECTION AND METHOD OF ADMINISTRATION
TREATMENT SELECTION

• The standard approach to use a platinum agent with a Taxane.

• For women with optimally reduced disease (<1 cm of residual disease), the two modalities
  • intravenous (IV) chemotherapy alone
  • a combination of IV and intraperitoneal (IP) chemotherapy (IV/IP therapy).

• Women with suboptimally reduced disease (≥1 centimeter of residual disease) are not candidates for IP therapy due to limited penetration into larger tumors. These women should therefore receive IV treatment.
Choice of agents

- **Carboplatin** rather than **cisplatin**

- Multiple trials have consistently demonstrated that carboplatin produces equivalent response rates and survival outcomes to cisplatin. But with less toxicity.

- Although both **paclitaxel** and **docetaxel** (the most commonly used taxanes for EOC) can be administered along with **carboplatin** in this setting.

- Paclitaxel preferred as less myelosuppressive.

- A consideration between these two taxanes can be individualized based on their differing toxicities. For paclitaxel, these include a higher risk of neuropathy, myalgias, and weakness compared with docetaxel; for docetaxel, these include a higher risk of neutropenia, hypersensitivity reactions, and nausea and vomiting.
• Recommendation to give a maximum of six cycles rather than more.

• there are no data that treatment beyond six cycles improves outcomes, although further treatment increases the risk of treatment-related toxicities.
Pegylated Liposomal Doxorubicin

• 2013 meta-analysis suggested that carboplatin plus pegylated liposomal doxorubicin (PLD) would be a reasonable alternative to carboplatin plus paclitaxel

• However, the data consisted of two trials and only 820 women.

• Given the limited data available in this meta-analysis compared with the 2006 meta-analysis above,

• Recommendation to continue use of carboplatin plus paclitaxel in this setting unless paclitaxel is contraindicated for whatever reason.

Cochrane Database Syst Rev. 2013;
Triplets

• In addition, attempts to incorporate additional agents into first-line treatment of EOC have not been successful.

• Multiple phase III trials have not shown a survival benefit with the addition of a third agent (including doxorubicin, epirubicin, topotecan, interferon gamma) to the carboplatin plus paclitaxel.
Women with suboptimally cytoreduced disease

- Women with suboptimally cytoreduced EOC are not appropriate candidates for IP treatment because IP administration of chemotherapy results in limited penetration into larger tumors and reduced effectiveness of treatment.

- Therefore, IV therapy is recommended.

- For such patients, it is preferred to use dose-dense IV therapy over conventional dosing, with the exception of patients with clear-cell or mucinous cancers, for whom standard-dose IV treatment is appropriate.
Dose-dense IV therapy

• For women with suboptimally cytoreduced disease,
• a dose-dense IV treatment schedule using carboplatin every three weeks with paclitaxel administered every week for a total of 15 weeks of treatment, with histologic subtype is not clear cell or mucinous.

• Data suggest that dose-dense administration of chemotherapy is associated with equivalent or improved outcomes relative to conventionally dosed regimens.
Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial

Noriyuki Katsumata, Makoto Yasuda, Seiji Isonishi, Fumiaki Takahashi, Hirofumi Michimae, Eizo Kimura, Daisuke Aoki, Toshiko Jobo, Shoji Kodama, Fumitoshi Terauchi, Toru Sugiyama, Kazunori Dchici, for the Japanese Gynecologic Oncology Group*
• A significant improvement
• PFS (median, 28 versus 17.5 months, respectively; HR 0.76, 95% CI 0.62-0.91)
• OS (median, 100.5 versus 62 months; HR 0.79, 95% CI 0.63-0.99) compared with conventional treatment.

• **Most Benefited subgroup**

• Women with at least 1 cm of residual disease

• PFS (median, 17.6 versus 12 months; HR 0.71, 95% CI 0.56-0.89)
• OS (median, 51 versus 33 months; HR 0.75, 95% CI 0.57-0.97).

• There was no significant advantage to dose-dense treatment for patients with optimally cytoreduced disease.
Conclusion

• Dose-dense treatment offers better survival than conventional treatment and is a potential new standard of care for first-line chemotherapy for patients with advanced epithelial ovarian cancer

• Despite these survival outcomes, treatment with the dose-dense schedule resulted in:
  • A higher rate of treatment discontinuation for toxicity (52 versus 37 percent) and higher proportion of patients who had at least one treatment cycle delayed because of toxicity (76 versus 67 percent).
  • A similar frequency of severe (grade 3 or 4) non-hematologic toxicity (including neurotoxicity), although there was no difference in the rate of febrile neutropenia (9 percent in both groups).
Weekly vs. Every-3-Week Paclitaxel and Carboplatin for Ovarian Cancer

Summary

• Overall, weekly paclitaxel, as compared with paclitaxel administered every 3 weeks, did not prolong progression-free survival among patients with ovarian cancer
Carboplatin plus paclitaxel once a week versus every 3 weeks in patients with advanced ovarian cancer (MITO-7): a randomised, multicentre, open-label, phase 3 trial

Sandro Pignata, Giovanni Scambia, Dionyssios Katsaros, Ciro Gallo, Eric Pujade-Lauraine, Sabino De Placido, Alessandra Bologna, Beatrice Weber, Francesco Raspagliosi, Pierluigi Benedetti Panici, Gennaro Cormio, Roberto Sorio, Maria Giovanna Covazzini, Gabriella Ferrandina, Enrico Breda, Viviana Murgia, Cosimo Sacco, Saverio Cinieri, Vonda Salutari, Caterina Ricci, Carmela Pisano, Stefano Greggi, Rossella Lauria, Domenica Lorusso, Claudia Marchetti, Luigi Selvaggi, Simona Signoriello, Maria Carmela Piccirillo, Massimo Di Maio, Francesco Perrone, on behalf of the Multicentre
Conclusion

• weekly regimen of carboplatin and paclitaxel might be a reasonable option for first-line treatment of women with advanced ovarian cancer
• Similar PFS (18 versus 17 months; HR 0.96, 95% CI 0.80-1.16) at a median follow-up of 22 months
• No difference in the estimated probability of survival at 24 months (77 versus 79 percent; HR 1.20, 95% CI 0.90-1.61)
• Better QOL
• Lower rate of serious Toxicity
• Acceptable option with poor Performance status
GOG 262 & ICON 7

• conventionally dosed carboplatin and paclitaxel or to dose-dense therapy (carboplatin every three weeks plus weekly paclitaxel)
• Bevacizumab administration was optional in both arms and was administered to 84 percent of patients.

• Addition of bevacizumab, No difference in PFS
• Benefit of dose dense was compensated by bevacizumab.
Women with optimally cytoreduced disease

• For patients with optimally cytoreduced EOC, prefer incorporation of IP treatment (IV/IP therapy) rather than IV treatment alone

• Choice of agents — The most commonly used IV/IP regimen comes from GOG 172 and consists of six cycles of:
  • IV paclitaxel (135 mg/m² over 24 hours) on day 1
  • IP cisplatin (100 mg/m² in a liter of normal saline) on day 2
  • IP paclitaxel (60 mg/m²) on day 8
HIPEC

• Not recommended outside clinical trial
• major concerns about this approach include its inherent potential morbidity,
• the lack of randomized trials confirming the theoretical advantage of hyperthermia,
• longer postoperative recovery time may result in delay, decreased dose intensity, or even withdrawal from subsequent systemic chemotherapy, thereby worsening prognosis.
MAINTENANCE THERAPY

• The majority of patients with epithelial ovarian cancer (EOC) achieve a complete clinical remission with first-line chemotherapy, but the majority will recur.

• This has led to trials of maintenance or consolidation therapy to improve the percentage of women who remain relapse-free.
• There is no evidence to suggest that the use of platinum agents, doxorubicin or paclitaxel used as maintenance chemotherapy is more effective than observation alone.

• Further investigations regarding the effect of paclitaxel used as maintenance chemotherapy are required.
Incorporation of angiogenesis inhibitors

• GOG 218 & ICON7
• Incorporation of the Bevacizumab into the standard Pacli/carb
  • Better PFS
  • Better overall response rate
  • More serious side effects
  • No significant change in OS
Maintenance Therapy

- Bevacizumab
- Pazopanib
- Ninetedanib
Thank you