



Preliminary results of a phase I/II study of intra-arterial chemotherapy with osmotic blood-brain barrier disruption for patients with recurrent or progressive CNS embryonal or germ cell tumors

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Introduction

Patients with refractory or recurrent CNS embryonal or germ cell tumors have poor prognosis and survivors suffer neuropsychological sequelae from radiotherapy and ototoxicity from chemotherapy. Prior retrospective studies suggest intra-arterial (IA) chemotherapy in conjunction with blood-brain barrier disruption (BBBD) may improve outcomes in patients with these challenging tumors.

Methods

In this prospective study, patients aged 1 to 30 with recurrent or refractory CNS embryonal or germ cell tumors were treated on 2 consecutive days, every 4 weeks, for up to a year with dose intensive IA carboplatin and IA melphalan with BBBD. The study objectives are to: determine the maximum tolerated dose of IA melphalan, estimate response rate, describe 2-year progression-free and overall survival, and describe overall toxicity.

Scheduled Tests

| Test/Procedure | Pre-Registration | Pre-treatment | Day 1: hospital admission (every 4-6 weeks) | Day 2: (BBBD #1) and Day 3: (BBBD #2) | Every 6 months | Follow up |
|---|------------------|------------------|---|---------------------------------------|----------------|----------------|
| Inclusion/Exclusion Criteria | X | | | | | |
| Informed Consent | X | | | | | |
| Physical Examination | X | | X | X | | X ^a |
| Laboratory Monitoring | | X | X | | | X ^b |
| MRI (brain) | | X ^d | | | | X ^a |
| CSF studies (cytology cell count, glucose, protein, AFP, HCG) | | X ^{c,d} | | | | X ^c |
| Hearing Examination | | X ^d | X | | | X ^e |
| Ophthalmologic examination | | X ^f | | | X | X ^e |
| Neuro psychological Assessment | | X ^g | | | | X ^h |
| Chest Xray | | X ^f | X ^c | | | |
| EKG | | X ^f | X ^c | | | |

Figure 1: a. Every 3 months for 1 year, every 6 months for a year, then annually. b. Yearly. c. As indicated. d. Within 4 weeks prior to first treatment. e. Within 30 days of last BBBD. f. Within 30 days of starting treatment. g. Within 60 days of starting BBBD. h. Within 90 days of last BBBD.

Patient Characteristics and Outcomes

| Patient Age/Sex | Tumor type | # of courses | # of treatments | Melphalan Dose | Best Response | Adverse events |
|-----------------|--------------------------------|--------------|-----------------|--------------------------|---------------------|---------------------------------------|
| 18M | Medulloblastoma | 2 | 4 | 6mg/m ² daily | Stable disease | None |
| 15M | Medulloblastoma | 3 | 6 | 4mg/m ² daily | partial response | thrombocytopenia |
| 16M | Medulloblastoma | 1 | 9 | 8mg/m ² daily | partial response | ischemic stroke |
| 2F | ATRT | 0 | 0 | 0 | progressive disease | None |
| 1F | ATRT | 1 | 2 | 4mg/m ² daily | progressive disease | hypokalemia seizure neutropenia |
| 22M | testicular teratoma metastasis | 4 | 8 | 4mg/m ² daily | partial response | None |
| 17M | Pineal CNS mixed germ cell | 1 | 2 | 6mg/m ² daily | progressive disease | seizure |
| 25F | Yolk sac tumor | 4 | 8 | 6mg/m ² daily | stable disease | hypocalcemia hyponatremia |
| 16M | PNET | 2 | 4 | 6mg/m ² daily | progressive disease | neutropenia |

Figure 2: The first three patients were treated with melphalan dose 4mg/m² which was dose level 1. As none of those three patient had dose limiting toxicity the dose was escalated to 6mg/m².

Pretreatment and Post Treatment Imaging

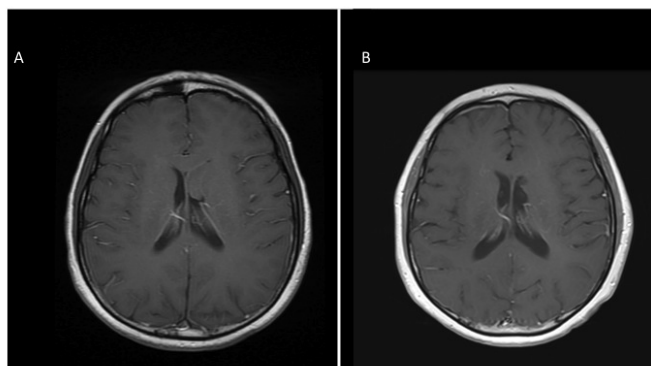


Figure 3: A) 16 yo M with biopsy proven metastatic medulloblastoma presented with new lesion on imaging. B) After nine treatments of two day BBBD and IA chemotherapy with carboplatin and melphalan.

Conclusions

This therapy is well tolerated and appears safe. The current melphalan dose is 8 mg/m². Toxicity is predominantly related to electrolyte disturbances and bone marrow suppression. There appears to be a subgroup that responds to this therapy but further investigation is needed. The trial continues with further enrollment.

Results

Nine patients were enrolled in the study (6 male) with a mean age was 14.75 years. There were three patients with medulloblastoma, two with atypical teratoid rhabdoid tumor, two with germ cell tumors, one with metastatic testicular teratoma, and one with PNET. The majority of patients thus far were treated at a melphalan dose of 6 mg/m² for two days. Of the study participants two had stable disease, three had partial response, and three had disease progression. There were a total of 16 adverse events of grades three and higher with the majority being grade 3 (63%). The most common adverse event was electrolyte disorder in 38% of patients, and bone marrow suppression in 25% of patients.

Selected References

- Doolittle ND, Miner ME, Hall WA et al: Safety and efficacy of a multicenter study using intrarterial chemotherapy in conjunction with osmotic opening of the blood-brain barrier for the treatment of patients with malignant brain tumors. *Cancer* 88: 637-47, 2000.
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