Cancer Research Consortium of West Michigan
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Fast Facts

A031102: A Randomized Phase III Trial Comparing Conventional-Dose Chemotherapy using Paclitaxel, Ifosfamide, and Cisplatin (TIP) with High-Dose Chemotherapy Using Mobilizing Paclitaxel Plus Ifosamide Followed by High-Dose Carboplatin and Etoposide (TI-CE) as First Salvage Treatment in Relapsed or Refractory Germ Cell Tumors

Male Gender Only

All drugs commercially available - See Study Schema on last page

Although they will not be considered formal eligibility (exclusion) criteria, physicians should recognize that the following may seriously increase the risk to the patient entering this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- Medical condition such as uncontrolled infection (including HIV), uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 2 years.
- Patients who cannot swallow oral formulations of the agent(s).
- Men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives or double barrier method (diaphragm plus condom).

Eligibility Criteria

1. Histologic Documentation:
   Confirmation of GCT histology (both seminoma and nonseminoma) on pathologic review at the center of enrollment. Tumor may have originated in any primary site.
   NOTE: In rare circumstances, patients will be allowed to enroll even if a pathologic diagnosis may not have been established. This would require a clinical situation consistent with the diagnosis of GCT (testicular, retroperitoneal or mediastinal mass, elevated tumor marker levels {HCG ≥ 500; AFP ≥ 500} and typical pattern of metastases).
2. Evidence of Disease:
   Must have evidence of progressive or recurrent GCT (measurable or non-measurable) following one line of cisplatin-based chemotherapy, defined as meeting at least one of the following criteria:
   Tumor biopsy of new or growing or unresectable lesions demonstrating viable nonteratomatous GCT (enrollment on this study for adjuvant treatment after

macroscopically complete resection of viable GCT is not allowed). In the event of an incomplete gross resection where viable GCT is found, patients will be considered eligible for the study.
Consecutive elevated serum tumor markers (HCG or AFP) that are increasing. Increase of an elevated LDH alone does not constitute progressive disease.
Development of new or enlarging lesions in the setting of persistently elevated HCG or AFP, even if the HCG and AFP are not continuing to increase.

3. Prior Treatment:
    a. Must have received 3-6 cycles of cisplatin-based chemotherapy as part of first-line (initial) chemotherapy. Prior POMBACE, CBOP-BEP, or GAMEC are allowed.
    Note: For patients requiring immediate treatment, 1 cycle of conventional-dose salvage chemotherapy is allowed (including TI or TIP). Therefore, these patients may have received 7 prior cycles of chemotherapy; 6 cycles as part of first-line chemotherapy and 1 cycle of salvage conventional chemotherapy.
    b. No more than one prior line of chemotherapy for GCT (other than the 1 cycle of salvage chemotherapy in Section 3.2.3.1)
        - Definition of one line of chemotherapy: One line of therapy can in some cases consist of 2 different cisplatin-based treatment combinations, provided there is no disease progression between these two regimens. For example, a patient could have received 2 cycles of BEP followed by 2 cycles of VIP if the switch from BEP to VIP was made due to pulmonary toxicity rather than disease progression. This would be considered 1 line of prior therapy. In addition, if a patient received 4 cycles of BEP and then underwent post-chemotherapy resection of residual tumor with findings of residual viable non-teratomatous GCT, and subsequently received 2 additional cycles of adjuvant chemotherapy (EP or an alternate regimen such as VIP) in the absence of disease progression, this would also be considered 1 regimen. However, if any change in therapy is prompted by tumor progression including rising tumor markers, this is considered to represent 2 lines of prior treatment.
        - Prior treatment with carboplatin as adjuvant therapy is allowed, provided patients meet other eligibility criteria (e.g., the patient has also received 3-4 cycles of cisplatin-based chemotherapy).
        - Prior treatment with 1-2 cycles of BEP or EP as adjuvant chemotherapy for early stage GCT is allowed, provided the patient also received 3-4 cycles of BEP or EP again at relapse. Patients treated with 3-4 cycles of VIP at relapse following 1-2 cycles of BEP/EP are not eligible as this would be considered more than 1 line of prior therapy.
    c. No prior treatment with high-dose chemotherapy (defined as treatment utilizing stem cell rescue).

d. No prior treatment with TIP with the exception when given as a bridge to treatment on protocol for patients with rapidly progressive disease who cannot wait to complete the eligibility screening process. Only one cycle is allowed.
e. No concurrent treatment with other cytotoxic drugs or targeted therapies.
f. No radiation therapy (other than to the brain) within 14 days of day 1 of protocol chemotherapy except radiation to brain metastases, which must be completed 7 days prior to start of chemotherapy.
g. No previous chemotherapy within 16 days prior to enrollment except for bleomycin which cannot have been given within 5 days prior to enrollment.
h. Must have adequate recovery from prior surgery (e.g., healed scar, resumption of diet, etc.).

4. Age ≥ 14 years (≥ 18 years in Germany)
5. ECOG Performance Status 0 to 2
6. Male gender
7. Required Initial Laboratory Values:
   - Absolute Neutrophil Count (ANC) ≥ 1,500/mm3
   - Platelet Count ≥ 100,000/mm3
   - Calc. Creatinine Clearance ≥ 50 mL/min *
   - Bilirubin ≤ 2.0 x upper limits of normal (ULN)
   - AST/ALT ≤ 2.5 x upper limits of normal (ULN)**
   - Estimated creatinine clearance for **patients ≥ 18 years old** will be estimated by the Jelliffe equation modified for BSA. Patients with creatinine clearance estimated > 70ml/min by this formula are eligible. If the creatinine clearance estimated by the Jelliffe method is ≥ 50 mL/min but ≤ 70 mL/min, then a second method to confirm a creatinine clearance of ≥ 50 mL/min is required. Methods of estimating GFR that can be used for this confirmation consist of a 12 or 24-hour urine creatinine clearance or a nuclear creatinine clearance (radioisotope) test. If the confirmatory creatinine clearance is < 50 mL/min, then the patient is not eligible. If the confirmatory creatinine clearance is ≥ 50 mL/min, the patient is eligible. If the cause of the patient's renal dysfunction is tumor obstructing the ureters, then eligibility can be determined by the study chair even if it does not meet these minimal requirements.

Jelliffee Equation for Estimated Creatinine Clearance:

$$GFR = \frac{98 - \left(16\ x \frac{[(age-20)]}{20}\right)}{serum\ creat} x \frac{BSA}{1.73}$$

** Unless due to hepatic metastases in which case levels ≤ 5 x ULN are allowed.

8. No concurrent malignancy other than non-melanoma skin cancer, superficial noninvasive (pTa or pTis) TCC of the bladder, contralateral GCT, or intratubular germ cell neoplasia. Patients with a prior malignancy, but at least 2 years since any evidence of disease are allowed.
9. Negative Serology (antibody test) for the following infectious diseases:

- Human Immunodeficiency Virus (HIV) type 1 and 2
- Human T-cell Leukemia Virus (HTLV) type 1 and 2
- Hepatitis B surface antigen
- Hepatitis C antibody

10. No late relapse with completely surgically resectable disease. Patients with late relapses (defined as relapse ≥ 2 years from the date of completion of the last chemotherapy regimen) whose disease is completely surgically resectable are not eligible. Patients with late relapses who have unresectable disease are eligible.
11. 11.0 No large (≥ 2 cm) hemorrhagic or symptomatic brain metastases until local treatment has been administered (radiation therapy or surgery). Treatment may begin ≥ 7 days after completion of local treatment. Patients with small (< 2 cm) and asymptomatic brain metastases are allowed and may be treated with radiation therapy and/or surgery concurrently with Arm A or cycles 1 and 2 of Arm B if deemed medically indicated. Radiation therapy should not be given concurrently with high-dose carboplatin or etoposide.
12. No secondary somatic malignancy arising from teratoma (e.g., teratoma with malignant transformation) when it is actively part of the disease recurrence or progression.

Pre-Study Parameters:

- History and Physical , ECOG PS
- AE Assessment, Fatigue/Uniscale Assessment
- CBC, CMP, Magnesium, AFP, HCG, LDH
- Testosterone, LH, FSH, lipid profile
- FACT blood tests; GFR estimation
- Histologic Confirmation of Diagnosis
- CT or MRI brain w/ and w/o contrast; CT chest w/ or w/o contrast; CT abdomen and pelvis w/contrast

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