THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

High-dose chemotherapy for poor-prognosis relapsed germ-cell tumors
2008-0378

Core Protocol Information

Short Title	HIGH-DOSE CHEMOTHERAPY FOR POOR-PROGNOSIS RELAPSED GERM-CELL TUMORS
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Full Title:	High-dose chemotherapy for poor-prognosis relapsed germ-cell tumors
Protocol Type:	Standard Protocol
Protocol Phase:	Phase II
Version Status:	Activated -- Closed to new patient entry as of 10/15/2018
Version:	42
Submitted by:	Peggy S. LeCompte--9/6/2017 2:08:22 PM
OPR Action:	Accepted by: Inar Y. Graur -- 9/13/2017 11:47:39 AM

Which Committee will review this protocol?

(●) The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

Primary Endpoint

To derive estimates of the event-free survival (EFS) in the bevacizumab and non-bevacizumab cohorts

Secondary Endpoints:

1. To estimate the response rate (RR) and complete response (CR) rate among patients with measurable disease in both cohorts
2. To describe the side effect profiles of Bevacizumab/Gemcitabine/Docetaxel/Melphalan/Carboplatin; Bevacizumab/Ifosfamide/Cartoplatin/Etoposide; and, Gemcitabine/Docetaxel/Melphalan/Carboplatin and Ifosfamide/Cartoplatin/Etoposide:
    - Extramedullary side effects
    - Engraftment rate.
3. To estimate the overall survival (OS) in both cohorts.
4. To compare the EFS in both cohorts.

2.0 Background

2.1. Current Status of High-Dose Chemotherapy (HDC) for Germ-Cell Tumors (GCT)

First-line cisplatin-based standard-dose chemotherapy (SDC) combinations yield long-term EFS rates around 90% and 50% in patients with good-risk and poor-risk advanced disease, respectively. Salvage SDC regimens cure about 25% of patients in first relapse. Patients in second relapse or beyond or those with cisplatin-refractory tumors are considered largely incurable with SDC.

The use of HDC with autologous hematopoietic progenitor-cell support (AHPCS) for GCT has been studied in two different settings: as part of first-line therapy for metastatic disease, and in relapsed or refractory tumors.

First-Line HDC for Metastatic NSGCT

Motzer and colleagues developed an elegant strategy of switching to HDC those patients with a reduced clearance of serum tumor markers during SDC [1, 2]. This approach yielded long-term 50% EFS, which seemed superior to their own historical controls. Schmoll et al. reported 69% long-term EFS rate in 221 patients with poor-prognosis advanced disease who received one cycle of SDC followed by three cycles of high-dose etoposide/ifosfamide/cisplatin.[3] Matched-pair comparisons with prior SDC trials suggested the superiority of HDC.[4]

A European randomized trial conducted in the 1980s that enrolled 115 untreated poor-risk patients failed to show differences between a control arm and an arm receiving a cisplatin-containing regimen at higher than standard doses with AHPCS.[5] The total platinum dose in this study was lower in the transplant than in the control arm. In an US Intergroup trial Bajorin et al. randomized 219 patients with newly diagnosed disease with intermediate or poor risk features to receive 4 cycles of SDC or 2 cycles of SDC followed by 2 cycles of HDC with cyclophosphamide/etoposide/carboplatin.[6] The complete remission rates did not differ significantly between the transplant and control arms (52% vs. 48%, p=0.5). There were no significant differences in EFS (p=0.4) or OS (p=0.9). A planned subset analysis according to early tumor marker clearance suggested a significant benefit of HDC among those patients experiencing a slow marker decline (p=0.03), in contrast with similar outcomes in both arms in the group of patients with a satisfactory marker drop (p=0.5).

HDC for Refractory/Relapsed GCT

The use of tandem cycles of high-dose carboplatin/etoposide in patients with relapsed tumors was pioneered by Einhorn and collaborators at Indiana University. In the latest update of their results at a median follow-up of 4 years (range, 1 to 10 years), they have reported 63% EFS in 184 consecutive patients, with 1.6% treatment-related mortality (TRM).[7] The EFS rates in patients transplanted in first or in second or later relapse were 70% and 45%, respectively. The outcome was similar in patients with seminoma and non-seminoma histologies (74% *v* 60%). Of note, none of their patients had primary mediastinal tumors.

Several groups have explored the addition of a third drug, such as ifosfamide or cyclophosphamide to the carboplatin/etoposide backbone. Margolin et al. treated 20 patients with tandem cycles of ifosfamide/carboplatin/etoposide (ICE) with a 40% long-term EFS rate.[8] Subsequently, these authors treated 31 patients with high-dose paclitaxel/carboplatin/etoposide followed by paclitaxel/carboplatin/ifosfamide, with 36% EFS rate at 5 years.[9] Overall, high-dose triplets achieve 40-50% EFS rate in patients with cisplatin-sensitive tumors, and 4-20% in those with refractory disease.[10, 11]

Beyer et al. conducted a multicenter multivariate analysis of 310 relapsed/refractory patients treated with high/dose carboplatin/etoposide.[12] These authors identified the following independent adverse predictors: refractoriness to cisplatin (progression within 4 weeks after treatment with cisplatin), absolute refractoriness to cisplatin (no response to initial platinum chemotherapy), primary mediastinal tumor, and high tumor markers (HCG >1,000 U/L) at the time of HDC. A prognostic score based on these variables was developed (Table 1). The resulting good, intermediate, and poor risk groups presented 2-year EFS of 51%, 27% and 5% (Table 2).

Table 1. Beyer's Prognostic Scoring

Factor	Score
Progressive disease before HDC	1
Mediastinal primary tumor	1

Refractory disease before HDC (prior relapse within 4 weeks of completion of 1st line chemotherapy)	1
Absolute refractory disease before HDC (PD as best response to prior therapy)	2
HCG > 1,000 U/L before HDC	2

Table 2. Beyer's Prognostic Model

Risk category	**EFS**	
	1 year	**2 years**
Good (score 0)	56%	51%
Intermediate (score 1 or 2)	28%	27%
Poor (score >2)	5%	5%

This prognostic score has been externally validated in an independent group of 45 patients with cisplatin-refractory relapsed disease, treated with HDC using ICE x 2.[13] At median FU of 32 months, the EFS and OS rates were both 23.5%, with EFS curves plateauing after 17 months. The groups with good, intermediate and poor risk according to the prognostic score had 62%, 13% and 0% EFS rates, respectively.

Randomized Trials of HDC for Relapsed GCT

Pico and colleagues randomized 280 relapsed patients to receive three cycles of SDC followed by a single course of high-dose carboplatin/etoposide/cyclophosphamide or one more cycle of SDC.[14] At median follow-up of 45 months, the differences in EFS (42% vs. 35%, P=0.1) or OS (53% in both arms) were not statistically significant.

Lorch et al. randomized 216 patients with relapsed or refractory disease to receive one cycle of very high-dose carboplatin/etoposide or two sequential cycles of those drugs at slightly lower doses, requiring in both arms AHPCS.[15] Accrual to this study stopped after an excessive 14% TRM was detected in the single cycle arm. At median FU of 3 years, the differences in favor of the sequential HDC arm in EFS (40% v 37%) and OS rates (80% v 61%) did not reach statistical significance.

In summary, there is no consensus yet as to whether HDC should be administered to all relapsed patients. Because of the excellent results of tandem cycles of HDC as salvage treatment many experts consider HDC a valuable salvage option.[16] The National Comprehensive Cancer Network (NCCN) guidelines contemplate HDC as the preferred option for patients with an incomplete response or relapse after salvage SDC, for those with unfavorable prognostic features for conventional salvage therapy, such as an incomplete response to 1st line treatment, or for patients requiring 3rd line therapy.[17]

It seems likely that more than one cycle of HDC is necessary, particularly in refractory patients, as it appears that a single cycle may either not be sufficient, or too toxic if administered at ultra-high doses.

2.2. High-Dose Gemcitabine/Docetaxel/Melphalan/Carboplatin (Gem-DMC).

The HDC regimen we will first use in our tandem cycle strategy, Gem/DMC, was developed by adding gemcitabine to a prior combination of docetaxel/melphalan/carboplatin (DMC). In the phase I trial of DMC, which enrolled 59 patients with advanced refractory tumors, the maximally tolerated dose (MTD) of docetaxel was established at 400 mg/m2, in combination with melphalan (150 mg/m2) and carboplatin (1,000 mg/m2).[18] Docetaxel presented linear pharmacokinetics (PK) over the range of doses tested. This regimen showed high activity with 97% response rate (RR), 47% CR rate, and 3-year EFS and OS rates of 26% and 36%, respectively.

In a subsequent phase I study that enrolled 52 patients, gemcitabine was administered at fixed dose rate of 10 mg/m2/min prior to DMC in each treatment day.[19] The MTD of gemcitabine was defined at 5 hours/day x 4 (total 20 hours, total dose 12,000 mg/m2). This dose level was tolerable, with a reversible profile of stomatitis (28% grade 3), enteritis (12% G3), diarrhea (8% G3), constipation (8% G3), and skin rash (8% G3), and no G4-5 toxicities. A high level of activity was again seen, with 97% RR, 50% CR rate, and encouraging 2-year EFS and OS rates of 56% and 78%, respectively. The PK exposure to gemcitabine across the dose range was linear, with no changes in clearance.

A total of 10 patients with refractory GCT were treated in these two trials: 6 with DMC and 4 with Gem-DMC. Eight patients had tumors in refractory relapse and 2 had relapsed primary mediastinal tumors. The median number of prior chemotherapy lines was 3 (1-5). Only 2 patients were in partial remission at the time of HDC, and the other 8 patients had progressive disease. All 10 patients responded to HDC, with 9 CRs and 1 PR. Six patients went on to receive a second cycle of HDC off study, with either carboplatin/etoposide or ICE. Six of the ten patients are alive in complete remission, 3 to 6 years after HDC.

2.3. Vascular Endothelial Growth Factor (VEGF) in Germ Cell Tumors

The VEGF family of ligands consistes of five glycoproteins referred to as VEGF-A (or VEGF), VEGF-B, C, D, and E. VEGF binds to two receptor tyrosine kinases: VEGFR-1 (Flt-1) and VEGFR-2 (Flk-1/KDR), which are present on the surface of endothelial cells (ECs), and bind with high affinity to VEGF. Activation of VEGFR-2 leads to autophosphorylation and signal activation. VEGFR-1 is thought to act as a decoy receptor on ECs, although it may play a role in hematopoiesis. There is a third receptor, VEGFR-3 (Flt-4), involved in the regulation of the lymphatic system, which preferentially binds VEGF-C and VEGF-D.

VEGF is one of the most potent inducers of tumors angiogenesis. The expression of VEGF depends on the oxygenation status and the *VHL* gene. Under normoxia and normal *VHL* function, oxygen promotes hydroxylation of the hypoxia inducible factor (HIF)-1alpha at a proline residue. VHL protein then binds to this hydroxylated residue, leading to ubiquitin attachment and proteasomal degradation of HIF-1alpha. Under

hypoxia, low pH or abnormal *VHL* function, HIF-1alpha dimerizes with HIF-1alpha, leading to transcription of hypoxia-inducible genes, such as *VEGF*. VEGF expression can also be triggered during early stages of neoplastic transformation by genetic mutations, e.g., K-ras, p53 or HER2. Antineoplastic treatment itself may increase VEGF production.

VEGF is overexpressed in most human tumors, with a direct correlation with tumor progression or risk of recurrence. Because of the relatively low expression levels in adult healthy tissues, VEGF constitutes an attractive therapeutic target. In the case of GCT, metastatic tumors express higher levels of VEGF than nonmetastatic tumors.[20] A direct correlation between tumor microvessel counts and VEGF levels in metastatic GCt has been reported, as well as an independent adverse prognostic effect of VEGF overexpression.[21]

2.4. Bevacizumab (Avastin ®)

Bevacizumab is a chimeric monoclonal antibody (mAb) that targets VEGF. Bevacizumab has a reduced immunogenicity and longer half-life than its murine counterpart. Phase I studies demonstrated linear pharmacokinetics and no interactions with chemotherapy.[22, 23]

A direct and rapid antivascular effect of bevacizumab has been shown on human tumors by Jain and coworkers.[24] Twelve days after a single dose of bevacizumab to patients with rectal carcinoma, bevacizumab decreased tumor perfusion, vascular volume, microvascular density, tumor interstitial fluid pressure (IFP), and circulating ECs and endothelial progenitor cells. Elevated IFP, a hallmark of solid tumors, is a result of abnormalities in tumor vessels, and constitutes a major impediment for drug access to the inner layers of the tumor lesion. These authors also observed an increase in vessel pericyte coverage after a single dose of bevacizumab, with no changes in tumor uptake in PET despite a 40-50% reduction in its microvessel density, suggesting that the residual normalized vasculature was more efficient.

Additionally, bevacizumab appears to have direct cytotoxic antitumor effects, through blockade of VEGF binding to the neuropilin-1 receptor, which can result in apoptosis. A single dose of bevacizumab has been shown to cause a 67% decrease in expression of phosphorylated VEGR-2 and a 130% increase in tumor apoptosis in breast cancer patients.[25]

In consequence, bevacizumab is synergistic with chemotherapy. VEGF inhibition transiently ‘normalizes’ the disorganized and dysfunctional tumor vasculature, improving the delivery of oxygen and cytotoxic drugs to tumor cells.[26] The bevacizumab-induced drop in IFP leads to a hydrostatic pressure gradient across the tumor vasculature, which enhances penetration of large molecules in tumors.[27] Additionally, increased oxygenation sensitizes cancer cells to cytotoxics. Finally, bevacizumab counteracts the chemotherapy-induced VEGF upregulation and increased tumor resistance.[28]

Phase III studies of bevacizumab combined with chemotherapy have shown efficacy in

multiple metastatic settings, such as colorectal cancer,[29, 30] breast cancer,[31] or non-small cell lung cancer.[32]

2.5. Toxicity Profile of Bevacizumab

1. Hypertension is its most common side effect, with a 10-15% incidence of grade 3 events, and rare grade 4 cases. Its mechanism may be the decrease of nitric oxide production. It responds well to treatment with angiotensin converting enzyme inhibitors or calcium channel blockers. It usually resolves once bevacizumab is discontinued.

2. Proteinuria is seen in 23% of patients, and is largely asymptomatic.

3. Minor bleeding complications, particularly epistaxis, occur in 20-40% of patients, without changes in biochemical, coagulation or hematologic parameters. Life-threatening intratumor hemorrhages have been reported in patients with centrally located, cavitated squamous cell lung cancer, or in parenchymal brain metastases.

4. While there appears to be no increase in the risk of venous thromboembolism, there is a small increase in the risk of arterial thrombosis (<4%).

5. Wound healing complications can occur in up to 10% of pts undergoing surgery during bevacizumab treatment, but there appears to be no increased risk in patients who had surgery more than 30 days prior to bevacizumab.

6. Bowel perforation. This complication has been observed in up to 11% of patients with heavily pretreated epithelial ovarian cancers. It has been reported in 1% of the patients with colorectal cancer treated with bevacizumab, and has not been seen in any other tumor type treated with bevacizumab.

2.6. Clinical Experience with Bevacizumab in Pediatric Patients

Bevacizumab is well tolerated in children at the same doses used in adults.[33, 34] The side effects in the pediatric population are mild and similar to that previously observed in adults: proteinuria, epistaxis, and neutropenia.

2.7. Rationale for Combining Bevacizumab with High-Dose Chemotherapy

The combination of bevacizumab and Gem/DMC and ICE may result in major synergy. In murine models, the combination of bevacizumab and paclitaxel significantly reduced tumor growth compared to paclitaxel alone.[35] In vitro and in vivo preclinical studies show that VEGF protects endothelial cells against the antiangiogenic effects of docetaxel and that this action is inhibited by bevacizumab.[36] Encouraging activity has been observed using bevacizumab and docetaxel in patients with metastatic breast cancer.[37] Synergy between platinum compounds and bevacizumab has also been shown in murine

models.[38] There is also good evidence of synergy between gemcitabine and bevacizumab [39,40].

The synergy between bevacizumab and chemotherapy seem to be due, at least in part, to bevacizumab-induced drop in intratumor IFP, which results in an improved chemotherapy delivery to the tumor cells. Thus, this augmentation effect likely depends on the peak concentration of the cytotoxic agent and a more rapid diffusion down a concentration gradient into the permeabilized tumor. This may explain why bevacizumab seems to add more efficacy to chemotherapy when this is administered intravenously than when given in prolonged oral treatments, such as capecitabine.[41]

Additionally, the IFP changes induced by bevacizumab are transient by nature,[42] which suggests that this benefit is likely to disappear through long-term chronic treatments, as seen in all randomized trials comparing chemotherapy with or without bevacizumab where the tails of the EFS curves merge. This should not apply to the limited use of bevacizumab prior to each of the two HDC cycles as proposed in this study.

We are currently testing the combination of bevacizumab with Gem/DMC in a separate phase II trial for patients with relapsed ovarian cancer (#2007-0368).

3.0 Patient Eligibility

3.1. Inclusion:

3.1.1. Male or female patients, age 12 to 65 years.

3.1.2. Patients with seminomatous or nonseminomatous GCT in one of the following groups:

3.1.2.1. First relapse/progression or second response, with an intermediate or high risk according to the Beyer model.

3.1.2.2. Second relapse or beyond.

3.1.3. Adequate renal glomerular and tubular function, as defined by estimated serum creatinine clearance >/=50 ml/min and/or serum creatinine </= 1.8 mg/dL, and urinary protein excretion </=500 mg/day.

3.1.4. Adequate hepatic function, as defined by ALT and AST</=3 x upper limit of normal (ULN); serum bilirubin and alkaline phosphatase </=2 x ULN or considered not clinically significant.

3.1.5. Adequate pulmonary function with FEV1, FVC and DLCO >/=50% of predicted, corrected for volume and/or hemoglobin.

3.1.6. Adequate cardiac function with left ventricular ejection fraction >/= 40%. No uncontrolled arrhythmias or symptomatic cardiac disease.

3.1.7. Zubrod performance status 0-2.

3.1.8. A minimum apheresis collection of 5 million CD34+ cells/kg of autologous hematopoietic progenitor cells (AHPC).

3.1.9. Written informed consent by patients and/ or their parents or legal guardians. Assent for those patients inclusive of ages 12 to 17.

3.2. Exclusion:

3.2.1. Growing teratoma syndrome, defined as enlarging tumor masses with normal serum markers during chemotherapy for nonseminomatous GCT.
3.2.2. Major surgery within 30 days before the initiation of study treatment.
3.2.3. Radiotherapy within 21 days prior to initiation of study treatment.
3.2.4. Prior whole brain irradiation.
3.2.5. Patients with active CNS disease, defined as brain or meningeal metastases that are not in complete remission.
3.2.6. Patients with active hepatitis B, either active carrier (HBsAg +) or viremic (HBV DNA >/=10,000 copies/mL, or >/= 2,000 IU/mL).
3.2.7. Evidence of either cirrhosis or stage 3-4 liver fibrosis in patients who either show chronic hepatitis C or positive hepatitis C serology.
3.2.8. Active infection requiring parenteral antibiotics.
3.2.9. HIV infection, unless the patient is receiving effective antiretroviral therapy with undetectable viral load and normal CD4 counts.
3.2.10. Patients who have had a previous autologous or allogeneic stem cell transplant in the previous 12 months.
3.2.11. Positive pregnancy test in a female patient of childbearing potential defined as not post menopausal for twelve months or no previous surgical sterilization.

4.0 Pretreatment evaluation

The following tests are performed to determine eligibility within 30 days before treatement, and do not need to be repeated prior to start treatment unless the treatment is delayed for more than 30 days.

For autologous stem cell transplantation:
a) History and physical examination.
b) CBC, differential and platelet count, coagulation profile (PT and PTT)
c) Chemistry panel including creatinine, albumin, electrolytes, glucose,albumin, total protein, alkaline phosphatase, ALT, AST, bilirubin, LDH.
d) Infection disease panel
e) β-HCG in women of child-bearing potential
g) Left ventricular ejection fraction by MUGA or echocardiogram, EKG
h) Spirometry with DLCO
i) Chest x-ray
j) Urine dipstick. If proteinuria >/= 2+, a 24-hour urine collection for total protein will be performed.

Disease specific:
k) CT scans of chest, abdomen, and pelvis.
l) Tumor markers (AFP and B-HCG)
m) MRI of the brain

5.0 Autologous HPCs Collection

A bilateral bone marrow aspiration and biopsy is recommended before mobilization of AHPCs. The collection of autologous hematopoietic progenitor cells will be performed following standard practice and is not part of this study. Either G-CSF alone or G-CSF plus chemotherapy can be use as a mobilization regimens as per the discretion of the treating physician. The target collection will be 10 million CD34+ cells/kg to support both high-dose cycles. A minimum of 5 million CD34+ cells/kg will be required. As an alternative, pelvic bone marrow may be used if it is not possible to collect sufficient AHPCs.

6.0 Treatment Plan

At least twenty-one days from patient's last radiation administration and or thirty days from major surgery must have elapsed prior to initiating study treatment.

6.1. High-dose course #1:
Gemcitabine/Docetaxel/Melphalan/Carboplatin

D-6	Admission and start hydration
D-5	Gemcitabine 1,800 mg/m2 IV over 3 hours / Docetaxel 300 mg/m2 IV over 2 hours
D-4	Gemcitabine 1,800 mg/m2 IV over 3 hours / Melphalan 50 mg/m2 IV over 15 minutes / carboplatin 333 mg/m2 IV over 2 hours
D-3	Gemcitabine 1,800 mg/m2 IV over 3 hours / Melphalan 50 mg/m2 IV over 15 minutes / Carboplatin 333 mg/m2 IV over 2 hours
D-2	Gemcitabine 1,800 mg/m2 IV over 3 hours / Melphalan 50 mg/m2 IV over 15 minutes / Carboplatin 333 mg/m2 IV over 2 hours
D-1	Rest
D0	Hematopoietic progenitor-cell infusion

Every effort will be made to admit the patient for prehydration on any day but Sunday or Monday, so that the AHPC infusion can proceed during a week day.

Gemcitabine will be administered on days -5 to -2, at 1,800 mg/m2 IV over 3 hours. Docetaxel will be administered at 300 mg/m2 IV over 2 hours on day -5, starting immediately after completion of the gemcitabine infusion. Dexamethasone premedication for docetaxel will be at 8 mg IV bid, from day -6 (PM dose) to day -2 (AM dose). Melphalan will be administered at 50 mg/m2, over 15 minutes, on days -4 to -2, starting immediately after completion of the gemcitabine infusion. Patients will keep ice chips or popsicles in their mouths during the infusion and for 15 minutes afterwards. Carboplatin will be administered at 333 mg/m2 over 2 hours, on days -4 to -2, starting immediately after completion of the gemcitabine infusion and at the same time as the melphalan infusion.

Patients with creatinine >1.2 mg/dL or performance status of 2 will receive a reduced version of this regimen:

D-6	Admission and start hydration
D-5	Gemcitabine 1,500 mg/m2 IV over 3 hours / Docetaxel 275 mg/m2 IV over 2 hours
D-4	Gemcitabine 1,500 mg/m2 IV over 3 hours / Melphalan 35 mg/m2 IV over 15 minutes / Carboplatin 275 mg/m2 IV over 2 hours
D-3	Gemcitabine 1,500 mg/m2 IV over 3 hours / Melphalan 35 mg/m2 IV over 15 minutes / Carboplatin 275 mg/m2 IV over 2 hours
D-2	Gemcitabine 1,500 mg/m2 IV over 3 hours / Melphalan 35 mg/m2 IV over 15 minutes / Carboplatin 275 mg/m2 IV over 2 hours
D-1	Rest
D0	Hematopoietic progenitor-cell infusion

Specific supportive care for HDC course #1:

- Caphosol mouthwashes (2-minute swishing and then spitting) will start on day -5 at 30 mL TID.
- Glutamine mouthwashes (2-minute swishing and then swallowing) will start on day -5,at 10 g TID, to be done 15 minutes following the caphosol rinse.
- From day +1 to day +10, 6-methylprednisolone will be administered at 40 mg IV bid.
- Piridoxine will be started at 100 mg IV/PO on day -1.

After the patient is released from the hospital, they will be seen in the Outpatient Clinic until reversal of the acute toxicities. Patients with increasing serum tumor markers or other clinical or radiographic evidence of tumor progression before HDC cycle #2 will be taken off protocol. Otherwise, all patients who have recovered from the acute toxicities associated with cycle 1 will start cycle 2 at 30-60 days from day 0 of HDC #1.

6.2. High-dose course #2: Ifosfamide/Carboplatin/Etoposide

D-7	Admission and start hydration
D-6 to -4	Mesna 3,000 mg/m2/day in 24-hour continuous infusion, starting 30 minutes prior to the first dose of ifosfamide Ifosfamide 3,000 mg/m2 IV over 6 hours Etoposide 200 mg/m2 IV over 3 hours Q12h Carboplatin 300 mg/m2 over 2 hours
D-3	Mesna 3,000 mg/m2/day in 24-hour continuous infusion, starting 30 minutes prior to the first dose of ifosfamide Ifosfamide 3,000 mg/m2 IV over 6 hours Carboplatin 300 mg/m2 over 2 hours
D-2	Rest
D-1	Rest

D0 Hematopoietic progenitor-cell infusion

Every effort will be made to admit the patient for prehydration on any day but Saturday or Sunday, so that the stem-cell infusion can proceed during a week day.

The order of chemotherapy on days -6 to -3 will be as follows: The 96-hour infusion of Mesna will be started on day -6 thirty minutes prior to the first dose of Ifosfamide.The first of the two daily doses of Etoposide will be given after the Ifosfamide infusion is complete. The daily dose of Carboplatin will be given after the first daily dose of Etoposide.

Patients with creatinine >1.2 mg/dL or performance status of 2 will receive a reduced version of this regimen:

D-7	Admission and start hydration
D-6 to -4	Mesna 2,500 mg/m2/day in 24-hour continuous infusion, starting 30 minutes prior to the first dose of ifosfamide Ifosfamide 2,500 mg/m2 IV over 6 hours Etoposide 200 mg/m2 IV over 3 hours Q12h Carboplatin 250 mg/m2 over 2 hours
D-3	Mesna 2,500 mg/m2/day in 24-hour continuous infusion, starting 30 minutes prior to the first dose of ifosfamide Ifosfamide 2,500 mg/m2 IV over 6 hours Carboplatin 250 mg/m2 over 2 hours
D-2	Rest
D-1	Rest
D0	Hematopoietic progenitor-cell infusion

Patients with prior allergic reactions to etoposide will receive, instead, the etoposide phosphate formulation at 200 mg/m2 IV over 3 hours Q12 hours on days -6 to -4 (same dose and schedule as regular etoposide for those patients without an allergy to this drug).

6.3. Concomitant medications for each course

G-CSF is administered at a dose of approximately 5 mcg/kg (given as the closest highest dose resulting in administration of a complete vial) daily from day +5 until granulocytes >1.0 x 10e9/l or longer per the discretion of the treating physician.

Administration of antiemetics during chemotherapy is recommended, following the departmental standards. The use of concomitant medications should be avoided whenever possible to minimize potentially harmful interactions. Medically necessary medications or procedures shall ultimately be at the discretion of the treating physician. Acetaminophen (Tylenol) shall not be administered for 72 hr before and on the day of administration of carboplatin or melphalan.

Prophylactic antimicrobials are not to be administered during the chemotherapy

treatments, and should start on day-1, following departmental standards.

6.4. Determination of Dosing Body Surface Area (BSA)

For patients whose actual body weight (BW) is </= 20% above the ideal BW, the actual BW is used to calculate the BSA. For patients whose actual BW is >20% above ideal BW, an "adjusted BW", defined as the midpoint between the actual and ideal BW, will be used to calculate an "adjusted BSA" for chemotherapy dosing calculation purposes.

7.0 Post Treatment Evaluation

During each course
Adverse events (toxicity) assessment while admitted in hospital, patients will be monitored on a daily basis by the in-patient team. Once discharged, once a week until admission for course 2.

Between course 1 and 2:
a) CBC, differential and platelet count, coagulation profile (PT and PTT)
b) Chemistry panel including creatinine, albumin, electrolytes, glucose,albumin, total protein, alkaline phosphatase, ALT, AST, bilirubin, LDH.
c) Chest x-ray
d) Urine dipstick. If proteinuria >/= 2+, a 24-hour urine collection for total protein will be performed.
e) Tumor markers (AFP and/or B-HCG)

On Approximately D+30, D+100, 6 month, and 1 year of treatment completion (course 2):

Once discharged, from course 2, the patient will come once a week or as determined by primary physician until day +30. From that time on, patients will be evaluated every 1-2 months until day +100, at which time treatment safety completion assessment will be performed with:

1- Adverse events (toxicity) assessment (standard for autologous stem cell transplantation):
- a) History and physical examination.
- b) CBC, differential and platelet count, coagulation profile (PT and PTT).
- c) Chemistry panel including creatinine, albumin, electrolytes, glucose,albumin, total protein, alkaline phosphatase, ALT, AST, bilirubin, LDH.

2- Disease specific:
- d) CT scans of chest, abdomen, and pelvis and/or PET/CT.
- e) Tumor markers (AFP and/or B-HCG)-HCG).
- f) MRI of the brain (if clinically indicated).

Six-month disease status evaluation: The disease status of each patient (progression/relapse vs. remission/no progression) will be assessed for purpose of the

early trial stopping rule for futility described in section 11.

Tumor response evaluation: will be assessed using response criteria appendix E.

Return visits: weekly while between courses, at approximately D+30, D+100, 6-month and 1-year of treatment completion (Course 2).

Off-Study Criteria:
Evidence of tumor progression.
Unexpected pattern of toxicity.
Patient request.
At 1 year of treatment completion (course 2).

8.0 Evaluation Criteria

8.1.1 Neutrophil recovery: is defined as the first day of a sustained absolute neutrophil count (ANC) $\geq$ 0.5 x 10^9/L for 3 consecutive days by day 28. Graft Failure is defined as failure to achieve an ANC $\geq$ 0.5 x 10^9/L for 3 consecutive days by day 28, with <10% cellularity on bone marrow biopsy. Secondary graft failure is defined as a sustained decline of ANC <0.5 x 10^9/L for 3 consecutive days after initial documented engraftment.

8.1.2 Response definitions: See Appendix E.

8.1.3 Overall survival will be estimated from HDC #1 start (day -6) until last clinic visit if the patient is alive, or death from any cause

8.1.4 Event-free survival will be estimated from the first day of HDC #1 (day-6) until tumor progression, relapse, or death from any cause.

9.0 Adverse Events and Reporting Requirements

The intensity of adverse events (AE) will be assessed according to the Common Terminology Criteria v3.0 (CTCAE). Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

Adverse events (toxicities) known to be produced by the chemotherapy regimen:

1- Mucositis: It starts early after transplant, peaks in severity around day +2.
2- Diarrhea: It presents in the first hospital week after transplant.
3- Constipation/Ileus: It can occur in the first week after transplant.

4- Enterocolitis (abdominal pain with/without bleeding, diarrhea or constipation): It can occur in the second week, and lasts for around one week.
5- Hepatic: early and transient elevations of liver function enzymes, typically starting around day -3 and resolving within 1 week.
6- Pulmonary: manifested as progressive or acute dyspnea, tachypnea, hypoxemia and pulmonary infiltrates on chest radiograph that are sometimes accompanied by fever and cough, due to pulmonary edema, egnraftment syndrome or, more rarely, toxic interstitial pneumonitis.
7- Skin: mild to moderate in severity, appearing in the first week after transplant as a macular or finely granular maculopapular pruritic eruption on the trunk and extremities usually responds to moisturizing petrolatum ("Aquaphore") or topical corticosteroids
8- Nails: Asymptomatic partial or complete nail loss can occur weeks after transplant. Nails grow back within 2 to 3 months.
9- Hand-foot syndrome: it appears in the first week after transplant and can be treated successfully with piridoxine.
10- Myoarthralgia: It appears early, typically around day -3, and lasts for around 2-3 more days.
11- Asthenia (fatigue): it is the most prominent symptom after hospital discharge. Most cases respond rapidly to mehtylphenidate ("Ritalin").
12- Neurologic: peripheral neuropathy that starts around 1-2 weeks after transplant and improves within a few weeks. A few patients can experience neuropathic pain.
13- Neutropenic fever of unknow origin with negative cultures during the second week. It is thought to be largely related to cytokine release. It can be prevented in many patients using steroids, a strategy that has been shown to be safe.

<u>Adverse events (toxicities) known to be produced by other components of the treatment:</u>
The following events are not considered to be significant in relationship with the study treatment, would not be considered adverse events, and would not be collected in the study database.

Nausea and vomiting, anorexia.
Events related to Myelosuppression: thrombocytopenia, bleeding, platelets and RBCs transfusions.
Flu-like symptoms: fever of any grade frecuently associated with headache, chills, cough, rhinitis, sweating and insomnia.
Mood alteration: depression, anxiety, and agitation
Readmissions (lasting <10 days)
Low blood pressure due to dehydration requiring fluid replacement
Fluid overload due to fluid replacement rarely leading to cardiac dysfunction
Laboratory serum metabolic values not reflecting end-organ (hepatic, renal) function and or those considered associated to the original disease
Events that are identified to be related to the supportive treatment (concomitant

medications) including steroid- related side effects.

Adverse Events Considered Serious (SAEs):
a) Prolonged hospitalization due to infections and/or organ failure requiring extensive supportive care (i.e. dialysis, mechanical ventilation)
b) Readmissions from any cause resulting in a prolonged hospitalization (>10 days).
c) Any expected or unexpected event resulting in an irreversible condition and/ or leading to death.

Reporting Requirements:
Drug toxicities will be evaluated according to CTC version 3 (Appendix A). Serious and unexpected adverse events occurring during the patient participation on this study will be reported to the PI or his designate, who in turn will notify the IRB and Clinical Research Compliance (CRC) office.

In order to assure appropriate monitoring for toxicities, each patient will be followed for 30 days after transplant or until documentation of reversal of all toxicities is obtained. Additionally, the patient will be seen approximately 3 months (range 2-4 months) after transplant for follow-up of therapeutic and toxic effects.

All other life-threatening (grade 4) or fatal (grade 5) events with possible, probable or definite attribution to the study drug must have a written report transmitted within 24 hours (next working day) of knowledge of the event to the CRC office and the original submitted to the IRB

This study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety and well-being of the patient requires immediate intervention, based on the judgment of the investigator or his/her designee. In the event of a significant deviation from the protocol, the investigator will notify the IRB.

All laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patient identity is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Information gathered for this study will not be reused or disclosed to any other person or entity, or for other research. Once the research has been completed, identifiers will be retained for as long as is required by law and by institutional regulations, and at that point will be destroyed.

10.0 Statistical Design

10.1. Objectives

The original primary objective of this phase II trial was to evaluate the efficacy of treating testicular cancer patients with the proposed treatment of tandem high-dose cycles of bevacizumab/gemcitabine/docetaxel/melphalan/carboplatin and bevacizumab/ifosfamide/carboplatin/etoposide. The primary endpoint is 2-year event-free survival (EFS). The currently used HDC regimens in patients with relapsed disease are associated with a 2-year EFS rate of 15% in the population targeted in this trial, and it is expected that the proposed treatment may increase 2-year EFS to 50%. In December 2014, because of data available from patients with the same indication treated without bevacizumab, the study will be modified to treat a new cohort of patients with a similar treatment regimen, which will no longer include bevacizumab. The modified primary objective is to evaluate EFS separately in the two patient cohorts. A secondary objective to compare outcomes between the two cohorts has been added. A total of 40 patients were treated as part of the original cohort, and we will treat a total of 40 patients in this new cohort.

10.2. Efficacy Monitoring

The efficacy of the original cohort of patients was monitored using a Bayesian one-arm time-to-progression (TTP) design. Details are provided in Appendix K. A total of 40 patients was treated in this cohort, and the trial did not stop early for lack of efficacy.

In February 2015 the trial is modified to add a second cohort of patients. This cohort will be treated with the same regimen as the original cohort, except that patients will not receive bevacizumab. We will use a similar monitoring rule to monitor patient data in the second cohort of patients treated without bevacizumab. We assume in this cohort that event-free survival (EFS) follows an exponential distribution and first note that, under this assumption, an EFS rate of 15% at 24 months corresponds to a median EFS of 8.77 months. Patients who are lost to follow-up before disease progression will be censored at the time of last follow-up in the calculation of EFS. We note that a 50% EFS rate at 24 months corresponds to a median EFS of 24 months. We assume that the median EFS for the standard of care (historical controls) has an inverse gamma (IG) distribution with parameters (21.23, 177.40), which has a mean of 8.77 months and a variance of 4.0 months. These prior parameters can be interpreted as providing information based on about 21 events observed over 177 months of trial time. The prior distribution for the median EFS for the experimental group in this trial is set to be IG(3, 17.54), which has the same mean, 8.77 months, but a greater variance of 77 months. This wider variance reflects our uncertainty regarding the EFS rate in the experimental group.

A maximum of 40 patients will be enrolled in this cohort. We will continuously monitor EFS in the cohort based on the following futility monitoring rule:

$$\text{Stop accrual if } \Pr(Te2 > Ts+15 \mid \text{data from the trial}) < 0.01$$

where Te2 and Ts are the median EFS of the experimental arm (without bevacizumab) and historical controls, respectively. Ts is distributed as IG(21.23, 177.40) as specified previously. In other words, if at any time during the course of the trial, the probability that the median EFS is at least 15 months longer than the median EFS for historical controls is less than 1%, we will stop the trial. The stopping boundaries for this trial will be incorporated into the Clinical Trial Conduct Monitoring website for this study found at https://biostatistics.mdanderson.org/ClinicalTrialConduct.

Assuming an accrual rate of 1 patient/2 months and following the monitoring boundaries according to the above rule, we summarize operating characteristics based upon 2000 simulations of the trial under two scenarios: 1) a true EFS rate of 15% at 2 years, and 2) a true EFS rate of 50% at 2 years. Under the first scenario, we will have a 98.2% chance of stopping the trial early and declaring that the treatment does not work (and thus a 1.2% chance of falsely concluding that the treatment dose work). An average of 14.3

patients will be treated in this scenario.

Under the second scenario, we will have a 4.0% chance of stopping the trial early and falsely concluding that the trial does not work. In this scenario, an average of 38.7 patients will be treated.

10.3. Safety Monitoring

In the original study design, in addition to monitoring EFS, we also used a monitoring rule to ensure that the rate of treatment-related mortality (TRM) at 3 months is low. Patients were monitored separately by risk (standard-risk and high-risk), and details are provided in Appendix K. Safety in the new cohort of patients treated without bevacizumab will be monitored using a similar rule, using the method of Thall, Simon, and Estey (1995) to monitor TRM, starting with the 5th patient in the trial. Separate monitoring rules are provided for standard-risk patients in the trial and high-risk patients, defined as those patients with a creatinine > 1.2 mg/dL or performance status of 2. We expect two-thirds of the new cohort (27 patients) to be standard-risk and the rest (13 patients) to be high-risk.

We will monitor the safety of the standard-risk patients by using the following Bayesian decision monitoring rule: stop accrual of standard-risk patients if at any time during the course of the trial

$$\Pr\{\text{TRM} > 5\% \mid \text{data from the trial}\} > 0.95$$

In other words, we will stop if the probability is > 95% at any time that the rate of 3-month TRM in the standard-risk patients is > 5%. We will assume a Beta(0.1,1.9) prior distribution for the TRM rate in these patients. A Beta(0.1, 1.9) prior distribution has a mean of 5%, the targeted maximum TRM rate, but carries little information. This decision rule leads to the following stopping rule: stop the trial if

[# of standard-risk patients with TRM at 3 months / # of standard-risk patients evaluated at 3 months]: >/= 2/2, 3/8, or 4/18

The operating characteristics of this rule based upon 10000 simulations of the trial are shown in the Table 4. The table provides the proportion of the time that the standard-risk group in the second cohort in the trial will stop early for different assumptions about the true 3-month TRM rate as well as the median and quartiles for the sample size. For example, if the true TRM rate in the standard-risk patients in this cohort is 5%, the cohort will stop early 8.5% of the time. If the true rate of TRM is 20%, the cohort will terminate early more than 80% of the time.

Table 4. Operating Characteristics for the TRM Monitoring Rule in Standard-Risk Patients

True TRM

True TRM Rate	Probability of Stopping Early	P25	Median	P75
2%	1.1%	27	27	27
5%	8.5%	27	27	27
10%	34.6%	16	27	27
20%	84.0%	5	12	21
30%	98.2%	4	6	11

We provide a separate monitoring rule for the high-risk patients in the second cohort. We expect to enroll 13 such patients. We will stop entry into this group if at any time during the course of the trial

$$\Pr\{\text{TRM} > 10\% \mid \text{data from the trial}\} > 0.95$$

In other words, we will stop entry in high-risk patients if the probability is > 95% at any time that the rate of 3-month TRM in the high-risk patients is > 10%. We will assume a Beta(0.2, 1.8) prior distribution for the TRM rate. This prior distribution has a mean of 10%, the targeted maximum TRM rate, but carries little information. This decision rule leads to the following stopping rule: stop the trial if

[# of high-risk patients with TRM at 3 months / # of high-risk patients evaluated at 3 months]: >/= 2/2, 3/4, or 4/9

The operating characteristics of this rule based upon 10000 simulations of the trial are shown in the Table 4. The table provides the proportion of the time that the high-risk group in the second cohort will stop early for different assumptions about the true 3-month TRM rate as well as the median and quartiles for the sample size.

Table 5. Operating Characteristics for the TRM Monitoring Rule in High-Risk Patients

True TRM Rate	Probability of Stopping Early	P25	Median	P75
2%	0.1%	13	13	13
5%	1.3%	13	13	13
10%	6.2%	13	13	13
20%	28.2%	11	13	13
30%	58.9%	5	11	13

10.4 Analysis Plan

The response rate (RR) and complete response (CR) rate will be estimated and reported along with 95% confidence intervals separately for each cohort and by risk subgroups.

Because the two cohorts of patients are not randomized, propensity score analysis will be used to compare EFS and OS between the two patient cohorts. We will explore both propensity score matching and inverse probability weighting techniques. The response rates RR and CR will also be compared between the two patient cohorts by using propensity score analysis methods.

Safety data will be summarized, including the extramedullary side effect profile and the engraftment rate for Bev/Gem/DMC and Bev/ICE. Overall survival (OS) and event-free survival (EFS) will be estimated using the method of Kaplan and Meier.

Categorical variables will be summarized using frequency tables. The Cox proportional hazards regression model will be used to assess the association between covariates of interest on EFS and OS. Logistic regression will be used to assess the effects of covariates of interest upon RR and CR.

11.0 Background Drug Information

11.1. Melphalan (Alkeran®)

Melphalan is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA,

probably by binding at the N^7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

Formulation: Melphalan for injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone.

Preparation: Melphalan for injection must be reconstituted by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilized powder using a sterile needle and syringe. This provides a 5 mg/mL solution of melphalan. Immediately dilute the dose to be administered in 0.9% Sodium Chloride Injection, USP, to a concentration not greater than 0.45 mg/mL. Administer the diluted product over a minimum of 15 minutes. Complete the administration within 60 minutes of reconstitution.

Storage and stability: Melphalan for injection vials should be stored at controlled room temperature 15° to 30° C (59° to 86° F) and protected from light. The time between reconstitution/dilution and administration of melphalan should be kept to a minimum because reconstituted and diluted solutions of melphalan are unstable. Over as short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted material from the reaction of melphalan with the diluent. Upon further dilution with saline, nearly 1% label strength of melphalan hydrolizes every 10 minutes. A precipitate forms if the reconstituted solution is stored at 5° C. Do not refrigerate the reconstituted product.

Adverse events associated with melphalan: The following information on adverse reactions is based on data from both oral and IV administration of melphalan as a single agent, using several different dose schedules for treatment of a wide variety of malignancies. Please refer to the Adverse Reactions and Warnings sections of the product package insert.

Hematologic: The most common side effect is bone marrow suppression. White blood cell count and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks after treatment. Irreversible bone marrow failure has been reported.
Gastrointestinal: Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral ulceration occur infrequently. Hepatic toxicity, including veno-occlusive disease, has been reported.
Hypersensitivity: Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving melphalan for myeloma. These reactions were characterized by urticaria, pruritus, edema, and in some patients, tachycardia, hypotension and bronchospasm. These patients appeared to respond to antihistamine and corticosteroid therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan.
Carcinogenesis: Secondary malignancies, including acute nonlymphocytic leukemia,

myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan).
Other: Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, vasculitis, alopecia, hemolytic anemia, pulmonary fibrosis and interstitial pneumonitis.

11.2. Gemcitabine

SYNONYM(S): Gemcitabine hydrochloride, difluorodeoxycytidine,2',2'-difluorodeoxycytidine, dFdC, LY 188011

COMMON TRADE NAME(S): Gemzar® (notice of compliance,1 December 1996; patent expires2 March 2004)

CLASSIFICATION: Antimetabolite, cytotoxic
Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:
Gemcitabine, a pyrimidine analog, is structurally similar to cytarabine, but has a wider spectrum of antitumour activity due to its different cellular pharmacology and mechanism of action.3 Gemcitabine is metabolized intracellularly to two active metabolites, gemcitabine diphosphate (dFdCDP) and gemcitabine triphosphate (dFdCTP). The cytotoxic effects of gemcitabine are exerted through incorporation of dFdCTP into DNA with the assistance of dFdCDP, resulting in inhibition of DNA synthesis and induction of apoptosis. emcitabine is a radiation-sensitizing agent.5 It is cell-cycle phase specific (S and G1/S-phases).

PHARMACOKINETICS:

Interpatient variability: 3- to 4-fold interpatient and intrapatient variability

Distribution: widely distributed into tissues; also present in ascitic fluid

Volume of distribution: IV infusion < 70 min: 50 L/m2;IV infusion 70-285 min: 370 L/m2

Plasma protein binding: < 10%

Metabolism: Metabolized intracellularly by nucleoside kinases to active metabolites dFdCDP and dFdCTP; also metabolized intracellularly and extracellularly by cytidine deaminase to inactive metabolite difluorodeoxyuridine (dFdU)

Excretion: Urine 92-98% over one week (89% as dFdU, < 10% as gemcitabine) after a single dose of 1000 mg/m2 given over 30 minutes

Half life: Terminal half life IV infusion < 70 min: 0.7-1.6 h. IV infusion 70-285 min:

4.1-10.6 h

Clearance: ClearanceIV infusion < 70 min: 41-92 L/h/m2 (male), 31-69 L/h/m2 (female)

Gender: decreased volume of distribution and clearance in women

Elderly: decreased clearance and increased half-life with increasing age

SPECIAL PRECAUTIONS:

Carcinogenicity: No information found.

Mutagenicity: Not mutagenic in Ames test but mutagenic in mammalian *in vitro* mutation test. Gemcitabine is clastogenic in mammalian *in vitro* and *in vivo* chromosome tests.

Fertility: Decreased spermatogenesis and fertility in male mice.5

Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (eg, if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Breastfeeding is not recommended due to the potential secretion into breast milk

SIDE EFFECTS:

ORGAN SITE	**SIDE EFFECT** Dose-limiting side effects are in ***bold, italics*** I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)	**ONSET**
Allergy/immunology	allergic reaction (4%, severe 0.2%)30	I
Blood/bone marrow	***anemia*** (68%, severe 8%)	E
	leukopenia (62%, severe 9%)	E
	neutropenia (63%, severe 25%) nadir 7-10 days, recovery within 7 days31	E
	thrombocytopenia (24%, severe 5%)	E

	nadir 7-10 days, recovery within 7 days31	
Cardiovascular (arrhythmia)	cardiac arrhythmia (2%, severe 0.2%)30	E
Cardiovascular (general)	edema/peripheral edema (28%, severe 3%)32	ED
Coagulation	hemolytic uremic syndrome (0.3%)	D
Constitutional symptoms	asthenia (42%, severe 2%)30	E
	fever (37%, severe < 1%)	IE
Dermatology/skin	*extravasation hazard:* none4,30	
	alopecia (14%)	D
	skin rash (25%, severe < 1%)	IE
Gastrointestinal	*emetogenic potential:* low moderate33	
	constipation (8%, severe < 1%)	E
	diarrhea (12%, severe < 1%)	E
	nausea and vomiting (64%, severe 18%)	I
	stomatitis (8%, severe < 1%)	E
Hemorrhage	hematuria (31%, severe < 1%)	E
Hepatic	elevated alkaline phosphatase (55%, severe 9%)	E
	elevated AST (67%, severe 9%)	E
	elevated ALT (68%, severe 10%)	E
	elevated bilirubin (13%, severe 2%)	E
Infection	infection (9%, severe 1%)	E
Neurology	decreased level of consciousness (9%, severe < 1%)	E
	peripheral neuropathy (3%)17	ED
Pain	pain (16%, severe 1%)	ED
Pulmonary	dyspnea (8%, severe 1%)	IE
Renal/Genitourinary	elevated BUN (16%, severe 0%)	E
	elevated creatinine (7%, severe < 1%)	E
	proteinuria (36%, severe < 1%)	E
Syndromes	flu-like symptoms (19%, severe 1%)30	E

Hemolytic uremic syndrome has been infrequently reported and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. The syndrome can present either acutely with severe hemolysis, thrombocytopenia and rapidly progressive renal failure, or more insidiously with mild or no thrombocytopenia and slowly progressive renal failure. The etiology of hemolytic uremic syndrome is unknown.The onset of the syndrome has been reported to occur during and shortly after gemcitabine therapy. If not treated promptly, the syndrome may result in irreversible

renal failure requiring dialysis. Therefore, patients with impaired renal function should be monitored closely while being treated with gemcitabine.

Elevated liver enzymes: Gemcitabine causes transient and reversible elevations of liver function enzymes in about two-thirds of patients. However, these increases are rarely of clinical significance and there is no evidence of increasing hepatic toxicity with either longer duration of gemcitabine treatment or cumulative dose.

Fever/Flu-like symptoms: Fever of any severity was reported in 37% of patients. It is frequently associated with other flu-like symptoms such as headache, chills, cough, rhinitis, myalgia, fatigue, sweating and insomnia. These symptoms are usually mild and transient, and rarely dose-limiting. The use of acetaminophen may provide symptomatic relief.

Severe pulmonary toxicity: Acute dyspnea may sometimes occur with gemcitabine therapy, but is usually self-limiting. However, severe pulmonary toxicities such as pulmonary edema, interstitial pneumonitis and adult respiratory distress syndrome have rarely been reported. The symptoms are manifested as progressive dyspnea, tachypnea, hypoxemia and pulmonary infiltrates on chest radiograph that are sometimes accompanied by fever and cough. Pulmonary toxicities usually occur after several cycles of gemcitabine, but have also been seen as early as the first cycle. Risk factors for pulmonary toxicities include prior radiation to the mediastinum. Because of its structural similarities to cytarabine, gemcitabine is thought to cause lung injury by the same mechanism by inducing pulmonary capillary leakage. Management of pulmonary toxicities consists of discontinuation of gemcitabine and early supportive care with bronchodilators, corticosteroids, diuretics, and/or oxygen. Although pulmonary toxicities may be reversible with treatment, fatal recurrence of severe pulmonary symptoms was reported in one patient upon rechallenge with gemcitabine.

Skin rash**:** Typically mild to moderate in severity, with macular or finely granular maculopapular pruritic eruption on the trunk and extremities. It is not dose-limiting and usually responds to topical corticosteroidsIf needed, antihistamines such as diphenhydramine can be used.

INTERACTIONS:

AGENT	**EFFECT**	**MECHANISM**	**MANAGEMENT**
Warfarin	increased anticoagulant effect of warfarin	possibly decreased metabolism of warfarin and decreased hepatic synthesis of clotting factors	monitor INR carefully during and for 1-2 months after gemcitabine therapy; adjust warfarin dose as needed

SOLUTION PREPARATION AND COMPATIBILITY:

Injection: 200 mg and 1000 mg vials (as the hydrochloride salt). Store at room temperature.

Reconstitute 200 mg vial with 5 mL of NS without preservative and 1000 mg vial with 25 mL of NS without preservative to yield a gemcitabine concentration of 38 mg/mL. Reconstitution of concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided. Reconstituted solution is stable for 24 hours at room temperature and should not be days at room temperature and under refrigeration. However, the manufacturer recommends that the admixture be used within 24 hours since the solution does not contain preservatives.

Bacterial challenge: Gemcitabine 2.4 mg/mL diluted in NS did not exhibit a substantial antimicrobial effect on the growth of four organisms inoculated into the solution. Diluted solutions should be stored under refrigeration whenever possible and that the potential for microbiological growth should be considered when assigning expiration periods.

Compatibility*:** The following are ***compatible via Y-site injection: amifostine, bleomycin, carboplatin, carmustine, cisplatin, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, dexamethasone, dexrazoxane, diphenhydramine, docetaxel, dopamine, doxorubicin, etoposide, fludarabine, fluorouracil, granisetron, heparin, hydrocortisone, hydromorphone, idarubicin, ifosfamide, leucovorin, lorazepam, mannitol, meperidine, mesna, metoclopramide, mitoxantrone, morphine, ondansetron, paclitaxel, plicamycin, potassium chloride, ranitidine, sodium bicarbonate, streptozocin, teniposide, thiotepa, topotecan, vinblastine, vincristine, vinorelbine.

Incompatibility: The following are ***incompatible*** via Y-site injection: furosemide, irinotecan, methotrexate, methylprednisolone, mitomycin, prochlorperazine.

11.3. Carboplatin

Carboplatin injection

WARNING
Carboplatin for injection should be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Appropriate management of therapy and complications is possible only when adequate treatment facilities are readily available.
Bone marrow suppression is dose related and may be severe, resulting in infection and/or bleeding. Anemia may be cumulative and may require transfusion support. Vomiting is another frequent drug-related side effect.

Anaphylactic-like reactions to carboplatin have been reported and may occur within minutes of carboplatin administration. Epinephrine, corticosteroids, and antihistamines have been employed to alleviate symptoms.

Carboplatin Description

Carboplatin for Injection USP is supplied as a sterile, lyophilized white powder available in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin for administration by intravenous infusion. Each vial contains equal parts by weight carboplatin and mannitol.
Carboplatin is a platinum coordination compound that is used as a cancer chemotherapeutic agent. The chemical name for carboplatin is platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-, (SP-4-2).

Carboplatin is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

Carboplatin - Clinical Pharmacology

Carboplatin, like cisplatin, produces predominantly interstrand DNA cross-links rather than DNA-protein cross-links. This effect is apparently cell-cycle nonspecific. The aquation of carboplatin, which is thought to produce the active species, occurs at a slower rate than in the case of cisplatin. Despite this difference, it appears that both carboplatin and cisplatin induce equal numbers of drug-DNA cross-links, causing equivalent lesions and biological effects. The differences in potencies for carboplatin and cisplatin appear to be directly related to the difference in aquation rates.

In patients with creatinine clearances of about 60 mL/min or greater, plasma levels of intact carboplatin decay in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m2 of carboplatin. The initial plasma half-life (alpha) was found to be 1.1 to 2 hours (N=6), and the post-distribution plasma half-life (beta) was found to be 2.6 to 5.9 hours (N=6). The total body clearance, apparent volume of distribution and mean residence time for carboplatin are 4.4 L/hour, 16 L and 3.5 hours, respectively. The Cmax values and areas under the plasma concentration vs time curves from 0 to infinity (AUC inf) increase linearly with dose, although the increase was slightly more than dose proportional. Carboplatin, therefore, exhibits linear pharmacokinetics over the dosing range studied (300 to 500 mg/m2).

Carboplatin is not bound to plasma proteins. No significant quantities of protein-free, ultrafilterable platinum-containing species other than carboplatin are present in plasma. However, platinum from carboplatin becomes irreversibly bound to plasma proteins and is slowly eliminated with a minimum half-life of 5 days.

The major route of elimination of carboplatin is renal excretion. Patients with creatinine clearances of approximately 60 mL/min or greater excrete 65% of the dose in the urine within 12 hours and 71% of the dose within 24 hours. All of the platinum in the 24-hour urine is present as carboplatin. Only 3 to 5% of the administered platinum is excreted in the urine between 24 and 96 hours. There are insufficient data to determine whether biliary excretion occurs.

In patients with creatinine clearances below 60 mL/min the total body and renal clearances carboplatin decrease as the creatinine clearance decreases. Carboplatin dosages should therefore be reduced in these patients.
The primary determinant of carboplatin clearance is glomerular filtration rate (GFR) and this parameter of renal function is often decreased in elderly patients. Dosing formulas incorporating estimates of GFR to provide predictable carboplatin plasma AUCs should be used in elderly patients to minimize the risk of toxicity.

Contraindications

Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or other platinum-containing compounds.

Carboplatin should not be employed in patients with severe bone marrow depression or significant bleeding.

Warnings

Bone marrow suppression (leukopenia, neutropenia, and thrombocytopenia) is dose-dependent and is also the dose-limiting toxicity. Peripheral blood counts should be frequently monitored during carboplatin treatment and, when appropriate, until recovery is achieved. Median nadir occurs at day 21 in patients receiving single-agent carboplatin. In general, single intermittent courses of carboplatin should not be repeated until leukocyte, neutrophil, and platelet counts have recovered.

Since anemia is cumulative, transfusions may be needed during treatment with carboplatin, particularly in patients receiving prolonged therapy.

Bone marrow suppression is increased in patients who have received prior therapy, especially regimens including cisplatin. Marrow suppression is also increased in patients with impaired kidney function. Initial carboplatin dosages in these patients should be appropriately reduced and blood counts should be carefully monitored between courses. The use of carboplatin in combination with other bone marrow suppressing therapies must be carefully managed with respect to dosage and timing in order to minimize additive effects.

Carboplatin has limited nephrotoxic potential, but concomitant treatment with aminoglycosides has resulted in increased renal and/or audiologic toxicity, and caution must be exercised when a patient receives both drugs. Clinically significant hearing loss has been reported to occur in pediatric patients when carboplatin was administered at higher than recommended doses in combination with other ototoxic agents.

Carboplatin can induce emesis, which can be more severe in patients previously receiving emetogenic therapy. The incidence and intensity of emesis have been reduced by using premedication with antiemetics. Although no conclusive efficacy data exist with the following schedules of carboplatin, lengthening the duration of single intravenous administration to 24 hours or dividing the total dose over five consecutive daily pulse doses has resulted in reduced emesis.

Although peripheral neurotoxicity is infrequent, its incidence is increased in patients older than 65 years and in patients previously treated with cisplatin. Pre-existing cisplatin-induced neurotoxicity does not worsen in about 70% of the patients receiving carboplatin as secondary treatment.

Loss of vision, which can be complete for light and colors, has been reported after the use of carboplatin with doses higher than those recommended in the package insert. Vision appears to recover totally or to a significant extent within weeks of stopping these high doses.

As in the case of other platinum coordination compounds, allergic reactions to carboplatin have been reported. These may occur within minutes of administration and should be managed with appropriate supportive therapy. There is increased risk of allergic reactions including anaphylaxis in patients previously exposed to platinum therapy.

High dosages of carboplatin (more than four times the recommended dose) have resulted in severe abnormalities of liver function tests.

Carboplatin may cause fetal harm when administered to a pregnant woman. Carboplatin has been shown to be embryotoxic and teratogenic in rats. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

General

Needles or intravenous administration sets containing aluminum parts that may come in contact with carboplatin should not be used for the preparation or administration of the drug. Aluminum can react with carboplatin causing precipitate formation and loss of potency.

Drug Interactions

The renal effects of nephrotoxic compounds may be potentiated by carboplatin.

Carcinogenesis, Mutagenesis, Impairment of Fertility

The carcinogenic potential of carboplatin has not been studied, but compounds with similar mechanisms of action and mutagenicity profiles have been reported to be carcinogenic. Carboplatin has been shown to be mutagenic both in vitro and in vivo. It has also been shown to be embryotoxic and teratogenic in rats receiving the drug during organogenesis. Secondary malignancies have been reported in association with multi-drug therapy.

Pregnancy

Teratogenic Effects; Pregnancy Category D.

Nursing Mothers

It is not known whether carboplatin is excreted in human milk. Because there is a possibility of toxicity in nursing infants secondary to carboplatin treatment of the mother, it is recommended that breast feeding be discontinued if the mother is treated with carboplatin.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

Of the 789 patients in initial treatment combination therapy studies (NCIC and SWOG), 395 patients were treated with carboplatin in combination with cyclophosphamide. Of these, 141 were over 65 years of age and 22 were 75 years or older. In these trials, age was not a prognostic factor for survival. In terms of safety, elderly patients treated with carboplatin were more likely to develop severe thrombocytopenia than younger patients. In a combined database of 1942 patients (414 were ·65 years of age) that received single agent carboplatin for different tumor types, a similar incidence of adverse events as seen in patients 65 years and older and in patients less than 65. Other reported clinical experience has not identified differences in responses between elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. Because renal function is often decreased in the elderly, renal function should be considered in the selection of carboplatin dosage.

Adverse Reactions

Hematologic Toxicity

Bone marrow suppression is the dose-limiting toxicity of carboplatin. Thrombocytopenia with platelet counts below 50,000/mm3 occurs in 25% of the patients (35% of pretreated ovarian cancer patients); neutropenia with granulocyte counts below 1000/mm3 occurs in 16% of the patients (21% of pretreated ovarian cancer patients); leukopenia with WBC counts below 2000/mm3 occurs in 15% of the patients (26% of pretreated ovarian cancer patients). The nadir usually occurs about day 21 in patients receiving single-agent therapy. By day 28, 90% of patients have platelet counts above 100,000/mm3; 74% have neutrophil counts above 2000/mm3; 67% have leukocyte counts above 4000/mm3.

Marrow suppression is usually more severe in patients with impaired kidney function. Patients with poor performance status have also experienced a higher incidence of severe leukopenia and thrombocytopenia.
The hematologic effects, although usually reversible, have resulted in infectious or hemorrhagic complications in 5% of the patients treated with carboplatin, with drug related death occurring in less than 1% of the patients. Fever has also been reported in patients with neutropenia.

Anemia with hemoglobin less than 11 g/dL has been observed in 71% of the patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure to carboplatin. Transfusions have been administered to 26% of the patients treated with carboplatin (44% of previously treated ovarian cancer patients).

Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy.

Gastrointestinal Toxicity

Vomiting occurs in 65% of the patients (81% of previously treated ovarian cancer patients) and in about one-third of these patients it is severe. Carboplatin, as a single agent or in combination, is significantly less emetogenic than cisplatin; however, patients previously treated with emetogenic agents, especially cisplatin, appear to be more prone to vomiting. Nausea alone occurs in an additional 10 to 15% of patients.

Both nausea and vomiting usually cease within 24 hours of treatment and are often responsive to antiemetic measures. Although no conclusive efficacy data exist with the following schedules, prolonged administration of carboplatin, either by continuous 24-hour infusion or by daily pulse doses given for five consecutive days, was associated with less severe vomiting than the single dose intermittent schedule.

Emesis was increased when carboplatin was used in combination with other emetogenic compounds. Other gastrointestinal effects observed frequently were pain, in 17% of the patients; diarrhea, in 6%; and constipation, also in 6%.

Neurologic Toxicity

Peripheral neuropathies have been observed in 4% of the patients receiving carboplatin (6% of pretreated ovarian cancer patients) with mild paresthesias occurring most frequently. Carboplatin therapy produces significantly fewer and less severe neurologic side effects than does therapy with cisplatin. However, patients older than 65 years and/or previously treated with cisplatin appear to have an increased risk (10%) for peripheral neuropathies. In 70% of the patients with pre-existing cisplatin-induced peripheral neurotoxicity, there was no worsening of symptoms during therapy with carboplatin. Clinical ototoxicity and other sensory abnormalities such as visual disturbances and change in taste have been reported in only 1% of the patients. Central nervous system symptoms have been reported in 5% of the patients and appear to be most often related to the use of antiemetics.

Although the overall incidence of peripheral neurologic side effects induced by carboplatin is low, prolonged treatment, particularly in cisplatin pretreated patients, may result in cumulative neurotoxicity.

Nephrotoxicity

Development of abnormal renal function test results is uncommon, despite the fact that carboplatin, unlike cisplatin, has usually been administered without high-volume fluid

hydration and/or forced diuresis. The incidences of abnormal renal function tests reported are 6% for serum creatinine and 14% for blood urea nitrogen (10% and 22%, respectively, in pretreated ovarian cancer patients). Most of these reported abnormalities have been mild and about one-half of them were reversible.

Creatinine clearance has proven to be the most sensitive measure of kidney function in patients receiving carboplatin, and it appears to be the most useful test for correlating drug clearance and bone marrow suppression. Twenty-seven percent of the patients who had a baseline value of 60 mL/min or more demonstrated a reduction below this value during carboplatin therapy.

Hepatic Toxicity

The incidences of abnormal liver function tests in patients with normal baseline values were reported as follows: total bilirubin, 5%; SGOT, 15%; and alkaline phosphatase, 24%; (5%,19%, and 37%, respectively, in pretreated ovarian cancer patients). These abnormalities have generally been mild and reversible in about one-half of the cases, although the role of metastatic tumor in the liver may complicate the assessment in many patients. In a limited series of patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests were reported.

Electrolyte Changes

The incidences of abnormally decreased serum electrolyte values reported were as follows: sodium, 29%; potassium, 20%; calcium, 22%; and magnesium, 29%; (47%, 28%, 31%, and 43%, respectively, in pretreated ovarian cancer patients). Electrolyte supplementation was not routinely administered concomitantly with carboplatin, and these electrolyte abnormalities were rarely associated with symptoms.

Allergic Reactions

Hypersensitivity to carboplatin has been reported in 2% of the patients. These allergic reactions have been similar in nature and severity to those reported with other platinum-containing compounds, i.e., rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Anaphylactic reactions have been reported as part of postmarketing surveillance. These reactions have been successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Injection Site Reactions

Injection site reactions, including redness, swelling, and pain, have been reported during postmarketing surveillance. Necrosis associated with extravasation has also been reported.

Other Events

Pain and asthenia were the most frequently reported miscellaneous adverse effects; their relationship to the tumor and to anemia waslikely. Alopecia was reported (3%). Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in 6% or less of the patients. Cardiovascular events (cardiac failure, embolism, cerebrovascular

accidents) were fatal in less than 1% of the patients and did not appear to be related to chemotherapy. Cancer-associated hemolytic uremic syndrome has been reported rarely. Malaise, anorexia and hypertension have been reported as part of postmarketing surveillance.

Overdosage

There is no known antidote for carboplatin overdosage. The anticipated complications of overdosage would be secondary to bone marrow suppression and/or hepatic toxicity.

Formula Dosing

Another approach for determining the initial dose of carboplatin for injection is the use of mathematical formulae, which are based on a patient's pre-existing renal function or renal function and desired platelet nadir. Renal excretion is the major route of elimination for carboplatin for injection. The use of dosing formulae, as compared to empirical dose calculation based on body surface area, allows compensation for patient variations in pretreatment renal function that might otherwise result in either underdosing (in patients with above average renal function) or overdosing (in patients with impaired renal function).
A simple formula for calculating dosage, based upon a patients glomerular filtration rate (GFR in mL/min) and carboplatin for injection target area under the concentration versus time curve (AUC in mg/mL•min), has been proposed by Calvert. In these studies, GFR was measured by 51Cr-EDTA clearance.

CALVERT FORMULA FOR CARBOPLATIN DOSING
Total Dose (mg) = (target AUC) x (GFR + 25)
Note: With the Calvert formula, the total dose of carboplatin injection is calculated in mg, not mg/m2.

The target AUC of 4 to 6 mg/mL•min using single agent carboplatin for injection appears to provide the most appropriate dose range in previously treated patients. This study also showed a trend between the AUC of single agent carboplatin for injection administered to previously treated patients and the likelihood of developing toxicity.

Geriatric Dosing

Because renal function is often decreased in elderly patients, formula dosing of carboplatin based on estimates of GFR should be used in elderly patients to provide predictable plasma carboplatin AUCs and thereby minimize the risk of toxicity.

PREPARATION OF INTRAVENOUS SOLUTIONS

Immediately before use, the content of each vial must be reconstituted with either Sterile Water for Injection, 5% Dextrose in Water (D5W), or 0.9% Sodium Chloride Injection, to a carboplatin concentration of 10 mg/mL.
Carboplatin for injection can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water (D5W) or 0.9% Sodium Chloride Injection.

STABILITY

Unopened vials of carboplatin for injection are stable for the life indicated on the package when stored at 20° to 25°C (68° to 77°F). See USP controlled room temperature and protect from light.
When prepared as directed, carboplatin solutions are stable for 8 hours at room temperature 25°C (77°F). Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

STORAGE

Store the unopened vials at 20° to 25°C (68° to 77°F). See USP controlled room temperature. Protect unopened vials from light. Solutions for infusion should be discarded 8 hours after preparation.

11.4. Docetaxel

WARNING
Docetaxel Injection Concentrate should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

The incidence of treatment-related mortality associated with Docetaxel therapy is increased in patients with abnormal liver function, in patients receiving higher doses, and in patients with non-small cell lung carcinoma and a history of prior treatment with platinum-based chemotherapy who receive Docetaxel as a single agent at a dose of 100 mg/m2 .

Docetaxel should generally not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with SGOT and/or SGPT >1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values should be obtained prior to each cycle of Docetaxel therapy and reviewed by the treating physician.

Docetaxel therapy should not be given to patients with neutrophil counts of < 1500 cells/mm3. In order to monitor the occurrence of neutropenia, which may be severe and result in infection, frequent blood cell counts should be performed on all patients receiving Docetaxel .

Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients who received the recommended 3-day dexamethasone premedication. Hypersensitivity reactions require immediate discontinuation of the Docetaxel infusion and administration of appropriate therapy. Docetaxel must not be given to patients who have a history of severe hypersensitivity reactions to Docetaxel or to other drugs formulated with polysorbate 80.

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites).

DESCRIPTION

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butyl ester, 13-ester with 5ß-20-epoxy-1,2α,4,7ß,10ß,13α -hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:

Docetaxel is a white to almost-white powder with an empirical formula of C43H53NO14• 3H2O, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water. Docetaxel Injection Concentrate is a clear yellow to brownish-yellow viscous solution. Docetaxel is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

Docetaxel Injection Concentrate requires dilution prior to use. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for Docetaxel contains 13% ethanol in water for injection, and is supplied in vials.

CLINICAL PHARMACOLOGY

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

HUMAN PHARMACOKINETICS

The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20-115 mg/m2 in phase I studies. The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives for the α, ß, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m2 and 113 L, respectively. Mean total body clearance for Japanese patients dosed at the range of 10-90 mg/m2 was similar to that of European/American populations dosed at 100 mg/m2, suggesting no significant difference in the elimination of docetaxel in the two populations.

A study of 14C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the *tert*-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

A population pharmacokinetic analysis was carried out after Docetaxel treatment of 535 patients dosed at 100 mg/m2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from phase I studies. The pharmacokinetics of docetaxel were not influenced by age or gender and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with clinical chemistry data suggestive of mild to moderate liver function impairment (SGOT and/or SGPT >1.5 times the upper limit of normal [ULN] concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should, in general, not be treated with Docetaxel .

Clearance of docetaxel in combination therapy with cisplatin was similar to that previously observed following monotherapy with docetaxel. The pharmacokinetic profile of cisplatin in combination therapy with docetaxel was similar to that observed with cisplatin alone.

The combined administration of docetaxel, cisplatin and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.

A population pharmacokinetic analysis of plasma data from 40 patients with

hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone.

A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m2), doxorubicin (50 mg/m2), and cyclophosphamide (500 mg/m2) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotherapy.

In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the *in vitro* binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as ketoconazole, erythromycin, troleandomycin, and nifedipine. Based on *in vitro* findings, it is likely that CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations. No clinical studies have been performed to evaluate this.

CONTRAINDICATIONS

Docetaxel is contraindicated in patients who have a history of severe hypersensitivity reactions to docetaxel or to other drugs formulated with polysorbate 80.

Docetaxel should not be used in patients with neutrophil counts of <1500 cells/mm3.

WARNINGS

Docetaxel should be administered under the supervision of a qualified physician experienced in the use of antineoplastic agents. Appropriate management of complications is possible only when adequate diagnostic and treatment facilities are readily available.

Premedication Regimen

All patients should be premedicated with oral corticosteroids (see below for prostate cancer) such as dexamethasone 16 mg per day (*e.g.*, 8 mg BID) for 3 days starting 1 day prior to Docetaxel to reduce the severity of fluid retention and hypersensitivity reactions. This regimen was evaluated in 92 patients with metastatic breast cancer previously treated with chemotherapy given Docetaxel at a dose of 100 mg/m2 every 3 weeks.

The pretreatment regimen for hormone-refractory metastatic prostate cancer is oral dexamethasone 8 mg, at 12 hours, 3 hours and 1 hour before the Docetaxel infusion.

Hypersensitivity Reactions

Patients should be observed closely for hypersensitivity reactions, especially during the first and second infusions. Severe hypersensitivity reactions characterized by generalized rash/erythema, hypotension and/or bronchospasm, or very rarely fatal anaphylaxis, have been reported in patients premedicated with 3 days of corticosteroids. Hypersensitivity reactions require immediate discontinuation of the Docetaxel infusion. Patients with a history of severe hypersensitivity reactions should not be rechallenged with Docetaxel .

Hematologic Effects

Neutropenia (< 2000 neutrophils/mm3) occurs in virtually all patients given 60-100 mg/m2 of Docetaxel and grade 4 neutropenia (< 500 cells/mm3) occurs in 85% of patients given 100 mg/m2 and 75% of patients given 60 mg/m2. Frequent monitoring of blood counts is, therefore, essential so that dose can be adjusted. Docetaxel should not be administered to patients with neutrophils < 1500 cells/mm3.

Hepatic Impairment

Docetaxel should generally not be given to patients with bilirubin > upper limit of normal (ULN), or to patients with SGOT and/or SGPT >1.5 x ULN concomitant with alkaline phosphatase > 2.5 x ULN. Patients with elevations of bilirubin or abnormalities of transaminase concurrent with alkaline phosphatase are at increased risk for the development of grade 4 neutropenia, febrile neutropenia, infections, severe thrombocytopenia, severe stomatitis, severe skin toxicity, and toxic death. Patients with isolated elevations of transaminase > 1.5 x ULN also had a higher rate of febrile neutropenia grade 4 but did not have an increased incidence of toxic death. Bilirubin, SGOT or SGPT, and alkaline phosphatase values should be obtained prior to each cycle of Docetaxel therapy and reviewed by the treating physician.

Fluid Retention

Severe fluid retention occurred in 6.5% (6/92) of patients despite use of a 3-day dexamethasone premedication regimen. It was characterized by one or more of the following events: poorly tolerated peripheral edema, generalized edema, pleural effusion requiring urgent drainage, dyspnea at rest, cardiac tamponade, or pronounced abdominal distention (due to ascites).

Acute Myeloid Leukemia

Treatment-related acute myeloid leukemia (AML) has occurred in patients given anthracyclines and/or cyclophosphamide, including use in adjuvant therapy for breast cancer. AML occurred in 3 of 744 patients who received Docetaxel , doxorubicin and cyclophosphamide and in 1 of 736 patients who received fluorouracil, doxorubicin and cyclophosphamide

Pregnancy

Docetaxel can cause fetal harm when administered to pregnant women. Studies in both rats and rabbits at doses $\geq$ 0.3 and 0.03 mg/kg/day, respectively (about 1/50 and 1/300 the daily maximum recommended human dose on a mg/m2 basis), administered during the period of organogenesis, have shown that Docetaxel is embryotoxic and fetotoxic

(characterized by intrauterine mortality, increased resorption, reduced fetal weight, and fetal ossification delay). The doses indicated above also caused maternal toxicity.

There are no adequate and well-controlled studies in pregnant women using Docetaxel . If Docetaxel is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy. Women of childbearing potential should be advised to avoid becoming pregnant during therapy with Docetaxel .

PRECAUTIONS

General

Responding patients may not experience an improvement in performance status on therapy and may experience worsening. The relationship between changes in performance status, response to therapy, and treatment-related side effects has not been established.

Hematologic Effects

In order to monitor the occurrence of myelotoxicity, it is recommended that frequent peripheral blood cell counts be performed on all patients receiving Docetaxel . Patients should not be retreated with subsequent cycles of Docetaxel until neutrophils recover to a level > 1500 cells/mm3 and platelets recover to a level > 100,000 cells/mm3.

A 25% reduction in the dose of Docetaxel is recommended during subsequent cycles following severe neutropenia (<500 cells/mm3) lasting 7 days or more, febrile neutropenia, or a grade 4 infection in a Docetaxel cycle.

Hypersensitivity Reactions

Hypersensitivity reactions may occur within a few minutes following initiation of a Docetaxel infusion. If minor reactions such as flushing or localized skin reactions occur, interruption of therapy is not required. More severe reactions, however, require the immediate discontinuation of Docetaxel and aggressive therapy. All patients should be premedicated with an oral corticosteroid prior to the initiation of the infusion of Docetaxel .

Cutaneous

Localized erythema of the extremities with edema followed by desquamation has been observed. In case of severe skin toxicity, an adjustment in dosage is recommended. The discontinuation rate due to skin toxicity was 1.6% (15/965) for metastatic breast cancer patients. Among 92 breast cancer patients premedicated with 3-day corticosteroids, there were no cases of severe skin toxicity reported and no patient discontinued Docetaxel due to skin toxicity.

Fluid Retention

Severe fluid retention has been reported following Docetaxel therapy. Patients should be premedicated with oral corticosteroids prior to each TAXOTERE administration to

reduce the incidence and severity of fluid retention. Patients with pre-existing effusions should be closely monitored from the first dose for the possible exacerbation of the effusions.

When fluid retention occurs, peripheral edema usually starts in the lower extremities and may become generalized with a median weight gain of 2 kg.

Among 92 breast cancer patients premedicated with 3-day corticosteroids, moderate fluid retention occurred in 27.2% and severe fluid retention in 6.5%. The median cumulative dose to onset of moderate or severe fluid retention was 819 mg/m2. 9.8% (9/92) of patients discontinued treatment due to fluid retention: 4 patients discontinued with severe fluid retention; the remaining 5 had mild or moderate fluid retention. The median cumulative dose to treatment discontinuation due to fluid retention was 1021 mg/m2. Fluid retention was completely, but sometimes slowly, reversible with a median of 16 weeks from the last infusion of Docetaxel to resolution (range: 0 to 42+ weeks). Patients developing peripheral edema may be treated with standard measures, *e.g.*, salt restriction, oral diuretic(s).

Neurologic

Severe neurosensory symptoms (paresthesia, dysesthesia, pain) were observed in 5.5% (53/965) of metastatic breast cancer patients, and resulted in treatment discontinuation in 6.1%. When these symptoms occur, dosage must be adjusted. If symptoms persist, treatment should be discontinued Patients who experienced neurotoxicity in clinical trials and for whom follow-up information on the complete resolution of the event was available had spontaneous reversal of symptoms with a median of 9 weeks from onset (range: 0 to 106 weeks). Severe peripheral motor neuropathy mainly manifested as distal extremity weakness occurred in 4.4% (42/965).

Asthenia

Severe asthenia has been reported in 14.9% (144/965) of metastatic breast cancer patients but has led to treatment discontinuation in only 1.8%. Symptoms of fatigue and weakness may last a few days up to several weeks and may be associated with deterioration of performance status in patients with progressive disease.

Drug Interactions

There have been no formal clinical studies to evaluate the drug interactions of Docetaxel with other medications. *In vitro* studies have shown that the metabolism of docetaxel may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4, such as cyclosporine, terfenadine, ketoconazole, erythromycin, and troleandomycin. Caution should be exercised with these drugs when treating patients receiving Docetaxel as there is a potential for a significant interaction.

Carcinogenicity, Mutagenicity, Impairment of Fertility

No studies have been conducted to assess the carcinogenic potential of Docetaxel . Docetaxel has been shown to be clastogenic in the *in vitro* chromosome aberration test in CHO-K1 cells and in the *in vivo* micronucleus test in the mouse, but it did not induce mutagenicity in the Ames test or the CHO/HGPRT gene mutation assays. Docetaxel

produced no impairment of fertility in rats when administered in multiple IV doses of up to 0.3 mg/kg (about 1/50 the recommended human dose on a mg/m2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at IV doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3 and 1/15 the recommended human dose on a mg/m2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

Pregnancy

Pregnancy Category D.

Nursing Mothers

It is not known whether Docetaxel is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Docetaxel , mothers should discontinue nursing prior to taking the drug.

Pediatric Use

The safety and effectiveness of Docetaxel in pediatric patients have not been established.

Geriatric Use

In a study conducted in chemotherapy-naïve patients with NSCLC (TAX326), 148 patients (36%) in the Docetaxel +cisplatin group were 65 years of age or greater. There were 128 patients (32%) in the vinorelbine+cisplatin group 65 years of age or greater. In the Docetaxel +cisplatin group, patients less than 65 years of age had a median survival of 10.3 months (95% CI : 9.1 months, 11.8 months) and patients 65 years or older had a median survival of 12.1 months (95% CI : 9.3 months, 14 months). In patients 65 years of age or greater treated with Docetaxel +cisplatin, diarrhea (55%), peripheral edema (39%) and stomatitis (28%) were observed more frequently than in the vinorelbine+cisplatin group (diarrhea 24%, peripheral edema 20%, stomatitis 20%). Patients treated with Docetaxel +cisplatin who were 65 years of age or greater were more likely to experience diarrhea (55%), infections (42%), peripheral edema (39%) and stomatitis (28%) compared to patients less than the age of 65 administered the same treatment (43%, 31%, 31% and 21%, respectively).

When Docetaxel was combined with carboplatin for the treatment of chemotherapy-naïve, advanced non-small cell lung carcinoma, patients 65 years of age or greater (28%) experienced higher frequency of infection compared to similar patients treated with Docetaxel +cisplatin, and a higher frequency of diarrhea, infection and peripheral edema than elderly patients treated with vinorelbine+cisplatin.

Of the 333 patients treated with Docetaxel every three weeks plus prednisone in the prostate cancer study (TAX327), 209 patients were 65 years of age or greater and 68 patients were older than 75 years. In patients treated with Docetaxel every three weeks, the following TEAEs occurred at rates $\geq$ 10% higher in patients 65 years of age or greater compared to younger patients: anemia (71% vs. 59%), infection (37% vs. 24%), nail changes (34% vs. 23%), anorexia (21% vs. 10%), weight loss (15% vs. 5%) respectively.

In the adjuvant breast cancer trial (TAX316), Docetaxel in combination with doxorubicin and cyclophosphamide was administered to 744 patients of whom 48 (6%) were 65 years of age or greater. The number of elderly patients who received this regimen was not sufficient to determine whether there were differences in safety and efficacy between elderly and younger patients.

Among the 221 patients treated with Docetaxel in combination with cisplatin and fluorouracil in the gastric cancer study, 54 were 65 years of age or older and 2 patients were older than 75 years. In this study, the number of patients who were 65 years of age or older was insufficient to determine whether they respond differently from younger patients. However, the incidence of serious adverse events was higher in the elderly patients compared to younger patients. The incidence of the following adverse events (all grades): lethargy, stomatitis, diarrhea, dizziness, edema, febrile neutropenia/neutropenic infection occurred at rates $\geq$ 10% higher in patients who were 65 years of age or older compared to younger patients. Elderly patients treated with TCF should be closely monitored.

Of the 174 patients who received the induction treatment with Docetaxel in combination with cisplatin and fluorouracil for SCCHN (TAX323), 18 (10%) patients were 65 years of age or older.

The clinical study of Docetaxel in combination with cisplatin and fluorouracil in patients with SCCHN (TAX323) did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience with this treatment regimen has in responses between elderly and younger patients.

11.5. ETOPOSIDE

DESCRIPTION: Etoposide (VP-16) is a semisynthetic podophyllotoxin derivative with antineoplastic activity.

PHARMACEUTICAL DATA: VP-16 is supplied as 100 mg/5cc ampules.

SOLUTION PREPARATION: The contents of the ampule are diluted with 50 volumes of NaCl solution for injection, USP.

ROUTE OF ADMINISTRATION: Oral or slow IV infusion

KNOWN SIDE-EFFECTS: Myelosuppression, primarily granulocytopenia is the dose-limiting toxicity. Other side effects include gastrointestinal toxicity comprising of nausea, emesis and mucositis. At high doses reversible hepatotoxicity is seen. Acute side effects include occasional bronchospasm and hypotension. These can be avoided by slow intravenous administration.

PHARMACOKINETICS: The main site of metabolism is in the liver. Major metabolites of etoposide are hydroxy acids and cistactone which appear in the plasma and urine. The

half-life of the drug is 4 to 11 hours.

MECHANISM OF ACTION: Two different dose dependent responses are seen. At high concentrations (10 ug/ml) lysis of cells entering mitosis is seen. At low concentrations (0.3 to 10 ug/ml) cells are inhibited from entering prophase. The predominant macromolecular affect of etoposide appears to be the induction of DNA strand breaks by an interaction with DNA topoisomerase II or by the formation of free radicals.

11.6. IFOSFAMIDE

DESCRIPTION: Ifosfamide is a chemotherapeutic agent chemically related to nitrogen mustards and a synthetic analogue of cyclophosphamide.

PHARMACEUTICAL DATA: Ifosfamide is available in vials of 1g or 3g.

SOLUTION PREPARATION: It is reconstituted with sterile water for an approximate concentration of 50 mg/ml. Intact vials should be stored at room temperature (22 to 25 degrees Centigrade) or below. Ifosfamide will liquefy at temperatures above 35 degrees Centigrade. Intact vials have an expiration date of 5 years from the date of manufacture. Reconstitution as recommended results in a solution that is chemically stable for 7 days when stored at room temperature and for 6 weeks when refrigerated (2 to 8 degrees Centigrade). Further dilution of the reconstituted solution to concentrations of 16 mg/ml and 0.6 mg/ml in compatible infusion solutions results in a 1 to 5% degradation in 7 days at room temperature and no degradation in 6 weeks under refrigeration. In 6 weeks at room temperature, decomposition generally ranges from 12 to 18%.

ROUTE OF ADMINISTRATION: IV infusion

EXPECTED ADVERSE EVENTS: Myelosuppression

UNEXPECTED ADVERSE EVENTS: Nephrotoxicity and urotoxicity. The incidence of urotoxicity can be reduced significantly by the use of Mesna, hydration and fractionation of the dose. Central nervous system toxicity like somnolence, confusion, hallucinations and coma is also seen and may require cessation of therapy.

PHARMACOKINETICS: Pharmacokinetics of Ifosfamide are dose-dependent. Single doses of 3.8-5 g/m^2 exhibit a biphasic elimination with a half-life of 15 hours; doses of 1.6 to 2.4 g/m2/day are eliminated monoexponentially with a terminal half-life of approximately 7 hours. Ifosfamide is extensively metabolized. The percent of metabolites and parent drug renally excreted is dose-dependent.

11.7. MESNA

Mesna is used to reduce the incidence of ifosfamide-induced hemorrhagic cystitis. Mesna disulfide is reduced to the free thiol compound, mesna, which reacts chemically with the urotoxic ifosfamide metabolites, resulting in their detoxification.

Pharmacokinetics
Absorption
Urinary bioavailability of oral mesna is 45% to 79%.

Distribution
Protein binding is 69% to 75%; Vd is 0.652 L/kg.

Metabolism
The major metabolite is dimesna.

Elimination
Approximately 32% is excreted in urine within 24 h. The $t_{½}$ is 1.2 to 8.3 h (after IV plus oral dose); the plasma Cl is 1.23 L/kg/h. The mesna disulfide is reduced to the free thiol compound that reacts chemically with the urotoxic ifosfamide metabolites, resulting in their detoxification. At doses of 2 to 4 g, the terminal elimination $t_{½}$ is approximately 4 to 8 h. It is rapidly eliminated by the kidneys.

Indications and Usage
Prevention of ifosfamide-induced hemorrhagic cystitis.

Unlabeled Uses
Prevention of cyclophosphamide-induced hemorrhagic cystitis.

Contraindications
Standard considerations.

Dosage and Administration
Adults
IV Mesna dose is given as bolus injections in a dosage equal to 20% of ifosfamide dose at time of administration, 4 h after, and 8 h after each ifosfamide dose (eg, for ifosfamide 1,200 mg/m^2, give mesna 240 mg/m^2 at 0, 4, and 8 h after each ifosfamide dose). The total daily dose of mesna is 60% of the ifosfamide dose. Repeat this dosing schedule on each day that ifosfamide is administered. When the dosage of ifosfamide is adjusted, modify the dose of mesna accordingly.

Adults
PO Following the initial IV mesna dose (20% of ifosfamide dose), the oral mesna dose is 40% of ifosfamide dose 2 and 6 h after each ifosfamide dose.

General Advice
Repeat the oral dose or administer IV bolus dose if patient vomits within 2 h of administration.
For IV bolus administration only. Not for intradermal, subcutaneous, IM, or intra-arterial administration.

Dilute IV concentrate to final concentration of 20 mg/mL with a compatible IV fluid following manufacturer's recommendations.
Do not administer injection if cloudiness or particulate matter is noted.

Storage/Stability
Store tablets at controlled room temperature (68° to 77°F). Store vials at controlled room temperature (68° to 77°F). Multidose vial can be used for up to 8 days following initial opening. Diluted solutions are stable for up to 24 h if stored at temperature less than 77°F. Discard any unused solution after 24 h.

12.0 References

1. Motzer RJ, Mazumdar M, Gulati SC, et al. Phase II trial of high-dose carboplatin and etoposide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. J Natl Cancer Inst 1993; 85: 1828-35.

2. Motzer RJ, Mazumdar M, Bajorin DF, et al. High-dose carboplatin, etoposide, and cyclophosphamide with autologous bone marrow transplantation in first-line therapy for patients with poor-risk germ cell tumors. J Clin Oncol 1997; 15: 2546-52.

3. Schmoll HJ, Kollmannsberger C, Metzner B, et al. Long-term results of first-line sequential high-dose etoposide, ifosfamide, and cisplatin chemotherapy plus autologous stem cell support for patients with advanced metastatic germ cell cancer: an extended phase I/II study of the German Testicular Cancer Study Group. J Clin Oncol 2003; 21: 4083-91.

4. Bokemeyer C, Kollmannsberger C, Meisner C, et al. First-line high-dose chemotherapy compared with standard-dose PEB/VIP chemotherapy in patients with advanced germ cell tumors: A multivariate and matched-pair analysis. J Clin Oncol 1999; 17: 3450-6.

5. Chevreau C, Droz JP, Pico JL, et al. Early intensified chemotherapy with autologous bone marrow transplantation in first line treatment of poor risk non-seminomatous germ cell tumors. Eur Urol 1993; 23: 213-8.

6. Bajorin DF, Nichols CR, Margolin KA, et al. Phase III trial of conventional-dose chemotherapy alone or with high-dose chemotherapy for metastatic germ cell tumors (GCT) patients (pts): A cooperative group trial by Memorial Sloan Kettering Cancer Center, ECOG, SWOG, and CALGB. J Clin Oncol 2006; 24: (suppl): abstract 4510.

7. Einhorn LH, Williams SD, Chamness A, et al. High-dose chemotherapy and stem-cell rescue for metastatic germ-cell tumors. N Engl J Med 2007; 357: 340-8.

8. Margolin K, Doroshow JH, Ahn C, et al. Treatment of germ cell cancer with two cycles of high-dose ifosfamide, carboplatin, and etoposide with autologous stem-cell

support. J Clin Oncol 1996; 14: 2631-7.

9. Margolin KA, Doroshow JH, Frankel, et al. Paclitaxel-based high-dose chemotherapy with autologous stem cell rescue for relapsed germ cell cancer. Biol Blood Marrow Transplant 2005: 11:903-11.

10. Siegert W, Beyer J, Strohscheer I, et al. High-dose treatment with carboplatin, etoposide and ifosfamide followed by autologous stem-cell transplantation in relapsed or refractory germ cell cancer: A phase I/II study. J Clin Oncol 1994; 12: 1223-31.

11. Motzer RJ, Mazumdar M, Bosl GJ, et al. High-dose carboplatin, etoposide, and cyclophosphamide for patients with refractory germ cell tumors: Treatment results and prognostic factors for survival and toxicity. J Clin Oncol 1996; 14: 1098-1105.

12. Beyer J, Kramar A, Mandanas R, et al. High-dose chemotherapy as salvage treatment in germ cell tumors: A multivariate analysis of prognostic variables. J Clin Oncol 1996; 14: 2638-45.

13. Lotz J-P, Bui B, Gomez F, et al. Sequential high-dose chemotherapy protocol for relapsed poor prognosis germ cell tumors combining two mobilization and cytoreductive treatments followed by three high-dose chemotherapy regimens supported by autologous stem cell transplantation. Results of the phase II multicentric TAXIF trial. Ann Oncol 2005; 16: 411-8.

14. Pico J-L, Rosti G, Kramar A, et al. A randomised trial of high-dose chemotherapy in the salvage treatment of patients failing first-line platinum chemotherapy for advanced germ cell tumours. Ann Oncol 2005: 16: 1152-9.

15. Lorch A, Kollmannsberger C, Hartmann JT, et al. Single versus sequential high-dose chemotherapy in patients with relapsed or refractory germ-cell tumors: A prospective randomized multicenter trial of the German Testicular Cancer Group. J Clin Oncol 2007; 25: 2778-84.

16. Einhorn LH. Curing metastatic testicular cancer. Proc Natl Acad Sci USA 2002; 99: 4592-5.

17. http://www.nccn.org/professionals/physician_gls/PDF/testicular.pdf

18. Nieto Y, Shpall EJ, Bearman SI, et al. Phase I and pharmacokinetic study of docetaxel combined with melphalan and carboplatin, with autologous hematopoietic progenitor cell support, in patients with advanced refractory malignancies. Biol Blood Marrow Transplant 2005; 11: 297-306.

19. Nieto Y, Aldaz A, Rifón J, et al. High-dose gemcitabine administered at fixed-dose rate, combined with docetaxel/melphalan/carboplatin, with autologous hematopoietic progenitor-cell support, in patients with advanced refractory tumors. Biol Blood Marrow

Transplant 2007; 13: 1324-37.

20. Fukuda S, Shirahama T, Imazono Y, et al. Expression of Vascular Endothelial Growth Factor in patients with testicular germ cell tumors as an indicator of metastatic disease. Cancer 1999; 85: 1323-30.

21. Bentas W, Beecken WD, Glienke W, Binder J, Schuldes H. Serum levels of basic fibroblast growth factor reflect disseminated disease in patients with testicular germ cell tumors. Urol Res 2003; 30:390-3.

22. Gordon MS, Margolin K, Talpaz M, et al. Phase I safety and pharmacokinetic study of recombinant human anti-vascular endothelial growth factor in patients with advanced cancer. J Clin Oncol 2001; 19: 843-50.

23. Margolin K, Gordon MS, Holmgren E, et al. Phase Ib trial of intravenous recombinant humanized monoclonal antibody to vascular endothelial growth factor in combination with chemotherapy in patients with advanced cancer: pharmacologic and long-term safety data. J Clin Oncol 2001; 19: 851-6.

24. Willett CG, Boucher Y, di Tomaso E, et al. Direct evidence that the VEGF-specific antibody Bevacizumab has antivascular effects in human rectal cancer. Nat Med 2004; 10: 145-7.

25. Bedam SB, Low JA, Yang SX, et al. Antiangiogenic and antitumor effects of bevacizumab in patients with inflammatory and locally advanced breast cancer. J Clin Oncol 2006; 24: 769-77.

26. Jain RK. Normalization of tumor vasculature: an emerging concept in antiangiogenic therapy. Science 2005; 307:58-62.

27. Tong RT, Boucher Y, Kozin SV, et al. Vascular normalization by vascular endothelial growth factor receptor 2 blockade induces a pressure gradient across the vasculature and improves drug penetration in tumors. Cancer Res 2004; 64: 3731-6.

28. Gorski DH, Beckett MA, Jaskowiak NT, et al. Blockage of the vascular endothelial growth factor stress response increases the antitumor effects of ionizing radiation. Cancer Res 1999; 59: 3374-8.

29. Kabbinavar F, Hurwitz H, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 2003; 21: 60-5.

30. Giantonio BJ, Catalano PH, Meropol N, et al. High-dose bevacizumab improves survival when combined with FOLFOX4 in previously treated advanced colorectal cancer patients: Results from the Eastern Cooperative Oncology Group (ECOG) study E3200. J Clin Oncol 2005; 23 (suppl): 2.

31. Miller K, Wang M, Gralow J, et al. Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357: 2666-76.

32. Sandler AB, Gray R, Brahmer J, et al. Randomized phase II/III trial of paclitaxel (P) plus carboplatin (C) with or without bevacizumab (NSC # 704865) in patients with advanced non-squamous non-small cell lung cancer (NSCLC): An Eastern Cooperative Oncology Group (ECOG) Trial – E4599. J Clin Oncol 2005; 23 (suppl): 4.

33. Glade Bender JL, Adamson PC, Reid JM, et al. Phase I trial and pharmacokinetic study of bevacizumab in pediatric patients with refractory solid tumors: a Children's Oncology Group Study. J Clin Oncol 2008; 26:399-405.

34. Benesch M, Windelberg M, Sauseng W, et al. Compassionate use of bevacizumab (Avastin) in children and young adults with refractory or recurrent solid tumors. Ann Oncol 2008; 19: 807-13.

35. Hu L, Hofmann J, Zaloudek C, et al. Vascular endothelial growth factor immunoneutralization plus Paclitaxel markedly reduces tumor burden and ascites in athymic mouse model of ovarian cancer. Am J Pathol 2002; 16: 1917-24.

36. Sweeney CJ, Miller KD, Sissons SE, et al. The antiangiogenic property of docetaxel is synergistic with a recombinant humanized monoclonal antibody against vascular endothelial growth factor or 2-methoxyestradiol but antagonized by endothelial growth factors. Cancer Res 2001; 61:3369-72.

37. Ramaswamy B, Elias AD, Gelbick NT, et al. Phase II trial of bevacizumab in combination with weekly docetaxel in metastatic breast cancer patients. Clin Cancer Res. 2006;12:3124-9.

38. Kabbinavar FF, Wong JT, Ayala RE, et al. The effect of antibody to vascular endothelial growth factor and cisplatin on the growth of lung tumors in nude mice. Proc Am Assoc Cancer Res 1995; 36: 488 (abstr 2906).

39. Baker CH, Solorzano CC, Fidler IJ. Blockade of vascular endothelial growth factor receptor and epidermal growth factor receptor signaling for therapy of metastatic human pancreatic cancer. Cancer Res 62:1996-2003, 2002.

40. Solorzano CC, Baker CH, Bruns CJ, et al: Inhibition of growth and metastasis of human pancreatic cancer growing in nude mice by PTK 787/ZK222584, an inhibitor of the vascular endothelial growth factor receptor tyrosine kinase. Cancer Biother Radiopharm 16:359-370, 2001.

41. Miller KD, Chap LI, Holmes FA, et al. Randomized phase III trial of capecitabine compared with bevacizumab plus capecitabine in patients with previously treated metastatic breast cancer. J Clin Oncol 2005; 23:792-9.

42. Yuan F, Chen Y, Dellian M, et al. Time-dependent vascular regression and

permeability changes in established human tumor xenografts induced by an anti-vascular endothelial growth factor/vascular permeability factor antibody. Proc Natl Acad Sci USA 1996; 93: 14765-70.

43. Thall PF, Wooten LH, Tannir NM. Monitoring Event Times in Early Phase Clinical Trials: Some Practical Issues, Clinical Trials, 2005, 2:467-478