THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER

Protocol Abstract Page

A Pilot Study Evaluating the Feasibility of an Intercontinental Phase III Chemotherapy Study for Patients with Choroid Plexus Tumors. 2005-0398

Core Protocol Information

Study Chairman:	Johannes Wolff
Department:	Pediatrics
Phone:	713-745-0774
Unit:	087
Full Title:	A Pilot Study Evaluating the Feasibility of an Intercontinental Phase III Chemotherapy Study for Patients with Choroid Plexus Tumors.
Protocol Phase:	Phase III
Version Status:	Activated 11/06/2007
Version:	07
Document Status:	Final

Abstract

Objectives:

OVERALL AIM

To improve choroid plexus tumor treatment through better understanding of the tumor biology and through increased knowledge about the benefit of specific treatment elements.

Specific Objectives:

The study will have a prephase to evaluate the feasibility of the following randomized study (main phase).

Pre-Phase (completed 2005) Primary Specific Objective:
To determine the number of patients accountable per year for randomization in a worldwide study.

Secondary Specific Objective:
To measure the number of drop outs and to describe the toxicity of the chemotherapy.

Main Phase (started in 2006) Primary Specific Objective:
To compare the survival times after cyclophosphamide based treatment with the survival times after carboplatin based treatment in choroid plexus tumor patients.

Main Phase Secondary Specific Objectives:

1. To compare the resectability of choroid plexus tumors after two blocks of cyclophosphamide based treatment with the resectability after two blocks of carboplatin based treatment.
2. To compare response rates of incompletely resected choroid plexus tumors to two blocks of cyclophosphamide based treatment with the response rates after two blocks of carboplatin based treatment.
3. To determine the prognostic relevance of histological atypia and SV40 in choroid plexus tumors.

Rationale: (Be as concise as possible)

Study will address the question, "which of the agent, carboplatin or cyclophosphamide, is more effective in CPT treatment" in a randomized phase III approach. Study will correlate with protocol Lab05-0503, "Registration for Newly Diagnosed Histologically Confirmed CPT Patients", which involves collecting tumor specimens and clinical data to analyze prognostic relevance of histological characteristics and SV40 expression in an intercontinental setting. In case of disagreement with treatment approach suggested, other patients will be followed in the documentation part of study.

Aim of the study is to start gaining specific information upon which further studies can build. Available evidence suggests benefit of surgery for all patients and irradiation for patients over 3 years of age. Among the chemotherapeutic agents, best evidence was found for etoposide, followed by vincristine, cyclophosphamide, and platinum drugs. Among many interesting treatment questions, only one variable can be compared in small number of patients available. International discussion around this study showed that comparison of cyclophosphamide with carboplatin is the best feasible question. Carboplatin was preferred over cisplatin because of lower ototoxicity and difficulties in testing hearing in infants. Study will result in the first reliable drug specific information.

Multiagent treatment is viewed as standard care in many groups. Therefore, most frequently used drugs, etoposide and vincristine, are added to both arms of the protocol. Combination of DNA-binding drugs, with topoisomerase inhibitors and mitosis inhibitors is well based on theoretical/preclinical thinking and is generally used in almost all pediatric brain tumor protocols. The majority of patients are young and the majority of physicians agree that they should not receive irradiation.

Eligibility: (List All Criteria)

Inclusion:

1) The reference centre has confirmed the receipt of slides sent (For randomization only = form 2)

2) The postoperative imaging has been done and the result is available (for randomization only = for form 2 only)

3) Indication criteria: Choroid plexus papilloma (Gr I) with histologically confirmed metastases. (For randomization only = use form 2).

4) Indication criteria: Atypical chorod plexus papilloma or anaplastic choroid plexus papilloma histology with either metastases or postoperative residual tumor. (For randomization only = use form 2).

5) Indication criteria: Choroid plexus carcinoma, regardless of histologically confirmed metastases or residual tumor. (For randomization only = use form 2).

6) Informed consent signed (required for registration = form 1, and for randomization = form 2)

7) Patients must have the following: WBC > 2000/ul, platelets >85 000/ul, serum creatinine in normal range, pregnancy test negative, hearing loss less than 30dB at 3000 Hz.

Exclusion:

1) Previous irradiation or chemotherapy. (Exclusion from randomization only)

2) The protocol did not pass the local centre required approvals, such as the Ethics Committee or the scientific review.

3) Previous immunotherapy or antiangiogenic therapy (Exclusion from randomization only)

Is there an age limit? No

Treatment/Study Plan:

Table 2: Indication Criteria for Newly Diagnosed* Tumors After Maximal Surgery

Histology (local neuropathologist)	Metastases	Residual Tumor	Additional Treatment
Choroid Plexus	No	regardless**	No
Papilloma Grade I (no doubt)	Yes	regardless**	Yes *consider surgery of metastasis*
Atypical or Anaplastic Choroid Plexus Papilloma (malignancy questionable)	No No yes	No yes ** regardless**	No Yes Yes
Choroid Plexus Carcinoma	*regardless*	*regardless***	*Yes*

*In recurrent or progressive Choroid plexus tumors additional treatment is indicated. In addition, when there is clear evidence of tumor growth, even when the histological diagnosis is choroid plexus papilloma.

** *reconsider further surgery!*

***in the case of APP all efforts should be done to reassure if it is really a complete resection before committing to watch and wait.*

Table 3: Chemotherapy start criteria:

White blood cell count:	> 2000 / ul
platelet count:	> 85,000 / ul
serum creatinine:	in normal range
pregnancy test :	negative (only females in relevant age)
audiology:	hearing loss less than 30 dB at 3,000 Hz.

Surgery: Recommended metastases resection, when the histology of the primary tumor is choroid plexus papilloma. Encouraged surgical resection after additional treatment at:

1. After response evaluation to the first two blocks of chemotherapy (= week 8)
2. After completing additional treatment (week 37 or 42)
3. At any timepoint when tumor grows despite additional treatment

Surgeons should use operative reports and appropriate forms to document modalities employed during surgery. Copies of operative notes and appropriate forms are to be sent to international study coordinator.

Pathology: Whether patients will receive additional therapy is based on the diagnosis of local neuropathologist. The local laboratory will submit 2 x H&E stained histological sections, and 6 unstained sections on coated (e.g APES) slides (or 8 unstained slides) to neuropathology reference centre for review at end of the study and possible research purposes. Histology of tumours will be examined systematically at the end of the study. This will not influence treatment decisions or the randomization.

Diagnosis according to WHO classification is preferred. Local neuropathologist is asked to provide detailed report of histology, including immunophenotype, when submitting slides to reference centre.

Chemotherapy: Randomization will be either to carboplatin arm of study or to cyclophosphamide arm.

Carboplatin Arm: One chemotherapy block contains: etoposide 100 mg/m^2 over 1 hour on days 1-5, carboplatin 350 mg/m^{2}over 2 hours on day 2 and 3, vincristine 1.5 mg/m^2 IV push on day 5. A total of six blocks are given in 4 weeks intervals (day1 to day1). After first 2 blocks, response will be evaluated including all exams done prior to second registration. Further surgery will be considered after these exams, and result will be reported in Form 3 to international study center and national representative. After surgery, chemotherapy carries on for 4 further blocks. Small group of patients, who are > 3 years of age, will receive radiation after 2 blocks of chemotherapy, followed by 4 further blocks of chemotherapy.

Cyclophosphamide Arm: One chemotherapy block contains: etoposide 100 mg/m^2 over 1 hour on days 1-5, cyclophosphamide 1 g/m^2 over 1 hour on day 2 and 3, vincristine 1.5 mg/m^2 on day 5. A total of 6 blocks are given in 4 week intervals (day1 to day1). After the first 2 blocks, response will be evaluated including all exams done prior to second registration. Further surgery will be considered after exams. Result will be reported in Form 3 to international study center and national representative. After surgery, chemotherapy carries on for 4 further blocks. The small group of patients, who are >3 years of age, will receive radiation after 2 blocks of chemotherapy, followed by 4 further blocks of chemotherapy.

Radiotherapy: Radiation therapy in CPT is standard treatment. Data concerning dose response relationship and necessary target volumes is largely unknown. Guidelines of protocol were defined in analogy to treatment of other malignant pediatric brain tumors such as medulloblastoma.

Radiation starts after response evaluation after 2 blocks of chemotherapy. Radiation will be given only to patients that have completed their 3rd year of life (after the 3rd birthday).

Disease Group: Pediatrics, Solid Tumors

Treatment Agent: Carboplatin, Cyclophosphamide, Etoposide, Vincristine

Statistical Considerations:

Prephase
(completed in 2005)
Prephase of study is observational. It serves to determine study feasibility. Most critical is number of randomized patients. Following experience of other international studies, it is assumed, enrollment will increase over first 3 years after study activation. Predicted numbers for 3 categories for first year: 8 – 4 – 0, and for second year: 30 – 20 – 4. Total number and increase with time will be used to estimate number of patients available for following main phase of study. Final analysis of prephase will be calculation of accrual time and observation time necessary for following main phase of study.

This open-label study will be considered feasible to continue after prephase, if sufficient numbers of patients can be randomized within 5 years to provide reasonably precise comparison of effect of Carboplatin vs. Cyclophosphamide on survival. Preliminary data are somewhat uncertain, it is reasonable to assume 50% of patients will be alive at 4 years and approximately 25% will be long-term survivors.

Table shows minimum yearly accrual rate as function of total years accrual and number of years of follow-up for last randomized patient. Computation is based on a two-sided log rank test with 5% type I error and 80% power to detect a halving of the failure rate, with a 2.5%/year loss-to-follow-up rate.

	3 yrs ff-up	4 yrs ff-up	5 yrs ff-up
5 yrs accrual	33	30	29
6 yrs accrual	27	25	24
7 yrs accrual	22	21	20
8 yrs accrual	19	18	17

Study will be considered feasible if final analysis within 10 years of study activation will result in power specified above. Based on table , minimum annual accrual of 20 randomized patients per year will be reasonable goal.

Main Phase
(started in 2006)
The primary objective will address a comparison of 2 randomized treatment groups using "intent to treat" definition for these groups. Only difference between 2 treatment groups is use of carboplatin in one and cyclophosphamide in the other arm of study. Primary endpoint is overall survival after start of additional treatment. Kaplan Meier-projected overall survival curves will be produced to make sure that curves do not cross. Log rank test will then be used to compare 2 treatment groups. Homogeneity of composed groups will be checked for: age, gender, tumor location, degree of resection, compliance to randomization, irradiation, and discontinuation of treatment.

Secondary objective resectability: Success of surgery after first 2 cycles of chemotherapy will be compared between 2 treatment arms. Percentage of patients with secondary complete

remission from those with incomplete primary resection, will be used to analyze question. Tumors with CR and tumors which could be completely resected after two cycles of chemotherapy, will be counted together. Frequency will be compared among the 2 treatment arms using Chi-square test.

Secondary Objective Response: Frequency of partial or complete response after 2 cycles will be compared among the 2 treatment arms using chi square test.

Secondary objective SV40: Prognosis of tumors with or without SV40 will be compared using overall survival time as endpoint, Kaplan Meier survival estimates and log rank tests as statistical methods similar to the analysis of primary objective.

Prognostic relevance of histological parameters, including SV40 detection, proliferation, and malignancy markers will be addressed in histological reference centre. Data will be used as a hypothesis generating tool to determine frequency of SV40 antigen in various subpopulations. It is possible that SV40 positive tumors have different age, gender or location distribution as compared to SV40 negative tumors. This will allow a generation of a hypothesis about pathogenesis of the tumors.

Multivariate analysis using Cox regression model will gain information on relevance of variables, and used for analyzing the treatment results when the groups turn out to be inhomogeneous in a prognostic relevant parameter.

Protocol Monitoring:

Who is monitoring the day-to-day implementation and performance of this study, i.e., Good Clinical Practice?
Johannes Wolff

Data Monitoring Committee:

Is this study randomized or blinded? Yes
Data Monitoring is required, please complete both A and B:

A. Please provide the name of the entity that will oversee the Data Monitoring: Jonathan Finlay, Children's Hospital Los Angeles, Hematology/Oncology, 4650 Sunset Blvd., Mail Stop 54, Los Angeles, CA 90027 Phone: 323-906-8147 Fax: 323-660-7128 email: jFinlay@chla.usc.edu is the official datamonitor. He has formed a committee by adding Dr. Richard Sposto (Los Angelels) as biostatistician and Dr Rejin Kebudi (Istanbul Turkey) as second pediatric oncologist to the group.

B. Who will be providing the randomization schema?	Other International Data Center: Dr Brigitte Wrede, Klinik St Hedwig, Steinmetzstr. 1-3, 93409 Regensburg, Germany, Tel.: +49 (0) 941 369 95129, FAX: +49 (0) 941 369 5405 or 5494 email: brigitte.wrede@barmherzige-regensburg.de

Describe the Schedule for Interim and Final analysis:
Survival time is defined as time after randomization until end of the observation or the death of the patient. For analysis, there will be no difference between death by tumor progression, treatment related (toxic) reasons, or unrelated reasons.

Patient/Participant Evaluation: (Pretreatment and Interim Testing)

After maximal initial surgery, tumor staging will be done. This will include a physical exam (including neurological exam), neuroimaging and a lumbar puncture (LP).

The diagnostic imaging is to be done earlier than 72 hours after tumor resection. Later scanning will not allow differentiation between reactive angiogenesis and residual tumor, both of which are contrast enhancing. The preferred method is magnetic resonance imaging (MRI). Axial T1 weighted images and proton weighted images of the brain without contrast, followed by contrast enhanced axial T1 and 2-3 further planes of the brain and sagittal and axial contrast enhanced spinal images should be done at this point in time.

At time of diagnosis and at completion of all treatments perform physical exam including neurological status, Neuroimaging of primary site, and all known metastatic sites, Spinal MRI, endocrine evaluation: ask for fluid intake and nucturia (diabetes insipidus?), measure body height and body weight, put points in growth chart! (Growth hormone deficiency), palpate thyroid, draw blood for thyroxin, TSH, Na, K. If age over 11, or signs of puberty: LH, FSH, urine analysis for blood, glucose and protein. Draw blood for creatinine, Ca, phosphate, CBC (complete blood count) and LP.

Prior to each cycle of treatment: perform physical exam, draw blood for thyroxin, TSH, Na, K, white blood cell count, hemoglobin, platelets, differential, Na, K, Ca, P, ALT/GOT, AST/GPT, bilirubin, LDH and Creatinine, Urea.

After the first two cycles, response will be evaluated including all exams done prior to the second registration. Neuroimaging of primary site, and all known metastatic sites, Spinal MRI, audiogram and LP will be done after 6 cycles of treatment at 4 week intervals and surgery will again be considered.

During radiotherapy: 2 x weekly: red and white blood cell counts, platelet counts. If the patient is receiving steroid medication: blood glucose 1x weekly. Before and at the end of radiotherapy: sodium, potassium, calcium, GOT, GPT, Gamma-GT, LDH, creatinine, BUN, AFP, ß-HCG, hormones of the pituitary axis (TSH, growth hormone, ACTH, FSH/LH).

Biosafety:

Does this study involve the use of Recombinant DNA Technology?	No
Does this study involve the use of organisms that are infectious to humans?	No
Does this study include any products manufactured or produced at MD Anderson Cancer Center?	No

Radiation Safety:

Does this study involve the use of radioisotopes?	No
Does this protocol include the administration of a radioactive drug to human research subjects intended to obtain basic information regarding the metabolism (including	No

kinetics, distribution, and localization) of the drug or regarding human physiology, pathophysiology, or biochemistry, but not intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e. to carry out a clinical trial)?

Where Will Study Be Conducted:

C) Independent Multicenter Arrangements

Study is being conducted internationally through collaboration with SIOP.

Is this an M. D. Anderson Cancer Therapy Evaluation Program (CTEP) Protocol? No

Estimated Accrual:

Total Accrual at M.D. Anderson Cancer Center:	5
Estimated monthly accrual at M.D. Anderson:	<1
Total accrual will be:	100

A minimum annual accrual of 20 randomized patients per year wordwide will be a reasonable goal.

Basis of Study:

This protocol is performed on an Inpatient AND Outpatient basis.

Length of Stay: (What is the length & frequency of hospitalization)

Treatment can be administered both in an outpatient and inpatient basis for each cycle and during the recovery period after surgery.

Return Visits: (How often must participants come to MDACC)

Patients that require chemotherapy will receive treatment for 5 days per course with 4 weeks interval for total of 6 courses in both arms.

Home Care: (Specify what (if any) treatment may be given at home)

NONE.

Name of Research Nurse/Data Manager Responsible for Protocol:

Margaret E. Nagel

Public Display of Protocol on the Office of Protocol Research Web Site:

The Office of Protocol Research maintains a website (www.clinicaltrials.org) listing protocols actively accruing patients. No information is given about drug dose or — Yes

schedule. Would you like this protocol listed on this website?

If this protocol has a corporate sponsor, we also need to get the sponsor's written approval to post the trial on the website. Shall OPR send a letter requesting this permission to your sponsor?	N/A

Prior protocol at M. D. Anderson:

List the protocol number for the last clinical treatment/behavioral protocol on which you were the Principal Investigator that accrued patients at M. D. Anderson. None

Space Requirements for Clinical Trials:

Will implementing this protocol require additional space (clinical, office, departmental)? No

Additional Space will not be made available in the future.

Sponsorship and Support Information:

Does the Study have a Sponsor?	No
Name of Sponsor or Supporter:	
Does the Sponsor Provide Funding for the conduct of the study?	No
Is this Protocol listed on any Federal Grant or Foundation Funding Application?	No
Grant Number:	
Does the Sponsor supply drug(s) or device(s)?	No
Name of Sponsor/Supporter ContactPerson:	
Telephone:	
Fax Number:	
E-Mail:	

Does this protocol require an IND? No

Please check the items below to verify that the following information is correct:
The data will not be used to expand the label or change the advertising for the drug.
There will be no substantial change in the dosage, drug, or route of administration or other factor that will significantly increase the risk to the patient.

Does this protocol use a "Combination" of drugs or other therapies (Drug, Radiation or Surgical Therapy) or Diagnostic Procedures that pose a significant risk to the patient?
No

If this protocol includes an FDA Approved Therapy, please list the disease, dose and route of administration:

	Approved Use	**Proposed Use in this Protocol**
Disease:	Cancers	Choroid Plexus Tumors
Dose:	Vincristine (1.5 mg/m², maximum dose 2.0 mg) Etoposide (VP-16, VePesid, Etopophos) - Testicular cancer: I.V.: 50-100 mg/m²/day on days 1-5 or 100 mg/m²/day on days 1, 3 and 5 every 3-4 weeks for 3-4 courses (pediatric not specified) Carboplatin 175-600 mg/m² MESNA (sodium 2-mercaptoethane sulfonate, Mesnex®) - 20% W/W of cyclophosphamide dose prior to administration and 3, 6, 9, 12 hours after cyclophosphamide dose (total daily dose = 120% to 180% of cyclophosphamide dose) Cyclophosphamide 400-1000 mg/m²	Vincristine (1.5 mg/m², maximum dose 2.0 mg) Etoposide 100 mg/m² Carboplatin 175-600 mg/m² Mesna 250 mg/m² Cyclophosphamide 1000mg/m²
Route of Administration:	All IV infusions	All IV infusions

Rationale For Planned Therapy:
It is the aim of this study to start gaining specific information, upon which further studies can build. There is some evidence that chemotherapy can be helpful, but the specific role of single agents remains unclear. The study will result in the first reliable drug specific information.

For FDA approved drugs
www.fda.gov/cder/da/da.htm

For the FDA Investigational New Drug (IND) Exemption Rationale
www.access.gpo.gov/nara/cfr/waisidx_03/21cfr312_03.html
Then select 312.2

For FDA approved biological therapies

www.fda.gov/cber/

Device:

Is this protocol testing a new device or a device in a new application? No

For a list of significant/non-significant risk devices
www.fda.gov/oc/ohrt/irbs/devices.html