A Phase II trial of intravenous bevacizumab, paclitaxel and intraperitoneal cisplatin followed by intravenous bevacizumab maintenance for treatment of stage II–III ovarian cancer

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Abstract

Objective: Acceptance of intraperitoneal (IP) chemotherapy has not been widespread with anticipated toxicity commonly cited as a limitation of this therapy. We evaluated a modified IP regimen with IV bevacizumab to determine feasibility and assess toxicities.

Methods: A phase II study was conducted in patients with advanced ovarian cancer following cytoreduction to <1 cm residual disease. The primary aim was to evaluate feasibility as defined as completion of 6 cycles. Patients received IV paclitaxel 135 mg/m² and IV bevacizumab 15 mg/kg (cycle 2-6) on day 1 followed by cisplatin 75 mg/m² IP day 2, repeated every 21 days x 6 cycles. Following primary therapy, patients received IV bevacizumab 15 mg/kg maintenance q21 days x 12 cycles. The FACT GOG NTX tool was used to prospectively monitor neuropathy scores over treatment.

Results: 20 evaluable patients are presented including 85% with stage III disease, and 75% with no gross residual. 85% received 6 cycles of IP therapy and 77% of these received all 12 cycles of maintenance. Scores for neuropathy worsened through cycle 6, peaked at 9 and improved by 18. Toxicity was acceptable with neutropenia the most common grade 3-4 adverse event, and 8 patients experienced grade 2-3 neuropathy. With a median follow-up of 63 months, the median PFS and OS is 50 and 71 months respectively.

Conclusions: Adding IV bevacizumab to a modified IP regimen is feasible. As compared to GOG 172, the lower cisplatin dose and omission of day 8 IP paclitaxel may allow a higher completion rate. Despite modifications, neuropathy remains important issue in IP based cisplatin regimens.

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chemotherapy alone (14.1 months vs. 10.3 months; hazard ratio (HR) 0.717, p<0.001). However, there was no difference in overall survival (OS) reported [10]. A subset analysis was performed on the patients with stage IV disease who received bevacizumab and did find an OS benefit of 40.6 compared to 32.8 months (HR=0.72; 95% CI 0.53-0.97) [12]. In parallel ICON 7 demonstrated an improvement in PFS (19 vs. 17.3 months; HR 0.81, p=0.004, no improvement in OS except in those with stage IV and sub-optimal residual disease who had a median OS of 39.7 vs. 30.3 months [13]).

This study sought to enhance IP chemotherapy delivery by reducing toxicity as well as combine IP chemotherapy with IV bevacizumab which had not been widely reported at the time of study inception. We sought to evaluate the feasibility of administering a modification of the GOG 172 IP regimen with the addition of IV bevacizumab. Feasibility would be judged based on the ability to complete 6 cycles of therapy and on the toxicity profile of the regimen.

Methods

After institutional review board approval, an open label phase II study was conducted in patients with stage II-III ovarian (epithelial and carcinosarcoma), fallopian tube, or primary peritoneal cancers with residual disease ≤ 1 cm following initial CRS. The primary aim of the study was to evaluate the feasibility of delivering IP cisplatin with IV paclitaxel and IV bevacizumab as defined by the proportion of patients able to complete 6 cycles of the IP based treatment. Eligible patients had a GOG performance status of 0-1, normal baseline hematologic, renal, and hepatic laboratory values, and had a protein/urine creatinine ratio < 1.0. All patients were to be treated within 12 weeks of surgery. Patients were required to maintain a home log of their blood pressures and these were assessed prior to each treatment cycle. Patients were removed from study if a delay of >3 weeks was required. Patients were required to manage a home log of their blood pressures and these were assessed prior to each treatment and used to assess whether bevacizumab would be administered. If blood pressure was ≤ 150 mmHg/90 mmHg bevacizumab was continued.

Grade 3 hypertension (HTN) was managed by use of anti-hypertensive medications and treatment delays, and grade 4 HTN required discontinuation of bevacizumab. Proteinuria was monitored prior to every cycle using the protein creatinine ratio, and were continued on treatment provided the ratio was <3.5.

Statistics

The GOG 172 study suggested that completion rates of 6 cycles of IP based therapy was ~40%. It was felt that improving the rate of successful completion to 80% would be clinically relevant. With a sample size of 20 patients, 13 or more completing therapy would exceed the historical rate of completion (40%) (95% CI 13/20: 40.7-84.6%).

Patients were assessed each treatment cycle, then every 3 months for two years, then every 6 months for 3 years. Imaging studies were performed based on presence of symptoms, clinical findings, or rising CA125 levels. PFS was measured from start of treatment to disease progression and OS was measured from diagnosis to death or last follow up.

Results

From August 2007 to September 2008, 22 patients were enrolled in the study and 20 were evaluable for feasibility of completion of 6 cycles. Of the 20 evaluable patients, median age was 59 years, 85% had stage III disease, 60% had high-grade and 20% had low-grade serous tumors (Table 2). All patients underwent primary CRS and were left with <1 cm residual disease (75% no gross).

During the cytotoxic treatment phase, 3 patients were unable to complete all 6 cycles of therapy. One patient had an IP port complication at cycle 4, another had persistent grade 3 neuropathy after cycle 4, and 1 patient received 5 cycles of IP based therapy but due to grade 3 abdominal pain with IP therapy received cycle 6 intravenously. Overall,
17/20 (85%) patients enrolled in the study completed 6 IP cycles of primary therapy.

Of the 17 patients who completed 6 cycles of combined IP chemotherapy with IV bevacizumab, 13/17 (77%) were able to receive all 12 cycles of maintenance therapy. One patient developed an enterovo-vesical fistula after completion of 6 cycles of therapy and did not continue on to maintenance therapy. One patient discontinued due to disease progression as well as grade 3-hypertension at cycle 8; 1 withdrew at cycle 9 secondary to fatigue (grade 3), and 1 patient withdrew at cycle 11 secondary to a personal hardship preventing completion of cycle 12. With a median follow-up of 63 months, 9/20 (45%) patients remain without recurrence. The median progression-free survival is 50 months and median overall survival is 71 months.

Adverse events recorded during the cytotoxic treatment phase (IP chemotherapy plus IV bevacizumab) were based on the frequency of AEs during 113 cycles of administered IP chemotherapy (Table 3). Only neutropenia (35%) and nausea (13%) were associated with a >10% frequency of grade 3-4 adverse events. Five and 3 patients respectively, reported grade 2 and 3 neuropathy. There were a total of 10 grade 3 or 4 toxicities during the maintenance phase of therapy. One patient had 4 episodes of grade 3 neutropenia that was ultimately improved with GSF support. One patient was noted to have transient elevation of transaminases (grade 3) that improved without intervention. Another patient had an IV port infection requiring antibiotic therapy. As noted above, one patient with bilateral hydrenephrosis secondary to disease progression and grade 3-hypertension came off study. Three patients reported grade 3 fatigue, of which 2 patients came off study before completion of maintenance therapy (Table 3).

The Fact-GOG NTX subscale instrument demonstrated a steady rate of increase in the NTX scores over cycle 1-6 (Figure 1). The rate of increase remained the same from cycles 6-9, despite IP chemotherapy being discontinued. The mean scores at cycle 9 were 3 fold higher than at cycle 6 (p=0.009). By cycle 18 there was recovery in NTX scores to a level seen following cycle 6 (p=0.15). Longer term NTX evaluation following 18 cycles was not performed. Statistical testing using a Spline model with knot at cycle 9 estimated a non-significant increasing trend following 18 cycles was not performed. Statistical testing using a Spline model with knot at cycle 9 estimated a non-significant increasing trend and slope from cycle 9 to 18 (95% CI -0.4719, 0.3528).

Discussion

Despite 3 positive phase III trials supporting IP chemotherapy [3-5], and a resulting NCI Clinical Announcement in 2006 recommending its use [15], IP therapy for advanced ovarian cancer has not been widely embraced. The grade 3-4 toxicity associated with GOG 172 included 4 times higher rates of fatigue, 3 times more infections and metabolic events, and a doubling in neurologic toxicity with the IP regimen [5]. In addition, only 42% of patients successfully completed 6 cycles of therapy. Yet, the overall survival difference favored IP therapy by nearly 16 months.

Following the publication of GOG 172 in 2006, the GOG instituted several phase Ib/II feasibility trials (GOG 9916, 9917, 9921) (Table 4) in an effort to develop alternative IP regimens which permitted an increase in the proportion of patients who successfully completed IP based regimens and reduce noted toxicities associated with prior studies. [16-18]. The modifications included substituting IP carboplatin for IP cisplatin, or substituting IV docetaxel for IV paclitaxel both while maintaining the day 8 IP paclitaxel (9916); substituting IP carboplatin for IP cisplatin and dropping the day 8 IP paclitaxel (9917) or dose reduction of the IP cisplatin from 100 mg/m² to 75 mg/m² (9921) [16-18].
The primary endpoint of these studies, following the determination of maximum tolerated doses, was feasibility of administering the regimen without an excessive frequency of grade 3-4 adverse events. In addition, studies were more proactive in specifying supportive care during therapy in an effort to manage or reduce toxicity. None of these trials included bevacizumab.

Given the difficulty in administering the GOG 172 IP regimen and excitement regarding the addition of bevacizumab to front line therapy, we evaluated a modified GOG-172 outpatient regimen and added IV bevacizumab both concurrently with and following IP chemotherapy. Our results showed that 85% of patients were able to complete 6 cycles of therapy, and 77% of these patients were able to receive 12 additional cycles of maintenance bevacizumab. With a median follow up of 63 months, 45% of patients remain recurrence free, with a median PFS of 50-100 mg/m2 when given intravenously [19]. We speculate that studies with cisplatin have not shown marked differences in outcome in the 50-100 mg/m2 range when given intravenously. We decreased the dose of IP cisplatin to 75 mg/m2 from 100 mg/m2 to lessen the metabolic, neurotoxic and renal complications of cisplatin and used aggressive pre and post dose hydration. Dose response studies with cisplatin have not shown marked differences in outcome in the 50-100 mg/m2 range when given intravenously [19]. We speculate that the reduced IP cisplatin dose would still expose the cancer cells in the peritoneum to platinum concentrations up to 20 fold greater than that achieved with systemic therapy [20]. We also eliminated day 8 paclitaxel in an effort to reduce neurotoxicity noted with GOG 172, but not seen in earlier IP trials with cisplatin.

Completion of 6 cycles of chemotherapy

In this study, with a drop in the dose of IP cisplatin and elimination of day 8 IP paclitaxel along with the addition of IV bevacizumab, we report a 6 cycle completion rate of 85%.

Konner and colleagues reported on a similar trial including 41 patients using an IP based regimen with 3 hr IP paclitaxel (135 mg/m2), IP cisplatin at 75 mg/m2, however, they maintained the day 8 IP paclitaxel (60 mg/m2) infusion and then combined this with IV bevacizumab/bevacizumab maintenance (X 17 cycles). They found that 73% received 6 cycles of therapy, and 36% received all planned doses of chemotherapy followed by bevacizumab consolidation[21]. Barlin et al. [22] reported on 102 patients who received 3 hr IV paclitaxel (135 mg/m2), IP cisplatin at 75 mg/m2, and day 8 IP paclitaxel (60 mg/m2). They had 6% grade 3/4 neurologic complications and 55% completed all 6 cycles.

Completion of 6 cycles is an important endpoint as demonstrated by Tewari et al. [23]. In an ancillary analysis of GOG 114 and 172, the risk of death decreased by 12% for each cycle of IP chemotherapy completed by any patient (adjusted HR 0.88; 95% CI, 0.83 – 0.94; p<0.001). Looking only at the 172 patients, completion of 6 cycles of IP chemotherapy was associated with better survival compared with 3 cycles of IP followed by 3 cycles of IV.

In GOG 172, catheter complications accounted for 33% of patients who completed <6 cycles of IP chemotherapy [24]. In our study, 2/22 (4.5%) of patients discontinued therapy (1 after cycle 1, 1 after cycle 4) due to IP port complications. In Konner’s study, 3 patients (7%) experienced a port malfunction. It appears that adding bevacizumab does not increase the rate of port complications appreciably.

Neuropathy

We prospectively monitored patient reported outcomes of neuropathy using validated survey instruments. Abdominal pain was reported in 6% of IP cycles administered including 1 patient who discontinued IP therapy at cycle 6. There were 5 patients with grade 2 and 3 with grade 3 neuropathy including one patient who discontinued therapy at cycle 5 for grade 3 neuropathy. Konner and colleagues reported 7% of patients had grade 3 abdominal pain, and there was no report of neuropathy. Patient reported outcomes were not prospectively monitored however. Barlin et al. [22] reported 6% G3/4 neuropathy.

Using the GOG NTX tool we found that even after completing IP chemotherapy at cycle 6, neuropathy scores worsened during bevacizumab maintenance from cycles 6 to 9 (first 3 maintenance cycles), then had recovery to the post 6th cycle levels by cycle 18. This might suggest that bevacizumab delays recovery from sensory neuropathy occurring following paclitaxel/cisplatin chemotherapy. However, in the health related quality of life analysis from GOG 172, chemotherapy induced neuropathy as measured by the NTX subscale worsened on both arms but more so on the IP arm. Even during the follow up period post therapy, there were higher (worse) NTX subscale...
scores among those patients in the IP arm (p<0.001) [25] This data suggests that the neuropathy induced by IP cisplatin may worsen and persist following chemotherapy independent of use of maintenance bevacizumab.

Larger prospective trials including bevacizumab have shown consistent results that chemotherapy produces neuropathy that extends beyond the treatment period. For example in GOG 218, using the FACT-O-TOI tool (cycles 1, 4, 7, 13 and 21 as well as 6 months after completion), analysis showed significantly lower FACT-O-TOI scores in both bevacizumab containing arms primarily at cycle 4 and persisting to cycle 7. There were no differences between the no bevacizumab and bevacizumab maintenance arm during the maintenance portion of therapy [26].

In the GOG 240 trial, a study of chemotherapy with or without bevacizumab in advanced/recurrent cervix cancer, the percentage of patients reported neurotoxicity symptoms increased over time in both the bevacizumab and non bevacizumab groups. However, the patients on bevacizumab reported neurotoxicity less frequently than those who were not on bevacizumab (OR 0.58 (98% -75% CI: 0.17-0.98)). Further, the FACT/GOG-Ntx score did not differ in severity when neuropathy was present between the two groups. (difference 0.23 (98-75% CI: 1.19 to 1.64; p=0.69)) [27].

GI Toxicity

Konner noted 3 cases of grade 3 small bowel obstruction (7%), and 1 case of anastomotic dehiscence (following cycle 4) which resulted in death. In our study, there were no cases of small bowel obstruction, but 1 vesicovaginal fistula was identified following cycle 6. Other adverse events reported in the present study are infrequent and do not suggest exacerbation of toxicities by combining IP chemotherapy with IV bevacizumab.

Since 2006, there has been a great interest in improving IV based regimens to increase completion rates and reduce toxicity. There was also limited data as to whether IV bevacizumab could safely be combined with IP chemotherapy. The results of this study adds to the literature demonstrating the feasibility of this approach. Downstream effects on efficacy following modifications of the GOG 172 regimen need to be assessed further. While the PFS and OS in our small study are promising, the study population included less common histologies and stages such as low grade serous (4), carcinosarcoma, mucinous and clear cell carcinomas (1 each) as well as stage II disease (3). Given the primary objective was to assess the ability to administer the combined IP regimen, study eligibility was set sufficiently broad to permit a variety of patients who may benefit from a platinum/taxane based therapy.

Efficacy of modified regimens with IV bevacizumab is being evaluated in the GOG 252 trial (NCT00951496) which compares dose dense chemotherapy to two IP chemotherapy regimens (substitution of carboplatin for cisplatin, and reduced dose cisplatin (75 mg/m²)). The contribution of IV bevacizumab to chemotherapy in ovarian cancer has been supported in two intravenous based phase III trials. Based on small studies, the addition of IV bevacizumab consolidation to IP therapy appears tolerable with no enhancement of acute or chronic toxicities. Validation of this concept in terms of efficacy and safety will be assessed with the forthcoming results of GOG 252 (NCT00951496).

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