

Current status of maintenance therapy for advanced ovarian cancer

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Abstract: Even after countered with and responding to maximal surgical and chemotherapy efforts, advanced ovarian cancer usually ultimately recurs. One strategy employed to forestall recurrence is maintenance chemotherapy, an extension of treatment following a complete response to conventional measures. Many agents have been studied and many more are currently under investigation in maintenance regimens. While phase III data suggest that taxane maintenance prolongs progression-free survival, no overall survival benefit has been established. This article reviews the current status of maintenance therapy for advanced ovarian cancer, including phase III evidence and new and upcoming trials.

Keywords: maintenance therapy, consolidation therapy, advanced ovarian cancer

Introduction

Ovarian cancer continues to be associated with very high morbidity and mortality. In 2009, there will be an estimated 21,550 new cases of ovarian cancer diagnosed in the United States and 14,600 deaths.¹ Even with optimal frontline treatment involving aggressive surgical cytoreduction followed by platinum and taxane-based chemotherapy, 5-year survival for women with advanced stage disease is only 45%. Furthermore, over 50% of women who achieve a complete response to initial treatment will relapse within 18 to 24 months.² While effective second-line treatments are available, response rates drop with each subsequent recurrence due to the onset of drug resistance. From this background, the notion of extended chemotherapy following complete response to conventional treatment has been developed in an effort to delay or even avoid recurrence completely.

Definitions

Two basic approaches have been taken to extended chemotherapy: 1) consolidation or intensification therapy, and 2) maintenance chemotherapy. These terms are indistinct and often confused in the literature. Consolidation therapy generally involves the addition of an intense short-term treatment immediately following the completion of front-line therapy. Whole abdominal radiation, radioimmunotherapy, intraperitoneal chromic phosphate (³²P), and high-dose cytotoxic chemotherapy with stem cell support have all been studied with little proven benefit but with substantial toxicity for ovarian cancer patients (see Table 1).^{3–18} Maintenance chemotherapy, on the other hand, involves lower-dose treatments over a more prolonged period following a clinical remission from a standard regimen. The data

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Table 1 Prospective randomized extended treatment trials in patients with complete response to initial treatment

Author	Year	Drug	n	Design	Results	P	Conclusion
Markman et al ⁸	2009	Paclitaxel	296	12 vs 3 months maintenance paclitaxel	PFS: 3 cycles (14 mo), 12 cycles (22 mo) OS: 3 cycles (48 mo), 12 cycles (53 mo)	0.006 0.34	12 mo of maintenance taxol after initial complete response improves PFS but not OS
Berek et al ¹³	2009	Oregovomab	373	Oregovomab vs observation	PFS: Oregovomab (10.3 mo), placebo (12.5 mo)	NS	No benefit to oregovomab maintenance
Conte et al ¹⁶	2007	Paclitaxel	200	6 cycles q3w paclitaxel maintenance vs observation	PFS: 6 cycles (34 mo), obs (34.5 mo) OS: 6 cycles (78%), obs (88%)	NS	No benefit to paclitaxel maintenance
Hirte et al ⁸	2006	BAY 12-9566, tanomastat	243	Tanomastat vs observation after complete response to frontline platinum/taxane	PFS: BAY (10.4 mo), placebo (9.2 mo) OS: BAY (13.9 mo), placebo (11.9 mo)	NS	Well tolerated but no evidence of benefit to BAY 12-9566 maintenance
AGO/GINECO	2005	Topotecan	1308	Carboplatin/taxol → 4 cycles topotecan vs observation	PFS: TC (18.5 mo), TC-topotecan (18.2 mo) OS: TC (44.5 mo), TC-topotecan (43.1 mo)	NS	No benefit to topotecan consolidation
De Placido et al ⁷	2004	Topotecan	273	4 cycles topotecan vs observation	PFS: Top (18.2 mo), control (28.4 mo)	NS	No benefit to topotecan consolidation
Cure et al ¹⁰	2004	Carboplatin, cyclophosphamide	110	Carboplatin/cyclophosphamide vs high dose carboplatin/ cyclophosphamide with stem cell support	PFS: High dose (17.5 mo), standard (12.2 mo) OS: High dose (49.7 mo), standard (42.7 mo)	NS	High-dose chemotherapy yields no benefit
Hall et al ¹¹	2004	IFN-α	300	IFN-α vs observation after chemotherapy	PFS: IFN-α (27 mo), control (32.7 mo) OS: IFN-α (10.3 mo), control (10.4 mo)	NS	No benefit to extended treatment with IFN-α
Berek et al ¹²	2004	Oregovomab	145	Oregovomab vs observation	PFS: Oregovomab (13.3 mo), placebo (10.3 mo)	NS	No benefit to oregovomab consolidation
Sorbe ¹⁴	2003	WART	172	WART vs chemotherapy, vs observation	5 yr PFS: WART (56%), chemo (36%), obs (35.5%) 5 yr OS: WART (68.8%), chemo (57.1%), Obs (64.5%)	0.032 NS	WART may improve PFS but not OS
Varia et al ¹⁵	2003	³² P	202	IP ³² P vs observation	5 yr PFS: ³² P (42%), obs (36%) 5 yr OS: ³² P (67%), obs (63%)	NS	No benefit to IP ³² P following negative second look
Lambert et al ⁶	1997	Cisplatin Carboplatin	233	5 vs 8 cycles of cis or carbo	OS: 24 months both groups	NS	No evidence based benefit to > 5 cycles front-line single-agent platinum therapy
Hakes et al ⁵	1993	Cyclophosphamide, doxorubicin, cisplatin	78	5 vs 10 cycles	RR: 5 cycles (34%) 10 cycles (35%)	NS	5 cycles equally effective, less toxic
Bertelsen et al ⁴	1993	Cyclophosphamide, adriamycin, cisplatin	202	6 vs 12 cycles	RR: 6 cycles (23%) 12 cycles (25%) OS: 6 (23 mo) 12 (27 mo)	NS	Increasing mean cumulative dose does not improve response or survival

Abbreviations: IFN, interferon; IP, intraperitoneal; obs, observation; PFS, progression free survival; OS, overall survival; RR, response rate; TC, taxol carboplatin; WART, whole abdominal radiotherapy.

here are more promising, and a review of the phase III evidence is the subject of this paper.

Rationale

The rationale supporting maintenance chemotherapy is based on the theory that slowly dividing tumor cells which were inadequately exposed to front-line cycle-dependent cytotoxic treatment may be effectively eliminated by continued treatment over time.^{19,20} In addition to targeting the remaining tumor burden, prolonged chemotherapy with known antiangiogenic agents may forestall new tumor growth. Opponents of maintenance therapy argue that resting after primary chemotherapy allows for recovery from the toxic effects, and that waiting for recurrence increases the likelihood of repopulation with chemo-responsive cells. These arguments are founded in the concern that maintenance treatment may obviate the benefit of retreatment when relapse occurs.⁶ Randomized controlled data have yet to resolve this debate definitively. Additionally, the effect of maintenance therapy on quality of life needs to be considered when making decisions about continuing or stopping treatment once complete response is reached.

Phase III clinical trials: a historical perspective

In the 1990s, several randomized trials addressed the question of whether extending the number of platinum cycles during front-line chemotherapy would benefit survival. Eight, 10, and 12 cycles were compared to the standard of 5 or 6, and no improvement in response or prolongation of survival was established.^{4–6} Patients in these trials were randomized prior to initiation of front-line treatment rather than after determination of clinical response. Therefore, platinum-resistant patients (roughly 25% of women with ovarian cancer) were randomized to receive more of a drug to which they were probably not responding in the first place. Furthermore, the cumulative toxicity of extended platinum therapy made it a questionable choice as a maintenance agent.

Many subsequent trials have sought to avoid similar design flaws by establishing documented complete clinical response as inclusion criteria. However, phase III trials of extended treatment with topotecan, whole-abdominal radiation, intraperitoneal ³²P, high-dose cytotoxic regimens, antiangiogenic matrix metalloproteinase inhibitors, and immunotherapies such as interferon alpha have all failed to demonstrate survival advantages (Table 1).^{3,7–16} The only positive randomized controlled data to date involve the use of paclitaxel. Taxanes are compelling as maintenance

agents because in addition to being cytotoxic, they have antiangiogenic activity which may be enhanced by prolonged and effectively spaced treatments.^{17,18}

In 2003, Markman et al published initial results from the SWOG S9761/GOG 178 collaborative trial in which advanced stage ovarian cancer patients with complete clinical response to platinum/taxane therapy were randomized to receive either 3 or 12 cycles of monthly paclitaxel (175 mg/m² in a 3-hour infusion).¹⁷ At the interim analysis, 34/112 patients in the 3-cycle arm had relapsed, compared to 20/110 patients in the 12-cycle arm ($P = 0.0023$), translating to a median progression-free survival advantage of 7 months (21 vs 28 months). The SWOG data safety and monitoring committee discontinued the trial on basis of a prespecified termination boundary of $P = 0.005$. At the time the study was closed, no significant overall survival advantage was demonstrable.¹⁷

In 2009, mature results from GOG 178 were published, confirming an 8-month progression-free survival advantage in the 12-cycle arm (22 vs 14 months, $P = 0.006$), but failing to establish a overall survival advantage (53 vs 48 months, $P = 0.34$).¹⁸ The authors hypothesized that a potential survival advantage may have been obviated by 1) insufficient sample size, 2) crossover patients in the 3-cycle arm who actually received more cycles (6%, or 9 patients), or 3) the equalizing effects of treatments initiated once relapse occurred. Of note, a second randomized trial of paclitaxel maintenance conducted by Conte et al failed to show either progression-free survival or overall survival benefit. In this trial, 200 advanced ovarian cancer patients with complete response to platinum/paclitaxel treatment were randomized to single-agent paclitaxel every 3 weeks for 6 cycles versus observation. At 44 months, median progression-free survival and 3-year overall survival were 34 months and 88%, respectively, in the observation arm, compared to 34.5 months and 78% in the paclitaxel arm.¹⁶

Ongoing randomized controlled trials

Several ongoing phase III clinical trials have been designed to determine whether maintenance chemotherapy confers a survival advantage in ovarian cancer patients (see Table 2). The taxane question will be addressed directly by GOG 212 – a 3-arm randomized trial of maintenance chemotherapy comparing 12 months of single-agent paclitaxel to polyglutamate paclitaxel (XyotaxTM, or PPX) or observation alone until documented relapse in stage III or IV ovarian epithelial ovarian or peritoneal cancers. PPX is a drug conjugate which links poly-L-glutamic acid, a biodegradable

Table 2 Ongoing phase III maintenance trials

Trial	Drug	Design	Research question	Primary endpoints	Secondary endpoints	Target accrual	Estimated completion
GOG 212 ²³	Paclitaxel, PPX	12 monthly cycles of paclitaxel vs PPX vs observation	Does monthly taxane maintenance therapy confer a survival advantage?	OS	Neuropathy QoL	1100	April 2008 (extended)
GOG 218 ²⁵	Bevacizumab	Carboplatin/taxol + bevacizumab/ placebo started on cycle and continued q21d × 6 or 21 cycles	Is survival improved by addition of bevacizumab to frontline therapy or as extended therapy?	OS	PFS Toxicity QoL	2000	June 2009
OCEANS ²⁶	Bevacizumab	Q21 day bevacizumab vs placebo maintenance following taxol for recurrence with either carboplatin/gemcitabine/bevacizumab or carboplatin/gemcitabine/placebo	Does q21d bevacizumab enhance PFS after complete response to second-line treatment?	PFS	Objective response Response duration OS GI perforation Safety Adverse events	450	June 2010
MIMOSA ²⁹	Abagovomab vaccine	Multicenter trial of immunotherapy vaccination q 4 weeks × 4 years or until recurrence	Does repeated vaccination with abagovomab create an immunoresponse which prolongs remission status and survival?	PFS	OS Safety	870	Dec 2015
ICON6 ²⁸	Cediranib	RCT of concurrent and maintenance cediranib in women with platinum-sensitive relapsed ovarian cancer	Is toxicity acceptable and survival improved by addition of cediranib to conventional therapy or as extended therapy?	Stage I: safety Stage 2: PFS Stage 3: OS	Stage I: none Stage 2: OS, toxicity Stage 3: PFS, toxicity, QoL	Phase I: 50 Phase II: 600 Phase III: 2000	Oct 2013
AGO-OVAR 16 ²⁷	Pazopanib	RCT of weekly pazopanib after completion of first-line chemotherapy in Stage II–IV ovarian, fallopian or primary peritoneal cancer	Does pazopanib maintenance prolong PFS in patients who have not progressed after completing first-line chemotherapy?	PFS	OS Toxicity QoL	900	Dec 2014

Abbreviations: GI, gastrointestinal; PFS, progression free survival; PPX, polyglutamate paclitaxel; QoL, quality of life; RCT, randomized controlled trial; OS, overall survival.

polymer, to paclitaxel. The conjugate confers molecular stability within the systemic circulation and enhances passive accumulation in tumor tissue where PPX progressively releases its active taxane constituent.²² Eligibility includes optimally surgically cyto-reduced patients (≤ 1 cm of residual disease) who have had a complete response to adjuvant platinum/taxane treatment as well as patients who have received neoadjuvant chemotherapy followed by surgery to no residual disease. Primary outcome of this trial is overall survival. Secondary outcomes include quality of life, peripheral neuropathy, and a series of exploratory angiogenic markers.²³

The use of biologic agents for maintenance therapy in both front-line and recurrent settings is currently the focus of avid ovarian cancer research. Bevacizumab is a humanized recombinant monoclonal antibody, which targets vascular endothelial growth factor (VEGF), an important factor in tumor angiogenesis. Preclinically, mouse xenograft models have demonstrated that bevacizumab inhibits recurrence and prolongs survival when given as maintenance therapy 3 weeks after induction combination chemotherapy.²⁴ Bevacizumab maintenance is addressed in GOG 218, a randomized controlled trial in which advanced ovarian, primary peritoneal, and fallopian tube cancer patients with measurable disease are treated with front-line carboplatin and paclitaxel. Bevacizumab or placebo is then added on cycle 2 and continued every 21 days for either 6 or 22 cycles. The primary endpoint is overall survival and secondary endpoints include progression-free survival, toxicity and quality of life. GOG 218 completed enrollment in June 2009, having achieved target accrual of 2000 patients.²⁵

Bevacizumab is also being investigated as maintenance after complete response to second-line treatment. The OCEANS trial is 2-part placebo-controlled, randomized, multicenter, industry-sponsored phase III study which compares bevacizumab in combination with carboplatin/gemcitabine to the same regimen with placebo in women with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube carcinoma.²⁶ In the OCEANS protocol, trial participants who demonstrate complete response to carboplatin/gemcitabine plus bevacizumab or placebo are then offered maintenance treatments with bevacizumab or placebo every 3 weeks for 1 year.

Other potent inhibitors of VEGF receptor tyrosine kinases are also under phase III investigation. In the front-line setting is pazopanib, a small-molecule inhibitor of cKit which targets platelet derived growth factor receptor as well

as VEGF receptors 1, 2, and 3. In the AGO-OVAR 16 trial, women who have not progressed after first-line chemotherapy for epithelial ovarian, fallopian tube, or primary peritoneal cancer are randomized to either pazopanib or placebo 800 mg daily for 52 weeks (12 months). The accrual goal is 900 with primary endpoint of progression-free survival and secondary endpoints including overall survival, toxicity, and quality of life.²⁷

In the setting of recurrence, the drug cediranib will soon be under investigation in the ICON6 trial. Cediranib (also known as AZD2171) is a once-daily oral therapy which targets VEGF 1, 2, and 3 and competes with adenosine triphosphate. ICON6 is a multicenter-multiphase trial in which patients with recurrent ovarian cancer will be randomized to A) carboplatin, paclitaxel and placebo for 6 cycles followed by placebo maintenance for 18 months; B) carboplatin, paclitaxel and cediranib with placebo maintenance; or C) carboplatin, paclitaxel and cediranib followed by cediranib maintenance. The trial incorporates a phase I, II, and III component with accrual goals of 50, 600, and 2000 for each phase, respectively.²⁸

Another innovative approach to maintenance involves the concept of immunotherapy. The MIMOSA trial (Monoclonal antibody Immunotherapy for Malignancies of Ovary by Subcutaneous Abagovomab) is a phase III trial involving the administration of an antibody which functionally mimics the CA125 antigen and induces humoral and cellular CA125-specific immunity.²⁹ The trial involves repeated vaccination every 4 weeks for up to 4 years or until recurrence in ovarian cancer patients with complete clinical response to front-line treatment. MIMOSA has now completed accrual and results are anticipated.

Of note, previously published phase III data on the related drug oregovomab (a monoclonal antibody to CA125) have not demonstrated benefit as either a maintenance or a consolidation agent. Berek et al investigated the role of maintenance mono-immunotherapy with oregovomab in a placebo-controlled blinded trial. Drug or placebo was given to ovarian cancer patients after complete clinical response from front-line therapy every 4 weeks for 3 cycles and then every 12 weeks for 5 years or until recurrence. In a 2:1 randomization, 251 patients were given drug and 100 given placebo, without difference in clinical outcome. A relatively modest immune response was seen in participants compared to the same drug given in front-line or in recurrent settings in combination with other chemotherapies. The authors postulated that the maintenance setting may not be the most effective time to administer immunotherapy, given the

Table 3 New maintenance agents under investigation for ovarian cancer^{3,4}

Drug	Trial	Design	Scientific basis	Primary endpoint	Secondary endpoint	Status	Sponsor
AZD2281	Phase II	RCT of oral BID AZD2281 vs placebo maintenance in platinum sensitive serous ovarian cancer patients with stable or complete response after ≥ 2 platinum regimens	Novel, potent orally active PARP inhibitor which targets homologous recombination repair defective cells such as BRCA-deficient tumors	PFS	OS, ca-125, adverse events	Target accrual: 250 Est completion: 6/2011	Industry
ALVAC(2)-NY-ESO-1 (M)/TRICOM vaccine	Phase I	ALVAC vaccine given q28d \times 6 cycles to patients after complete response to primary treatment or after treatment for recurrence with residual asymptomatic disease	Gene-modified virus may help the body build an effective immune response to kill tumor cells	Safety and tolerability	Treatment response immune response	Target accrual: 12 Est completion: 2/2011	NCI
BIBF 1120	Phase II	RCT of continuous maintenance treatment with BIBF 1120 following chemotherapy in patients with relapsed ovarian cancer	Antiangiogenic compound which inhibits vascular endothelial growth factor receptors, platelet-derived growth factor receptors, and fibroblast growth factor receptors	PFS	OS, ca-125, adverse events	Complete awaiting results	Industry
IT-101	Phase II	RCT study of maintenance IT-101 in platinum sensitive ovarian cancer patients who received 4–6 cycles of a second-line platinum-based regimen without disease progression	IT-101 is a conjugate of camptothecin, a topoisomerase I inhibitor, designed to increase drug exposure of tumor cells while minimizing the toxic effects	PFS at 30 weeks	Toxicity QoL	Closed. Est completion: 5/2010	Industry
Erlotinib	Phase I, II	Daily oral erlotinib as maintenance \times 12 months following front-line treatment with docetaxol/carboplatin/erlotinib in patients with stable or responding disease	EGFR antagonist blocking cell growth and	MTD of frontline erlotinib	Toxicity of maintenance erlotinib	Closed	Puget Sound Oncology Consortium
GDC-0449	Phase II	RCT of GDC-0449 as maintenance therapy in patients with ovarian cancer in a second or third complete remission	Targets Hedgehog signaling pathway which plays important role in tissue growth and repair	PFS	OS Adverse events	Target accrual: 100 Est completion: 1/2012	Industry
Green tea	Phase II	Green tea intake 3 h after meals and 1 h before next meal for 18 mo or until relapse as maintenance of complete remission in women with advanced ovarian cancer	Green tea extracted from steam treated leaves contains catechins with antiprotease activity	PFS	Toxicity	Target accrual: 42 Est completion: 6/2011	University of Quebec
Sorafenib	Phase II	RCT of sorafenib vs placebo in patients with complete clinical response after standard platinum	Small molecular inhibitor of Raf kinase, platelet derived growth factor, VEGF receptors 2 and 3, and cKit	PFS	OS, ca-125	Target accrual: 250 Est completion: 1/2011	Industry

Abbreviations: MTD, minimum tolerated dose; PARP, polyADP-ribose polymerase; RCT, randomized controlled trial; PFS, progression-free survival; OS, overall survival; VEGF, vascular endothelial growth factor.

relatively low tumor burden and hence minimal circulating tumor antigen targeted by this approach.^{12,13}

Toxicity and quality of life considerations

When considering whether to give extended and potentially morbid treatments to women in clinical remission, the question of quality of life (QoL) must be addressed. Without clear evidence of survival advantage, causing patients to potentially feel sicker during times of clinical remission is of utmost concern. Unfortunately, data addressing the impact of maintenance chemotherapy on QoL are currently lacking. GOG 178 did not include a QoL component, leaving unanswered questions about treatment-associated neurotoxicity from prolonged taxane exposure. Markman reported major differences in treatment-related sensory neuropathy between the 3- and 12-cycle arms of GOG 178: 35/149 grade 2 events and 9/149 grade 3 events in the 12-cycle arm compared with 20/136 grade 2 and 1/136 grade 3 events in the 3-cycle arm. The trial did not prospectively evaluate the duration of neuropathy or the persistence of symptoms after discontinuation of treatment.¹⁸

Robinson et al also addressed the taxane question in a phase II feasibility trial of paclitaxel maintenance therapy following front-line intravenous/intraperitoneal (iv/ip) cisplatin/paclitaxel versus iv carboplatin/paclitaxel. Robinson found that completion rates of the maintenance portion of the regimen were higher in the iv/ip group. Patients who stopped maintenance therapy usually stopped early (within 3 cycles) and the most common reasons in descending order included neuropathy, fatigue, myelosuppression, and disease progression.³⁰ The ongoing GOG 212 does include QoL as a secondary endpoint. In addition, a variety of novel taxanes and taxane-like compounds are under investigation which may have more acceptable toxicity profiles as maintenance agents.^{22,31–33}

Into the future

Looking beyond phase III data, the notion of extended chemotherapy treatment is an active area of research extending far beyond the realm of traditional cytotoxic regimens. In a host of ongoing phase I and II trials, polyADP-ribose polymerase (PARP) inhibitors, immuno-vaccinations, endothelial and epithelial growth factor inhibitors, novel VEGF receptor inhibitors, and even concentrated green tea are being explored for their potential maintenance benefits (see Table 3).³⁴ For patients who want to take proactive therapeutic measures to delay recurrence, these maintenance

trials may offer an opportunity to meet this need. For clinicians, these trials represent cutting edge scientific efforts to tackle one of the most significant problems in ovarian cancer treatment – prevention of recurrence.

Conclusion

The question of the utility of maintenance chemotherapy in ovarian cancer has not been answered. Yet there is promising research underway and patients should be encouraged to participate. Within the coming years, a host of novel more targeted and less toxic therapies can be expected to enter the line-up for phase III maintenance therapy interrogation.

Disclosures

The authors have no conflicts of interest to disclose.

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