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Bevacizumab Added to Moderate-dose Chemotherapy for Refractory Uterine Cancer

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Abstract. *Background/Aim: Bevacizumab (bev), when added to a moderate dose combination of previously failed cytotoxins, as a third- and fourth-line therapy for refractory gastric, cholangiocarcinoma, and ovarian cancers, produced high-quality responses. The regimen was based on preclinical models designed in order to simultaneously partner both bev and each of the cytotoxins with 4-5 synergistic drugs. Patients and Methods: Eligible patients (n=9) had high-grade endometrial tumors and had failed standard chemotherapy. Bev (10 mg/kg every 2 weeks) and cyclophosphamide (150-250 mg/m^2), were added to a combination of gemcitabine, fluorouracil, leucovorin, irinotecan and a platinum analogue –first without and then with docetaxel– each at approximately 1/2 to 1/3 of their standard dosage. Dose modification aimed at a repeated absolute neutrophil count (ANC) of 750-1,500 μl or platelets of 125,000-75,000 μl. Safety measures included stop-go use (intermittent, as needed, brief withholding of bev with resumption when again tolerated), of bev, and both prospective and ongoing dose modification in order to protect the bowels. Results: Induction treatment was free of life-threatening complications. Nine consecutive patients, 3 under second- and 6 under multi-line treatment, had 9 objective responses and 8 produced long clinical benefits, 2 of which were complete responses. Seven responses created opportunities for personalized added treatment and research. Absolute median survival was 21.5 months for the 8 patients with platinum-resistant tumors. One patient was unable to tolerate a first standard adjuvant dose of paclitaxel. After rapid peritoneal progression of disease, treatment has produced 52+ months of unmaintained complete remission. Conclusion: Bev, in the combination that was used in this study, meets response, survival, and toxicity criteria for further testing against second- or multi-line chemotherapy-resistant tumors and also when a standard treatment is not safe.*

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The chemotherapy regimen for resistant pancreatic cancer has been designed according to evidence from literature, in order to maximize favorable drug interactions and minimize drug toxicity (1). It initially consisted of gemcitabine (G), fluorouracil (F), leucovorin (L), irinotecan (Iri), and a platinum-analogue (cisplatin or oxaliplatin), without and then, on progression of disease, with docetaxel (D) (2, 3). Bevacizumab (bev) was added to the regimen on further progression of the disease (3-6). Evidence from *ex vivo* ATP assay systems, have shown that the cytotoxic drugs are synergistic; each drug in the regimen had 3 or 4 synergistic partners, with the potential to reverse resistance to each drug (1, 6-9). The drugs for inclusion in the regimen were selected to optimize safety, as they were effective at moderate drug concentrations and dosages, while cumulative toxicity was minimized (1-6).

Previous reports have shown that the chemotherapy regimen of cytotoxins was safe and produced high rates of –often long-term– responses in patients with both primary and heavily treated gastric, pancreatic cancers, and cholangiocarcinomas (1-3, 5, 6). Overall median survival was more than 1 year in each of these disease specific series. Responses created opportunities for sequential added treatments (3-6).

Subsequently, after the regimen had failed, bev was added to the identical regimen. It resulted in increased objective response rates, clinical benefits, and disease-specific survival, which had never been observed in Phase II trials for a similar series of patients given bev either alone or in combination with a single cytotoxin (5, 6). Responses of resistant gastric cancer were sometimes complete and enabled surgical, R0, neoadjuvant-like treatments (5).

The regimen has been modified and prospectively applied to multi-line (median four) chemotherapy-resistant high-

grade ovarian cancers (ROC). Both bev and cyclophosphamide (Cy) were added to GFLI carboplatin (C) and GFLIC-D, as synergistic targeted therapy (TT). We have already shown that carboplatin is the least neurotoxic platinum-analogue, and therefore it is used in patients with gynecological tumors. Response rates, complete response rates, and survival of patients with highly refractory tumors, exceeded standard expectations by 2 to 3 folds (10-12). Individually, patients with endometrioid ROC benefit from treatment with the TT regimen (11, 12). The first endometrioid ROC patient that was treated with the TT regimen was initially cachectic, resistant to 5 standard lines of chemotherapy, and had 5 organ systems severely involved. The patient lived 4 additional years. The ROC series now contains 60 reviewed patients with the same pattern of safety, response, and survival (unpublished data).

As it has been previously stated, the addition of bev in chemotherapy regimens did not result in limiting or irreversible toxicity, neither cytopenia perforations nor bleeding. There has been reported only 1 brief episode of bleeding (pre-existing unreported duodenal ulcer) and 1 possible perforation, though both patients were able to resume effective chemotherapy without either surgery or lengthy hospitalizations (6).

High-grade refractory uterine adenocarcinomas (RUCs) have all the preclinical and clinical characteristics, which prompted the above clinical development steps for patients with ROC. RUC has been projected to cause 10,900 deaths, in 2017, in the USA. The incidents in the EU are ¾ of that in the USA (13, 14). One third of all RUC patients are over 65, they have worse cancers, and often have urgent critical needs for effective well-tolerated treatments (14). Therefore, in the present study, we evaluated the response of high-grade RUC patients with poor prognostic characteristics to the TT regimen therapy.

Patients and Methods

The primary objectives of this retrospective analysis were to evaluate feasibility of the bev regimen to safely produce a 50% radiologic response rate, with clinical benefit for patients with high-grade metastatic endometrial RUCs, according to Response Evaluation Criteria in Solid Tumors (RECIST). The intent of the study was to prospectively duplicate the ROC experience and patients were entered case by case. Stopping criteria were approved by an IRB, for each, gastrointestinal (GI) and gynecological cancer (GYN) series. Criteria allowed a maximum of two limiting induction adverse events (AE) and required a minimum of a 50% response rate in the GYN series. The treatment regimen is described in Table I.

All patients had large (>2 cm), metastatic RUC tumors with active growth (progression of the tumor), urgent symptoms -some life-threatening-, performance status 0-2, grade 0-2, major organ function and a reasonable expectation of safe treatment (14). All participants provided informed consent according to the Declaration of Helsinki. All patients had failed active treatment (elsewhere) with a standard carboplatin and paclitaxel regimen. Specifically, they all presented with platinum-resistant disease progression, except one that developed life-threatening heart failure. Patients were also eligible after sequential use of all or many of the test drugs given either as high-dose single agents or drug pairs, –/+ bev, –/+ Cy. Additional patient characteristics were, age of less than 80 years, –/+ neuropathy, and –/+ comorbidity conditions controlled with concurrent (non-cancer) treatments. Expected survival without treatment was less than 6 months.

Patients were excluded if i) they were ineligible for either bev [due to prior bleeding, severe hypertension (HTN), or heart failure] or all the platinum analogues (unsuitable for desensitization), ii) they had nadir hematologic counts, not recovered [absolute neutrophil count (ANC)<1500/μl platelets <120×10^3/μl], iii) poor organ function (creatinine >2 mg/dl; bilirubin >2 mg/dl), iv) poorly controlled infection, v)uncontrolled co-conditions, v) severe cachexia, vii) CNS involvement, and viii) performance status 3-4 or if they were dependent on home hydration, total parenteral nutrition, or hospitalization within the past 2 weeks.

Monitoring included: physical every 2 weeks, GYN examination every 3 months, and computed tomography (CT) scans on week 1, week 6, week 12, and then every 12 weeks- and also for any 10-day delay in treatment or confirmed rise in a tumor marker. Other tests included: complete blood count weekly; comprehensive metabolic panel, liver and renal function, K, Mg, and Ca weekly (for 4 weeks) and then every 2 weeks; full routine urine, red blood cell and protein, every 4 weeks and for patients with HTN every 2weeks. Additionally, patients with HTN self-monitored daily blood pressure and weight. Biomarkers were largely examined in retrospect; descriptions were limited to actionable biomarkers. Tests were performed in the accredited Caris and Foundation 1 laboratories.

AEs were scored according to the NCI 2.0 toxicity scale (15). Prospective real time, electronic databases recorded every visit and drug for every patient with every diagnosis. Notes described patient characteristics; prior treatment extent of disease and prior disease and treatment related AEs.

Responses were based on “tumor protocol" CT images (reviewed by a radiologist) (16). In addition, responses should have a minimum duration of 4 months and improved symptoms (poor performance status, pain, and dry weight- nutrition). Treatment continued in case of responses, stable disease (SD) or a well-tolerated mixed response (including clinically insignificant new small, ≤1 cm, indeterminate lesions or "trace new ascites", provided that such findings did not worsen over 12 weeks).

Dose adjustment scheme is presented in Table I. Dosages of the drugs responsible for specific adverse events were decreased and then re-escalated in order to control the grade of the adverse events. Modifications aimed to produce uncomplicated repeated 750-1500 μl ANC nadirs, minimize frequency of ANCs either below 1000 μl, or above 5000 μl and platelets below 75×10^3μl. Re-escalation of dosage was allowed in half steps (10% per cycle), in order to achieve a best response, or to return to (uncomplicated) ANC or platelet target nadirs, but not to exceed initial full starting dosages. Full re-escalation dosages of the drugs responsible for a delay of treatment were allowed following an AE, or less than 1000 μl ANC nadirs, if 2×300 μg doses of granulocyte colony stimulating factor (G-CSF) could prevent reoccurrence of the laboratory test AEs. Treatments resumed 24 h after use of G-CSF produced recovery of the ANC. Dosage was re-escalated in 20% steps in case of disease progression. G-CSF was

Table I. *Dosing schedule for treatment of resistant endometrial cancer.*

Drug (Day 1)	Dose (mg)	Add D (mg)	Time (min)	Rate (min)	AE, Drug Modified	Reduction of drug dosage (%)
Bevacizumab	10/kg	10/kg	00	90	GI, oral, renal, HTN	50
Cyclophosphamide	150/m^2	150/m^2	100	30		20
Gemcitabine	500/m^2	400/m^2	140	Fixed rate 10 mg/m^2/min	Plts, WBC, GI, skin, renal, hepatic	20
Leucovorin	200/m^2	200/m^2	190	30	-	
Irinotecan	80/m^2	60/m^2	240	90>60>30	GI	25
5-Fluorouracil	1,500/m^2	1,200/m^2	340	24 h CI	GI, oral, skin	20
Drug (Day 2)	**Dose (mg)**	**Add D (mg)**	**Time (h)**	**Rate (min)**	**AE, Drugs Modified**	**Reduction of drug dosage (%)**
Cyclophosphamide	150/m^2	150/m^2	21	30	WBC, plts	33
Docetaxel	(0)/m^2	25/m^2	22	60>45>30	Plts, WBC, oral	20
Carboplatin	2 AUC	1.5 AUC	23	60	Plts, WBC	25

Titration: Dosages of the drugs responsible for specific adverse events were decreased and then re-escalated in order to control the grade of adverse events. Measures included intermittent, as needed, ideally brief, withholding of bev, with resumption after resolution of: severe HTN; severe abnormal urine protein or blood; new bleeding, or any gastroenteritis. Prospectively, any one drug could initially be withheld and introduced once safety concerns were resolved. Add D: further reduce other drugs in the percentage shown. Then, as tolerated, re-escalate in half of the % shown, monthly. There are no re-escalations after moderate or worse renal or hepatic AEs. Maximum dosage did not exceed initial dosage. GFLIC –/+ D: Gemcitabine, fluorouracil, leucovorin, irinotecan, carboplatin without and with docetaxel; AE, adverse event; GI, gastrointestinal; HTN, hypertension; plts, platelets; WBC, whole blood count; CI, continuous infusion 24 h.

increased or decreased, 1 dose at a time, whenever possible in order to avoid anti-metronomic surges in cells and cytokines (17).

Dose modification for stomatitis or gastroenteritis (GE)- or radiologic (asymptomatic) GE included: for grade 1 GE: bev and iri were held until recovery, while F and D were reduced one step; for grade 2 GE both F and D were reduced 2 steps, and G 1 step. For concurrent stomatitis and GE F, G, and D were reduced 1 extra step. On recovery, bev was resumed at full dose. Iri was resumed but reduced two steps; iri, D and G were re-escalated in 1/2 steps every two weeks. For any 14 days delay, the drugs responsible for the AE were reduced 50%. For bev, prospective safety precautions included: ulcer drugs, low roughage diets, humidification and saline nose drops (8, 9).

G-CSF (300 U×2) allowed safe treatment with chemotherapy on the first day of recovery, as it was effective within 24-48 h. The safety and efficacy of D was not analyzed for this report.

Results

Patient characteristics are shown in Table II. All 9 patients had poor prognostic characteristics, including high-grade tumors, minor Clear Cell elements (n=3), radiotherapy (RT) (n=6), >2 standard lines of chemotherapy (n=5), and age >60 years old (n=4). Every patient had an independent Cancer Center consultation before treatment with TT, bev, Cy, and GFLIC.

Safety. Induction with the TT regimen did not result either in hospitalization or in complicated hematologic AEs. There were not observed any severe or limiting (only brief use of stop-go for mild epistaxis) hemorrhage, or any perforations. Prior neuropathy was not limiting. After achieving a PET scan complete remission, one patient, scored as a non-responder, Table II, refused to continue because of depression and fatigue.

There were allergic reactions to carbo, twice, and docetaxel, once, none of which were life threatening. Allergies were managed with outpatient, skin test directed use of cisplatin or oxaliplatin, or controlled with added premedication and slow infusions.

Late AEs were also uncomplicated, however, they forced multi-step dose reduction (or temporary stopping) of the drug responsible for the nadir, gemcitabine (platelets- reversible), carboplatin, (platelets- reversible) and stop-go treatment with bev (HTN, urine proteins, blood urea nitrogen- reversible).

Response Case Report (Table II). A 56-year old patient (DC), morbidly obese cardiac, post ideal R0 resection, had near fatal heart failure with arrhythmias due to her first dose of standard adjuvant paclitaxel and carboplatin, (due to the paclitaxel.) She was advised to stop chemotherapy. Observation alone was followed by radiologic, pelvic, and lymph node (LN) progression after 2 months. This was confirmed when tests found new severe peritoneal carcinomatosis, 1 month later. CA125, a tumor marker in ovarian cancer, reached 1,250 U/ml. TT GFLIC produced an uncomplicated complete response (CR). The patient remains in unmaintained remission for 52+ months.

Radiological response was demonstrable for 9/9. Eight of 9 patients had useful clinical responses; AM stopped due to

Table II. *Characteristics of the disease of patients with resistant endometrial cancer. Bevacizumab and cyclophosphamide added to GFLIC-/+D.*

Patient	Start	Last alive	Survival (months) and response (R)	Date of birth (age)	Initial diagnosis	Pathology	Prior treatment/ Clinical course
1. IG	1/28/13	12/15/14	22.5 PET & R	11/5/58 (55)	1/10/11 (9/2010) recurrent 7/2012	Endometriod trace clear	RT/BT CT>Doxil3rd-line Wt loss, pain, DVT, pelvic, retroperitoneal, liver, allergic
2.DC	2/9/13	7/7/17 +	52+ CR	6/19/62 (51)	12/12	Endometriod	CT once Cardiac failure and pain peritoneum & pelvic
3.HL	4/8/13	11/17/14	19.25 PET & CR	3/2/44 (69)	2007	Endometrial	LN morbid obesity S×3 RT AC>taxol> topotecan>Doxil 5th-line
4.TM	8/15/12	5/8/14	21.75 PET & R	12/3/74 (36)	8/29/11	Mixed clear cell	Neuropathy RT>CT 2nd-line
5.ES	3/12/14	7/15/15	16 R	8/22/35 (84)	2010	Endometriod	LN vagina cuff CT>GCbev> G>topotecan 5th-line
6.FK	7/14/14	4/16/16	21.5+ R	10/20/60 (52)	4/2012	Endometriod	Failure due to poor drug tolerance, ostomy, ascites C>DC>RT>DCis> ACis 5th-line
7.AM	7/2/14	9/2015	14 PET & R	11/10/40 (73)	2009	Serous endometrioid	Bone, LN, SBO, peritoneum, reaction-allergic to Cis RT>AT 2nd-line
8. MKF	11/12/14	7/7/17+	31+ R	9/14/55 (59)	11/2010	Serous	Lung bilateral, LN, bone, refused fatigue neuropathy lupus lymph edema CT>liverS>CT> HIPEC>CisG 5th-line
9.DB	6/2/15	7/7/17+	25+ R	11/7/52 (62)	6/2014	Serous with RD51D mutation, 25% clear cells	Peritoneum CT>doxil 3rd-line Perit fluid, lung pleural fluid, bone, liver

GFLIC -/+ D: Gemcitabine, fluorouracil, leucovorin, irinotecan, carboplatin without or with docetaxel; PET, positron emission tomography; RT, radiotherapy; BT, brachytherapy; CT, carboplatin- paclitaxel (T); DVT, deep vein thrombosis; Wt, weight; CR, complete response; LN: lymphadenopathy; A, doxorubicin; Cis, cisplatin; S, surgery again; SBO, small bowel obstruction; HIPEC, hyperthermic intraperitoneal chemotherapy.

depression although she had a PET CR. Two patients had CRs with clinical benefit. Of note, the initial 6/6 responded, 5/5, excluding the case report. The response rate for patients with E RUC is ≥50% (p=0.015).

Absolute median survival was 21.5 months for the 8 platinum-resistant patients excluding DC, whose resistance was unknown (Table II). One patient that discontinued treatment, at the point of a PET CR, lived for a total period of 14 months, 10 of which with no further treatment.

Tumor testing for multiple actionable biomarkers revealed biochemical evidence that suggest sensitivity of the individual tumors to specific drugs. For example, 6/7 patients were biochemically ideal for 2 or more of the GFLIC drugs; 3/6 for taxanes; 3/6 for one or more GFLIC drugs plus a taxane; 5/7 for cytotoxins other than GFLIC D; 4/7 for HER2-targeted drugs; 6/7 for other targeted therapy; 3/7 for actionable research target molecules; 4/8 for immunotherapy; 3/7 for poly (ADP-ribose) polymerase (PARP) inhibitors (BRCA or RAD51D mutations); and 3/3 for anti-hormones, 3/7 for estrogen receptor (ER) progesterone receptor (PR) (all of which had also an androgen receptor, additionally to ER). Only 2/7 expressed DNA excision repair protein ERCC1, a carboplatin target molecule.

Discussion

The objective of this study was to evaluate strategies for the development of bev and TT GFLIC as treatment for endometrial RUC. This analysis was prompted by the success of the same TT regimen for patients with ROC and similar regimens, without cyclophosphamide, for patients with resistant gastric and cholangiocarcinomas (3-6, 11, 12).

The TT regimen met pre-set criteria concerning safety, objective response, length of response with benefit, and survival. All findings strongly support its further development, and direct comparisons against the best regimens for second- and multi-line RUC therapy. TT regimens warrant prospective evaluation when there is need for a rapid response and also when there are concerns that the patient cannot safely tolerate a standard drug or dosages. These are ultimately novel unmet niche needs for the majority of patients with RUC. The unmaintained CR of "DC" patient and 5/5 CRs of patients with second-line ROC, support tests of early treatment (12).

Tests for the safe expansion of eligibility for chemotherapy can include patients with: advanced age; many lines of therapy; prior treatment with the GFLIC agents, (reversing resistance); prior clinically severe AEs, or grade 2-3 neuropathy (3-6, 11, 12).

Findings support prospective studies of bev to reduce AEs. These include stop-go use of bev, and both titrated dose modification of specific cytotoxins and 1/2 or more reduction of initial dosages of specific cytotoxins. The latter dose modifications were adjusted in order to minimize the risk of gastrointestinal AEs. The ROC experience also supports investigation of these safety and expanded eligibility objectives (11, 12).

The safety of the TT regimen can be of clinical value because it appears to offer a partial solution to the standard risk of bleeding and perforation. This may in itself be a reason to re- examine TT with addition of the novel precautions applied herein. The precautions included step wise introduction of drugs, stop-go, and drug specific modifications in order to minimize GE.

Incidental observations found that either delay of bev or 40% reduced dosage of gemcitabine or carboplatin were sometimes associated with progression of the tumor growth. Re-escalation appeared to benefit 50% of the patients. The tumors decreased in size or were stable for greater than 4 months. Such possible impact of dose modification warrants systematic prospective monitoring.

F and iri are not included in the NCCN drug guidelines for RUC treatment. *In vitro*, in our laboratory F was active and synergistic; it can reverse resistance to Carboplatin for many types of cancer. Iri was used rather than topotecan as we have evidence that it is safer to be used as part of our regimen. Also, iri alone has produced well tolerated high quality responses when used as a last resort. It can be a critical drug for future investigations (not published data).

Targeted drugs as treatment for patients with RUC are noteworthy for their potentially valuable 40-50% rates of stable disease. Such rates have been observed with bev, tevorlimus, sorafenib and erlotinib (18-20). Some of these agents might meet the preclinical and drug interaction criteria for testing as additions to our regimen and, like bev they might reverse resistance to cytotoxins.

The high rates of response and good tolerance provide reason to consider testing closer surveillance for patients in the process of standard treatment, as TT regimens are options for patients with threatening disease. Closer surveillance could prevent crises and complications. Response to treatment would improve survival and quality of life.

The TT regimen produced opportunities for further ideal research for treatments. In the parallel ROC experience, TT regimens have been identified as a potential bridge treatment; following a response simpler biomarker-directed maintenance treatments can be considered as test worthy. TT regimens reconditioned patients, corrected nutrition and immunity (11, 12, 21). They reversed ineligibility for clinical research. Responses to treatment left small residual, ideal sized, tumors and thus, won time for tumor biomarker tests, vaccine production, and treatment (11, 12).

Especially in the case of RUC, selection of further treatment is often supported by biomarker tumor tests, which can identify personalized treatment options and guide modification of the TT regimen. All tumors (5/5) had 4 or more clinically actionable biomarker targets – other than for D or C. However, absence of a single, drug-specific biomarker is not an ideal indicator of resistance. Biomarker absence is not a reason to bypass the drug as part of standard potentially curative treatments.

The cytotoxic regimens are viewed as a safe platform for drug development based on their large number of potentially favorable interactions when added to chemotherapy in many disease-specific series (1-6). They are also a platform for fast track development efforts to gain approval for an empirical application of a cytotoxic or targeted drug which has a problematic toxicity or marginal effectiveness when tested alone or in combination with a standard regimen.

Since dose intensity or a specific drug may be critical to cure a disease, TT regimens are theoretically unsuitable as a substitute for safe standard adjuvant or first-line treatment. Therefore, these regimens were designed to fill a niche for a large number of patients with an unmet need for safe palliative treatment and drug development (22). TT regimens can facilitate as tests of novel high priority solutions applicable to reconditioning patients, drug resistance, and safety.

Conflicts of Interest

None.

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