Phase VII Trial Of Multicycle Paclitaxel, Carboplatin, Topotecan, Etoposide And Thiotepa With Peripheral Blood Progenitor (P13p) Support In Ovarian Cancer

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A. Study Purpose and Rationale

Objectives -To determine the maximal tolerated dose (MTD) of topotecan combined with a fixed dose of etopophos as a component of a multi-cycle dose chemotherapy regimen supported by peripheral blood progenitor cells. -To evaluate the response, time to progression, disease free survival and overall survival of ovarian cancer patients with persistent, refractory, or recurrent disease, treated with these regimen. -To evaluate the feasibility and toxicity of this regimen. -To characterize the pharmacokinetic behavior of escalating doses of topotecan during a 72h infusion.

B. Background

Approximately 21,000 new cases of epithelial ovarian cancer are diagnosed annually in the USA, making it the third most common gynecologic malignancy. However, with 13,000 deaths, it is the most lethal of these tumors, and the fourth most frequent cause of cancer death in women.

Among the minority of women presenting with early stage disease many are cured with appropriate surgery, often with adjuvant chemotherapy. Systemic platinum-based chemotherapy in combination with debulking surgery has become the standard for initial therapy with reported response rates ranging from 50-80% (1). The majority of patients, however, present with advanced cancer, and while aggressive platinum-based chemotherapy produces frequent responses, including pathologically documented complete responses in 25% of optimally debulked patients, only 10-15% of advanced stage patients will achieve 5 year disease-free survival. More effective therapy is clearly needed for patients with refractory, persistent, and recurrent disease following initial standard platinum based therapy.

Chemotherapy dose and dose-intensity are important determinants of outcome in some cancers, and are the subject of investigation in ovarian cancer, with studies demonstrating evidence that response rates and overall survival correlate with both dose intensity and the use of combination therapy as opposed to single agents(2, 3). Several factors make ovarian cancer an ideal candidate neoplasm for evaluation of high intensity therapy with hematopoletic support, namely, its relative chemosensitivity, the availability of active drugs with limited non-myeloid toxicity, and the rarity of bone marrow involvement. The use of hematopoietic growth factors alone has not resulted in substantial dose intensification, as thrombocytopenia remains dose-limiting. Peripheral blood or bonemarrow derived hematopoietic progenitors can accelerate hematopoletic recovery in patients receiving high-intensity chemotherapy. Multiple clinical studies have been reported documenting promising preliminary results with the use of high dose chemotherapy and peripheral blood progenitor support in patients with refractory (4-7), persistent(8-11), and recurrent(12,13) ovarian cancer. With the advent of the use of peripheral blood progenitor cells for hematological support, multi-cycle high dose therapy, with close attention to abbreviated intertreatment interval, became a feasible and safe alternative approach to further increasing the dose-intensity of a given regimen(14-21).

C. Study Drugs

a. Background

The first cycle of high dose therapy will be composed of high dose paclitaxel and carboplatin. Many of the patients will have already received platinum and paclitaxel based regimens as part of their initial standard therapy. However, there are several clinical studies documenting efficacy of high dose platinum retreatment after failure of standard dose platinum(22-24). In addition, selected Invites and clinical studies suggest a dose response effect of paclitaxel(25-30).

Topotecan, a topoisomerase I inhibitor, recently FDA approved for use in ovarian cancer due to its promising activity in phase II and III trials(31-33), is also and ideal drug for dose escalation to myeloablative doses due to its lack of documented nonhematologic dose limiting toxicity. Activity of topotecan appears to be dose related with the maximum inhibition of tumor growth and/or prolongation of survival time achieved at a MTD of the drug in animal tumor models(34). The activity of topotecan in many multi-drug resistant cell lines suggests that the drug may have efficacy in relapse after primary therapy with other classes of antitumor drugs(35).

Invitro and invivo, data have demonstrated that the combination of topoisomerase I and H inhibitors produces a synergistic effect when given sequentially(36-39). Etopophos, another agent with known activity in refractory ovarian cancer(40), is also a common component of conditioning treatments for transplantation due to its lack of nonhematologic toxicity and resultant feasibility for dose escalation. To explore the concept of synergy between these drugs, escalating dose topotecan will be combined with a fixed dose of etopophos in a sequential fashion for the second high dose cycle.

The third high dose cycle will consist of single agent thiotepa, a trifunctional alkylating agent, which is essentially a pure myelotoxin at doses up to 10-20 fold above standard (approx. 700mg/m), at which stage mucosal toxicity becomes severe(41,42). Thiotepa has been evaluated as a component of high dose regimens in ovarian cancer in multiple clinical studies which gave demonstrated impressive response rates(43).

b. Toxicity

Toxicities of high dose CT can be divided into two groups. The first group consists of unavoidable complications in patients with aplasia (sepsis and hemorrhage) and thus should not be considered dose -limiting. The second group, true dose-limiting toxicities, consist of lethal or life-threatening (grade4-5) organ damage, i.e. gastrointestinal toxicity, cardiac toxicity, interstitial pneumonitis, unacceptable delay in engraftment, etc.

High dose cyclophosphamide: myelosuppression (in 100% of patients and which can predispose to infection, anemia, bleeding), bladder irritation, alopecia, irregular menstrual cycle, hypertension or hypotension, gastrointestinal toxicity (nausea and vomiting), and mucositis.

High dose paclitaxel: hypersensitivity reactions including hypotension, angioedema, and generalized urticaria (approx. 2%). It is presumed to be histamine -related and remedication with corticosteroids, histamine antagonists, and diphenhydramine are the routine premedications used. Myelosuppression (especially neutropenia, which can result in higher incidence of infection) is dose-dependent and usually dose-limiting, severe conduction abnormalities (<I%), alopecia, peripheral neuropathy and mucositis.

High dose carboplatin: myelosuppression (100%), hepatic toxicity, renal toxicity (<10% and generally reversible), neuropathy, hearing and/or visual impairment.

High dose topotecan: myelosuppression (100%), mucosids, gastrointestinal toxicity, CNS toxicity (rare), rarely severe allergic reaction, skin ulceration, alopecia, hypotension, rarely secondary leukemia.

High dose thiotepa: myelosuppression (100%), mucositis (>50%), gastrointestinal toxicity, hepatic toxicity (veno-occlusive disease), cutaneous erythema and skin darkening, almost universal and generally resolves spontaneously, renal toxicity and pulmonary toxicity rarely, CNS toxicity(not reported at dose used in this study)

G-CSF. fatigue, headache anorexia, flu like symptoms, bone pain and abnormal taste.

Stem cell infusion: rarely respiratory distress, renal failure due to hemoglobinuria, and non engraftment

The NO Common Toxicity Criteria will be used. Hematologic toxicity will be graded by the Autologous Bone Marrow Transplant Studies Supplementary Toxicity Criteria.

D. Study Design

Study Subjects Patients must fulfill the following criteria:

- Histologically confirmed and reviewed at CPMC persistent, refractory, or recurrent epithelial ovarian cancer following at least 3 cycles of initial standard platinum-based therapy. Histologic tissue may be obtained through fine needle biopsy (including cytology), outpatient biopsy, or operative laparoscopy or laparotomy. Disease must be either measurable or evaluable on imaging study, physical examination, and/or laparoscopic examination.
- Ineligible of other high priority national or institutional study.
- No prior peripheral stem cell or autologous bone marrow supported therapy
- >3weeks since RT or CT (6 weeks for nitrosureas)
- Clinical parameters: life expectancy >2mo; brain CT or MRI
- no metastases; LVEF>=45%; Performance status- O-I(ECOG); HIV negative.
- Initial laboratory data: YVBC>3000lul; ANC>1500/ul; plt>100000/ul; BUN<1.5xnl; creatinine<1.5xnl; creatinine clearance>55mg/min; bilirubin<1.5xnl; AST or ALT<1.5xnl; PT/PTT wnl; CA 125 baseline obtained
- Informed consent
- No prior malignancy other than curatively treated carcinoma in-situ of the cervix, nonmelanoma skin cancer, or breast cancer under the following conditions: stage I or II disease with <4 involved lymph nodes; 2 or more years since breast cancer diagnosis; any recurrences following high dose CT for ovarian cancer will be blopsied to determine whether they represent a breast or ovarian recurrence.
- No serious medical of psychiatric illness preventing informed consent or intensive treatment.
- Non pregnant, non lactating.
- Patients may participate in other research protocols including studies relating to the use of other colony stimulating factors, gene therapy, stem cell mobilization.
- Consent for insertion of indwelling catheter appropriate for leukopheresis

E. Treatment Plan

Actual body weight will be used for body surface area (BSA) calculations. For patients >40% above their body weight, the BSA will be calculated twice, once using ideal body weight and once with actual body weight; the treatment dose will be the mean of these BSA calculations.

Mobilization therapy will consist of paclitaxel 250nig/M2 given over 3 hours or cyclophosphamide 1.5g/M2. GCSF will be given at a dose of 5mcg/kg (300mcg vs. 400mcg, whichever is closer to 5mcg/kg) sq. commencing 24h following paclitaxel or cyclophosphamide. Leukapheresis will commence when the NVBC is recovering the induced nadir, provided the total leukocyte count is 1000/ul. A minimum of RIO CD34+ peripheral blood stem cells/kg using CU BMT standard harvesting techniques. If fewer than the required number of stem cells are obtained, the patient may undergo a second cycle of paclitaxel or cyclophosphamide mobilization a minimum of 2 weeks following the first cycle with leukapheresis. Paclitaxel will be administered with standard premedication (dexamethasone 20mg PO 12 and 6h before infusion, cimetidine 300mg iv and benadryl 50mg iv).

Cycle 1 of high dose therapy will commence at a minimum of 2 weeks following mobilization provided the patient has been off GCSF for a minimum of 36h, has recovered from any grade II or greater toxicity (excluding alopecia), has recovered a neutrophil count>1000/ul, plt (self- sustaining g)>3 5000/ul

and is off antibiotics. This will consist of carboplatin AUC of 20 given over 2 days and paclitaxel 250g/M2 over 3h on day I of carboplatin. Cryopreserved peripheral blood progenitors will be infused with standard hydration measures approximately 72h following the completion of CT, GCSF, 5mcg/kg will commence following the infusion of stem cells and will continue until the patient's ANC>10000/ul or sooner if clinically indicated. The dose of carboplatin will be calculated by the formula of Calvert et al with a target of AUC of 20. (Calvert formula: carboplatin dose(mg)= target AUC x (GFR + 25), for the purpose of this protocol, the GFR is considered to be equivalent to the creatinine clearance.)

Cycle 2 will commence at a minimum of 2 weeks following cycle 2 provided the patient has been off GCSF for a minimum of 36h, has recovered from any grade 11 or greater nonhematologic toxicity (excluding alopecia), has recovered a neutrophil count> 1000/ul, plt (self-sustaining) >35000/ul and is off antibiotics. This will consist of topotecan given as a 72h continuous infusion followed 48h later by etopophos 60OMg/M2 over 1-2h. The topotecan will be given in escalating doses without any inpatient dose escalation. The starting dose level will be a total dose of 5Mg/M2 and will be escalated in increments of 2Mg/M2 until the MTD is reached. Doses will be escalated in cohorts of 3 to 6 patients. Topotecan will be given to 3 patients at each dose level. If dose-limiting toxicity (DLT) develops in any two cases, then the prior dose will be defined as the MTD. If only one of the first three patients has DLT, then two additional patients will be treated at that dose. If the fourth and fifth patients do not have DLT, the dose can be escalated. Otherwise the previous dose will be considered the MTD. No patient may be entered at a higher dose level until the last patient at the lower dose level reaches day 14 of treatment. Cryopreserved peripheral blood progenitors will be infused with standard hydration measures approximately 72h following the completion of CT, GCSF, 5mcg/kg will commence following the infusion of stem cells and will continue until the patient's ANC>10000/ul or sooner if clinically indicated.

Cycle 3 will commence at a minimum of 2 weeks following cycle 2 provided the patient has been off GCSF for a minimum of 36h, has recovered from any grade II or greater nonhematologic toxicity (excluding alopecia), has recovered a neutrophil count>1000/ul, plt; (self- sustaining)>3 5000/ul and is off antibiotics. This will consist of thiotepa 500mg/m given over 3h. Cryopreserved peripheral blood progenitors will be infused with standard hydration measures approximately 72h following the completion of CT, GCSF, 5mcg/kg will commence following the infusion of stem cells and will continue until the patient's ANC>10000/ul or sooner if clinically indicated.

Patients will receive full supportive care including transfusions of irradiated blood and platelet products, antibiotics, antiemetics, etc., when appropriate. In the absence of bleeding standard criteria for transfusion of packed RBCs are hemoglobin <= 8 g/dI and platelets<=20000/ul.

F. Pharmacokinetics

Blood sample collection times

Whole blood sample should be drawn at the following times following the start of the continuous infusion: 0 (within 30min prior to administration), 1, 3, 6, 9, 12, 24, 48, 72 (end of infusion), and 5, 15, 30min, 1, 6, 12, 24h following the end of the infusion. The total amount of blood drawn over the 84h study is: 80 (5ml x 16) Analysis For each patient the following pharmacokinetic parameters will be calculated for both topotecan and its lactone metabolite from infusion and post-infusion data:

- Ke, terminal elimination rate constant, derived from a least-squares linear regression analysis of the terminal slope of the transformed [plasma] concentrations vs. time t-, the elimination half-life
- AUCo-, the area under the plasma concentration vs. time curve from time zero to infinite time, where AUCo-t +Ct/Z, Ct is the last quantifiable concentration and Z is the terminal elimination rate constant.

For patients achieving steady-state (5xt) during the continuous infusion:

- CPss ave, the mean plasma level attained after steady-state, up to and including the 72h blood draw
- Cl, total body clearance, which is equal to (infusion rate/CPss ave)

- Vd, volume of distribution, which is equal to (Cl/Ke)

Individual pharmacokinetic data will be combined, and the parameters described above will be provided for each dose group. From the combined pharmacokinetic data, the active lactone of topotecan and total topotecan will be plotted together in order to compare the ratio of lactone and total drug concentrations.

Study Procedures

Methods of evaluation					
Tests	On study	carbo/tax	Topo/VP	thiotepa	FU*
history	x				
Neuro eval		weekly			
PE	*x*	weekly	weekly	weekly	*x*
PS	x	*x*	*x*	*x*	*x*
drug toxicity		weekly/prn	x		
CBC	x	daily	daily	daily	x
electrolytes	*x*	biw	biw	biw	*x*
creatine clearance	x		*x*		
LFTs	x	x	x	x	prn
EKG	x				
HIV,CMV,HSV,Hep B/C	x				
CA125**	*x*	x	x	x	x
PT/PTT	x				
CT abd, pelvis	x				x
CTIMRI brain	x				
Ejection fraction	x				
CXR	x				
laparoscopy/lap arotomy	x				x

*q month x3, then q3month x 1 yr., then q 4 months

**CA 125 should be drawn on the first day of each cycle of high dose chemotherapy. A CA 125 should be drawn at the completion of the protocol at the time of post-chemotherapy disease assessment.

Criteria for valuation:

Complete response: disappearance of all measurable/ evaluable disease, signs, symptoms, and biochemical changes related to the tumor, for >4weeks, during which no new lesions may appear and no existing lesion may enlarge.

Partial response: when compared with pretreatment measurements/evaluation, a reduction of >50% in the sum of the products of the perpendicular diameter of all measurable lesions lasting >4 weeks, during which no new lesions may appear.

Stable disease: a <50% reduction of <25% increase in the sum of the products of two perpendicular diameters of all measured lesions, and the appearance of no new lesions for >8 weeks.

Disease progression: an increase in the product of two perpendicular diameters of any measured lesion by >25% over the size present at entry on study or for patients who respond the size at the time of maximum regression; the appearance of new areas of malignant disease except for CNS lesions.

a. Statistical Aspects

Phase 1: The following scheme will be used to escalate topotecan dosages. Dosages can be escalated if three to six patients have survived for at least 14 days after PBPC reinfusion and none have

had dose-limiting toxicity. If DLT develops in two cases then the prior dose will be defined as the MTD. If one of the first three patients has DLT, then two additional patients will be treated at that dose. If the fourth and fifth patients do not have DLT, the dose can be escalated. Otherwise the previous dose will be considered the MTD.

To ensure that the toxicity at the MTD is acceptable, an additional ten patients will be accrued at the MTD. This will allow the estimation of toxicity rates to within +/27% (95% confidence interval). It is estimated that 25-30 patients win be accrued on study over a period of one to three years.

Phase II: The primary endpoints for the patients on study will be response rate, disease free survival (DFS) and overall survival (OS). The Kaplan-Meier estimator will be computed to assess DFS and OS for this treatment plan. Conventional therapy yields a 2 year DFS of 45%. The proposed treatment modality will not be of further interest if the 2 year DFS is less than 45%. Furthermore, we anticipate an increase in the 2 year DFS to 75%. If 16 or more subjects are alive and free of disease at 2 years, then this treatment should be considered for further study. The significance level (i.e., the probability of incorrectly declaring that the treatment is worthy of further study when the true DFS is 45%) for this design is 4.4%. Power (i.e., the probability of correctly declaring the treatment worthy of further study when the true DFS is 75%) is 92.9%. Twenty-five patients will be treated in the phase II portion assessing response, DFS, and OS using an intent to treat analysis.

G. Confidentiality of Study Data

All study data will be coded and will be stored in a secure location available only to the investigators and coordinators of the study.

H. Potential Conflict of Interest:

N/A

I. Location of the Study

The location of the study will be the ICCR at CPMC. All treatment will be administered in house with outpatient follow up, except for cycle 2 of the study where patients require hospitalization for the 72h continuous infusion of topotecan and to facilitate the frequent blood draws for the pharmacokinetic aspect of the study.

J. Potential Risks

refer to Toxicities

K. Alternative Therapies

refer to Study Design Background

L. Compensation to Subjects

N/A

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