Essai Clinique

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Titre	A Phase 2 Trial of Chemotherapy Followed by Response-Based Whole Ventricular &Amp; Spinal Canal Irradiation (WVSCI) for Patients With Localized Non-Germinomatous Central Nervous System Germ Cell Tumor
Protocole ID	ACNS2021
ClinicalTrials.gov ID	NCT04684368
Type(s) de cancer	Cerveau (SNC)
Phase	Phase II
Type étude	Clinique
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But étude	This phase II trial studies the best approach to combine chemotherapy and radiation therapy (RT) based on the patient's response to induction chemotherapy in patients with non-germinomatous germ cell tumors (NGGCT) that have not spread to other parts of the brain or body (localized). This study has 2 goals: 1) optimizing radiation for patients who respond well to induction chemotherapy to diminish spinal cord relapses, 2) utilizing higher dose chemotherapy followed by conventional RT in patients who did not respond to induction chemotherapy. Chemotherapy drugs, such as carboplatin, etoposide, ifosfamide, and thiotepa, work in different ways to stop the growth of tumor cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Radiation therapy uses high energy x-rays or high-energy protons to kill tumor cells and shrink tumors. Studies have shown that patients with newly-diagnosed localized NGGCT, whose disease responds well to chemotherapy before receiving radiation therapy, are more likely to be free of the disease for a longer time than are patients for whom the chemotherapy does not efficiently eliminate or reduce the size of the tumor. The purpose of this study is to see how well the tumors respond to induction chemotherapy to decide what treatment to give next. Some patients will be given RT to the spine and a portion of the brain. Others will be given high dose chemotherapy and a stem cell transplant before RT to the whole brain and spine. Giving treatment based on the response to induction chemotherapy may lower the side effects of radiation in some patients and adjust the therapy to a more efficient one for other patients with localized NGGCT.
Critères d'éligibilité	• Patients must be >= 3 years and < 30 years at the time of study enrollment • Patients must be newly diagnosed with localized primary CNS NGGCT of the suprasellar and/or pineal region by pathology and/or serum or cerebrospinal fluid (CSF) elevation of AFP above institutional normal or > 10 ng/mL or human chorionic gonadotropin (hCG) beta > 100 mIU/mL. Suprasellar, pineal and bifocal tumors are included. (CSF tumor markers and cytology must be within 21 days prior to enrollment and within 35 days prior to start of protocol therapy [repeat if necessary]. Serum tumor markers, AFP and hCGbeta must be within 7 days prior to enrollment and start of protocol therapy [repeat if necessary]). Basal ganglia or other primary sites are excluded • Patients with any of the following pathological elements are eligible: endodermal sinus (yolk sac), embryonal carcinoma, choriocarcinoma, malignant/immature teratoma and mixed germ cell tumor (GCT) (i.e., may include some pure germinoma) if malignant elements listed above are present. Patients with only mature teratoma are excluded. Patients with pure germinoma admixed with mature teratoma are excluded (would be eligible for pure germinoma protocols) • Patients must have a cranial magnetic resonance imaging (MRI) with and without gadolinium at diagnosis/prior to enrollment. If surgical resection is performed, patients must have pre-operative and post operative brain MRI with and without gadolinium. The post operative brain MRI should be obtained within 72 hours of surgery. If patient has a biopsy only, post-operative brain MRI is recommended but not required (within 14 days prior to study enrollment)

- Patients must have a spine MRI with gadolinium obtained at diagnosis/prior to enrollment. Spine MRI with and without gadolinium is recommended (within 14 days prior to study enrollment)
- Lumbar CSF must be obtained prior to study enrollment unless medically contraindicated. If a patient undergoes surgery and lumbar CSF cytology cannot be obtained at the time of surgery, then it should be performed at least 10 days following surgery and prior to study enrollment. False positive cytology can occur within 10 days of surgery
- Patients must have CSF tumor markers obtained prior to enrollment unless medically contraindicated. Ventricular CSF obtained at the time of CSF diversion procedure (if performed) is acceptable for tumor markers but lumbar CSF is preferred. In case CSF diversion and biopsy/surgery are combined, CSF tumor markers should be collected first
- Peripheral absolute neutrophil count (ANC) >= 1000/uL (within 7 days prior to enrollment)
- Platelet count >= 100,000/uL (transfusion independent) (within 7 days prior to enrollment)
- Hemoglobin >= 8.0 g/dL (may receive red blood cell [RBC] transfusions) (within 7 days prior to enrollment)
- Creatinine clearance or radioisotope glomerular filtration rate (GFR) >= 70 mL/min/1.73 m^2 or a serum creatinine based on age/gender as follows (within 7 days prior to enrollment):
    - Age: Maximum serum creatinine (mg/dL)
        - 3 to < 6 years: 0.8 (male), 0.8 (female)
        - 6 to < 10 years: 1 (male), 1 (female)
        - 10 to < 13 years: 1.2 (male), 1.2 (female)
        - 13 to < 16 years: 1.5 (male), 1.4 (female)
        - >= 16 years: male (1.7), 1.4 (female)
- Total bilirubin =< 1.5 x upper limit of normal (ULN) for age (within 7 days prior to enrollment)
- Serum glutamate pyruvate transaminase (SGPT) (alanine aminotransferase [ALT]) =< 135 U/L (within 7 days prior to enrollment)
    - Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L
- Central nervous system function defined as:
    - Patients with seizure disorder may be enrolled if on anticonvulsants and well controlled
    - Patients must not be in status epilepticus, coma or assisted ventilation prior to study enrollment
- Protocol therapy must begin within 31 calendar days of definitive surgery or clinical diagnosis. If a biopsy only was performed, the biopsy date will be considered the date of definitive surgery. For patients who have a biopsy or incomplete resection at diagnosis followed by additional surgery, the date of the last resection will be considered the date of definitive surgery.
- All patients and/or their parents or legal guardians must sign a written informed consent
- All institutional, Food and Drug Administration (FDA), and National Cancer Institute (NCI) requirements for human studies must be met
- NEUROCOGNITIVE FUNCTION AND QUALITY OF LIFE ASSESSMENT:
- English-, Spanish-, or French- speaking
    - Note: Patients who speak a language other than English, Spanish, or French will be allowed to participate in ACNS2021 but will not complete the neurocognitive and quality of life assessments
- No known history of neurodevelopmental disorder prior to diagnosis of NGGCT (e.g., Down syndrome, fragile X, William syndrome, intellectual disability). Patients with NF1 will be allowed to participate
- Additional eligibility criteria for the COG Standardized Neuropsychological Battery only: must be at a site that has a psychologist to administer the battery
    - Note: If not eligible for the COG Standardized Battery, patients should still complete the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2), Pediatric Quality of Life Inventory (PedsQL), Adaptive Behavior Assessment System Third Edition (ABAS-3), and Behavior Assessment System for Children, Third Edition (BASC-3) questionnaires

Critères d'exclusion

- Patients with tumors located outside the ventricles (i.e., basal ganglia, thalamus)
- Patients with only mature teratoma and non-elevated markers upon tumor sampling at diagnosis
- Patients who have received any prior tumor-directed therapy for their diagnosis of NGGCT other than surgical intervention and corticosteroids
- Patients with metastatic disease (i.e., MRI evaluation, lumbar CSF cytology or intraoperative evidence of dissemination)
- Female patients who are pregnant, since fetal toxicities and teratogenic effects have been noted for several of the study drugs
    - Note: Serum and urine pregnancy tests may be falsely positive due to HCGbeta-secreting germ cell tumors. Ensure the patient is not pregnant by institutional standards
- Lactating females who plan to breastfeed their infants
- Sexually active patients of reproductive potential who have not agreed to use an effective contraceptive method for the duration of their study participation