High-dose chemotherapy associated with bevacizumab for metastatic germ-cell tumors: the TAXIF 3 trial

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BACKGROUND
Germ cell tumors (GCTs) are a model of curative disease. 5-year overall survival (OS) rates for metastatic patients, reached according to prognosis, 92% (good), 80% (intermediate) and 48% (poor).

The current first-line therapy is the combination of bleomycin, etoposide, and cisplatin (BEP). Despite the high cure rate of BEP, 10 to 20% of patients relapse. These patients are then candidates for initial salvage therapy with VeIP (vinblastine-ifosfamide-cisplatin), VIP (VeIP with etoposide in place of vinblastine), or a combination of ifosfamide and platinum salts with paclitaxel (TIP).

Another option is intensification therapy.

We previously developed two clinical trials (TAXIF 1, TAXIF 2) using three sequential cycles of high-dose chemotherapy (HDCT) with autologous hematopoietic stem-cell transplant (HSCT). These approaches showed encouraging activity in both relapsed and refractory patients. However, they did not prevent emergence of resistance and, for many patients, disease progressed.

To improve outcomes, we set up the TAXIF 3 clinical trial.

PREVIOUS TRIALS : TAXIFS

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<tr>
<th>TAXIF 1</th>
<th>TAXIF 2</th>
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<tr>
<td>22 pts completed the treatment</td>
<td>29 pts completed the treatment</td>
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<td>A final ORR of 37.7% was achieved for 17 patients</td>
<td>A final ORR of 48.8% was achieved for 22 patients</td>
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<tr>
<td>Prm1: - 9 pts (20%) [95% CI, 9.6–34.6]</td>
<td>Prm1: - 12 pts (26.6%) [95% CI, 20–33.2]</td>
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<tr>
<td>Prm2: - 4 pts (8.9%) [95% CI, 2.5–21.2]</td>
<td>Prm2: - 3 pts (6.8%) [95% CI, 0–13.8]</td>
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<tr>
<td>CR : 4 pts (8.9%) [95% CI, 2.5–21.2]</td>
<td>CR : 7 pts (15.5%) [95% CI, 5–24]</td>
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<td>3-year PFS : 23.5% (median 6 months)</td>
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<td>3-year OS : 34.6% (median 11.8 months)</td>
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The Beyer score predicts the outcome after HD-CT: highly refractory patients and particularly patients with resistant/refractory primary mediastinal GCTs did not benefit from HDCT.

The TAXIF 2 program can be used as an alternative option of salvage treatment (after failure of 1 or 2 lines of CT) for GCTs poor prognosis patients with a recurrent non-refractory disease.

CLINICAL TRIAL IN PROGRESS : TAXIF 3

Multicentric phase II study supported by the French Ministry of Health - PHRC (ClinicalTrials.gov Identifier NCT01966913)

Combination of HDCT with the endothelial growth factor (VEGF) antibody bevacizumab

RATIONAL : to explore both the mechanisms of disease etiology and drug resistance

- Angiogenesis plays a functional role in testicular GCTs growth and progression and is an indicator of metastatic disease
- Bevacizumab should improve drug delivery through normalization in tumor vasculature
- HDCT after bevacizumab should contribute to minimal residual disease
- The administration, in a unique way, of semi-intensive doses of Epi-Tax prior to HDCT should allow:
  - to mobilize and collect an adequate number of hematopoietic stem-cells
  - to sensitize patients to chemotherapy before HDCT

INCLUSION CRITERIA

- GCTs pts with any histology (seminoma and nonseminoma)
- age ≥ 18 years old
- pts who failed CT platinum-based
- RELAPSED or REFRACTORY

PRIMARY END-POINT : complete response rates
SECONDARY END-POINTS : ORR, PFS and OS

- TAXIF 3 started in October 2013 and is still recruiting patients
- The study planned to include 50 patients
- The trial has so included about 50% of the expected patients
- Statistical analyses are performed through a Bayesian approach


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