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Tandem Thiotepa with Autologous Hematopoietic Cell Rescue in Patients with Recurrent, Refractory or Poor Prognosis Solid Tumor Malignancies

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Abstract

Background—The purpose of this study was to determine the feasibility and tolerability of tandem courses of high-dose thiotepa with autologous hematopoietic cell rescue (AHCR) in patients with recurrent, refractory solid tumors who were ineligible for a single course of high-dose therapy due to greater than minimal residual disease. Patients with decreased hearing or poor renal function were eligible.

Procedure—Thiotepa was administered intravenously at a dose of 200 mg/m^2/day (6.67mg/kg/day) daily for three days followed by AHCR. A second course of thiotepa was given four weeks later provided blood counts recovered sufficiently without evidence of tumor progression.

Results—Fifty-eight patients received 96 courses. Thirty-eight (65%) patients received two courses of therapy. Twenty-seven courses (28%) were administered completely in the outpatient setting. A toxic mortality rate of 3.4% was observed. Five of 26 patients with medulloblastoma were alive at a median of 35 months while 21 patients died at a median of 11.7 months. Four of five patients with central nervous system germ cell tumors (CNS GCT) were alive 68–103 months following AHCR.

Conclusions—Two cycles of high-dose thiotepa with AHCR were well-tolerated even in these heavily pre-treated patients. This therapy may provide prolonged survival in patients with recurrent malignant brain tumors, particularly medulloblastoma and CNS GCT.

Keywords

Thiotepa; Tandem; Transplant; Hematopoietic Cell; Neoplasm; Malignancy

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Conflict of Interests for Dr. Ira Dunkel: Consultant for Bayer, Bristol-Myers Squibb, and Pfizer. Recent past was a consultant for Ipsen (ended 8-20-15) and Eisai (ended 10-1-16).

Introduction

The prognosis for children, adolescents and young adults with recurrent or refractory malignant solid tumors remains poor. Many studies have reported on the efficacy of myeloablative chemotherapy with autologous hematopoietic stem cell rescue (bone marrow or peripheral blood) for patients, predominantly using a single cycle of myeloablative therapy.[1–6] There are some encouraging data utilizing this approach for patients with CNS tumors such as medulloblastoma and primary CNS germ cell tumors (GCT),[7–9] neuroblastoma,[10,11] and Wilms tumor.[12,13] Most studies report that if benefits are seen, they are in patients with minimal residual disease and good organ function.

Unfortunately many patients are unable to achieve a state of minimal residual disease despite the use of chemotherapy, irradiation and/or surgery following tumor recurrence. In addition, these patients often have toxicity from prior therapy, rendering them poor candidates for high dose chemotherapy regimens incorporating multiple drugs.

The primary goal of the current study was to determine the feasibility and toxicity of administering two consecutive myeloablative courses of thiotepa each with autologous hematopoietic cell rescue (AHCR) in a multicenter trial for children, adolescents and young adults with recurrent/refractory solid tumors who were not eligible for a single myeloablative multi-drug regimen due to residual disease. In addition, we report data on the tumor response to this tandem regimen.

Materials and Methods

Patient population

Data were collected prospectively following approval by the institutional review board at participating centers: New York University Langone Medical Center, Memorial Sloan Kettering Cancer Center, Children’s Hospital of Pittsburgh and Stamford Hospital in Connecticut.

Eligibility criteria

Patients were required to have recurrent, refractory disease with pathologic or cerebrospinal fluid (CSF) cytology confirmation of malignancy by their respective pathology departments. Exceptions included patients with ophthalmologic exams consistent with retinoblastoma or serum or CSF tumor markers positive for primary CNS GCT. Measurable disease was required for this study either by MRI or CT Scans. Life expectancy of greater than 8 weeks was required. A Lansky or Karnofsky performance of 60 or greater, and recovery from the non-hematopoietic and hematopoietic effects of previously administered chemotherapy, was necessary for study entry. Patients had to be at least four weeks from the last administered dose of chemotherapy and/or radiation therapy, have sufficient hematopoietic cells harvested for two hematopoietic cell rescues and have an absolute neutrophil count (ANC) and platelet count equal to or above 1000/uL and 75,000/uL, respectively.

Patients with tumors involving the bone marrow had to be free of disease in the marrow at the time of hematopoietic cell harvesting, proven by morphologic and cytogenetic evaluations. Adequate organ function was measured by the following: bilirubin less than or equal to 1.5x the upper limit of normal, ALT and AST less than or equal to 2.5x the upper limit of normal unless the liver was involved with tumor; serum creatinine within the normal range or, if the serum creatinine was outside the normal range, then patients were required to have a creatinine clearance greater than or equal to 70 ml/min/1.73 m^2; a fractional shortening greater than 28% or ejection fraction greater than 55% on echocardiogram prior to the first course of thiotepa; asymptomatic for pulmonary disease or, if symptomatic, the patient had to have a diffusion capacity greater than 50% of predicted (corrected for hemoglobin). Pregnant or lactating women were excluded. Patients did not receive concurrent radiotherapy and/or chemotherapy. Corticosteroids were permitted for their anti-edema effects and were not used solely as an anti-emetic.

Treatment

Thiotepa was administered as a three-hour daily infusion for 3 consecutive days at a dose of 200mg/m^2/day, equivalent to 600mg/m^2/course for those patients weighing more than 25 kg. For patients weighing 25 kg or less, thiotepa was dosed as 6.67 mg/kg, equivalent to 20 mg/kg/course. A second course of thiotepa was administered at least 4 weeks following the initiation of the first course in patients with responsive or stable disease, an ANC ≥ 1000/μL without growth factor and when the patient was no longer platelet transfusion dependent. All patients were intended to undergo two courses of thiotepa.

Patients were required to have adequate numbers of hematopoietic progenitor cells for two reinfusions collected prior to the first course of thiotepa. The target dose for hematopoietic cell rescue was at least 2.5×10^6 CD34+cells/kg. Autologous peripheral blood hematopoietic progenitor cells were re-infused approximately 72 hours following the completion of each course of thiotepa.

Toxicity

Toxicity data were obtained from the patients' medical records and graded in accordance with Common Toxicity Criteria from the National Institutes of Health, United States, version 1 (1988–1998) and version 2 (1999–2006). The data toxicity grades of interest were those ≥ grade III; because grades I and II toxicities were considered acceptable given the lack of treatment alternatives for this patient population at that time.

Supportive measures

Patients received supportive care including anti-emetics, as well as blood product transfusions as needed to maintain adequate hematologic parameters. Febrile neutropenia was treated with standard intravenous antibiotic therapy, and antifungal treatment was administered as per the institutional guidelines. Prophylaxis for pneumocystis pneumonia and herpes virus was provided as per institutional preference.

Required observations

Blood work including complete blood count (CBC), comprehensive chemistry profile and creatinine clearance were performed prior to each course of thiotepa. Pulmonary function tests were obtained prior to each course in patients who were symptomatic. Tumor response was assessed radiographically and, if indicated by CSF cytology and/or serum and CSF tumor markers, prior to each course of thiotepa and every three months for one year following the last course of thiotepa or until there was evidence of progressive/recurrent disease.

Disease response criteria

Treatment response was determined within each of four sub-groups according to their tumor type. The four sub-groups of tumors were 1) neuroectodermal CNS tumors 2) non-neuroectodermal CNS tumors 3) non-CNS round blue cell tumors and 4) other non-CNS tumors.

Response rate

Response to therapy was defined as: 1) Complete response (CR): complete radiographic and/or cytological disappearance of all lesions. 2) Partial response (PR): ≥50 and <100% decrease in the sum of the products of the maximum perpendicular diameters of all measurable lesions; no evidence of progression in any lesion and no new lesions for at least 4 weeks. 3) No response (NR) or stable disease: < 50% decrease in the size of measurable lesions lasting at least four weeks or a steady state not qualifying for progressive disease. 4) Progressive disease (PD): > 25% increase in the size of measurable lesions at any involved site and/or appearance of new lesions.

Results

Between September 1997 through September 2002, 58 patients with a variety of recurrent, refractory, poor prognosis malignancies diagnosed between ages 0.1 to 40.1 years old (median: 7.7 years old) were enrolled (see Table 1). All patients had recurrent, refractory of progressive tumor following standard treatment approaches for their disease, the majority having received a combination of surgery, chemotherapy and radiation therapy as further described in Table 1. Thirty-six patients (62%) had metastatic disease prior to initiating their first course of thiotepa.

Of the 58 patients who underwent their first course of thiotepa, one patient experienced grade III hepatic toxicity attributed to thiotepa. Two patients experienced CNS-general grade IV events that were transient, characterized by altered mental status, and possibly attributable to thiotepa. One of these events occurred shortly after the AHCR. The etiology remained unclear and the patient's EEG did not reveal any seizure activity. Another patient was admitted for a grade 3 infection, fever and bacteremia with *stenotrophomonas maltophilia*. His catheter was removed and he was treated with IV antibiotics with full recovery. (Table 2)

There were two toxic deaths experienced in this protocol. The first patient was a five year old male with an incompletely resected medulloblastoma treated with chemotherapy followed by craniospinal irradiation (CSI) which was administered 6 months prior to being enrolled on to our study. He never engrafted and died 3 months after his first course. The cell dose administered for this patient was 2.5×10^6 CD34+cells/kg. Of note, there were 12 other patients who received CSI prior to AHCR; 10 of which successfully underwent two thiotepa courses. The second patient who died of toxic death was an eight year old male with medulloblastoma who had undergone surgery, chemotherapy and CSI tolerated the first course well; however, just prior to the planned start of cycle 2 he developed respiratory problems, with patchy lung parenchymal infiltrates and a pericardial effusion, but no tamponade. Both bronchoalveolar lavage and lung biopsy were non-diagnostic and he ultimately died of respiratory failure. It was suspected he had contracted a virus or some other infectious agent while severely T-cell suppressed from his prior thiotepa, and that this caused severe pericardial and pulmonary disease. Alternative hypotheses included thiotepa pulmonary toxicity versus irradiation-induced cardio-pulmonary disease. Of the 38 patients who underwent two courses of thiotepa, only two patients experience grade III toxicities, one respiratory and one gastrointestinal. Interval range between day 1 of course 1 and day 1 of course 2 was 27 – 86 days with a median of 42 days. Of the 38 patients who received a second course, 15 of 38 patients (39%) had less than or equal to 35 days between courses. The three patients who received 2 courses of AHCR and had ≥grade III toxicities had 34 days (grade III gastro-intestinal toxicity), 44 days (grade IV neurotoxicity) and 50 days (grade III respiratory toxicity) interval days between courses 1 and 2. We did not find there was a correlation with toxicity and interval between first and second thiotepa courses.

Days of hospital stay ranged from 0–34 days in the first course (median: 6 days) and 0–54 days in the second course (median: 4 days) (Table 2). The number of patients with zero days of hospitalization received treatment *solely as an outpatient*: thirteen patients (22%) never required hospitalization during the first thiotepa course and 9 patients (23%) never required hospitalization during the second thiotepa course (Table 2). The median days to ANC engraftment for the first course was 11 days (range: 7–78 days) and 11 days for the second course (range: 7–51 days). Two patients did not engraft during the first course, one of whom engrafted after the second course.

Intravenous antibiotics were utilized in 40 (72%, n=55) patients in the first course, in 23 (61%, n=38) patients in the second course. Intravenous amphotericin was administered to 5 (9%) patients in the first course and to 4 (11%) patients in the second course. Morphine was administered in 9 (18%) patients in the first course, 4 (13%) patients in the second course. Parenteral nutrition was required in 10 (20%) patients in the first course and in 6 (19%) patients in the second course. Platelet transfusions were required in 43 (74%) patients in the first course (range: 0–136 transfusions; median: 17 transfusions) and in 31 (78%) patients in the second course (range: 0–53 transfusions; median 18 transfusions). (Table 3)

Best response to therapy was measured as described in the Methods section and was evaluable in 54 of 58 patients after the first cycle and in 20 of 38 patients after the second cycle. Five patients achieved a complete response, 12 had a partial response, 22 had no response or stable disease, and 15 had progressive disease (Table 4). The various disease

statuses at study entry are also detailed in Table 4. Of the 12 long-term survivors, seven were reported to be without evidence of disease in follow-up for 2 to 5.8 years (median 3.6 years). Five additional patients were reported as long-term survivors with disease 1.4 to 3.2 years (median 2 years) from thiotepa administration. Patients with recurrent CNS GCT (n=5) composed the largest number of survivors free of disease: four with no evidence of disease 3 to 5 years following thiotepa and one lost to follow-up after completing one cycle of treatment. Two of 18 patients with medulloblastoma had no evidence of disease at 2 and 6 years from thiotepa therapy, 5 patients were alive with disease at 1 to 3 years from thiotepa and 2 patients experienced toxic deaths during the first cycle of thiotepa. The remaining 44 patients died of tumor progression. (Table 5)

Data regarding treatments offered to survivors after the study were not captured since the main focus of our study was safety, feasibility and tolerability of this regimen. Patients were not routinely offered or placed on any post-transplantation maintenance regimens and our study was not powered to analyze survival outcomes.

Discussion

Thiotepa is a polyfunctional alkylating agent which has been used in clinical trials since the 1950's.[5,14–16] These early studies demonstrated that thiotepa had activity against a wide variety of neoplasms; however, thiotepa was not widely used because of its association with severe myelosuppression even at modest doses. Over the years, improvements in supportive care measures as well as the development of recombinant growth factors and the use of AHCR have significantly reduced complications associated with myelosuppressive chemotherapy.

Phase I studies using thiotepa as a single agent with autologous bone marrow rescue have established a maximum tolerated dose of 1000–1125 mg/m[15,17,18]. Heidemann *et al* examined the pharmacokinetics of thiotepa in plasma and CSF and found that both thiotepa and TEPA have excellent CSF penetration with nearly identical penetration for both the parent compound and its metabolite.[19]

Dunkel *et al* evaluated the use of high-dose carboplatin, thiotepa and etoposide with AHCR in patients with recurrent medulloblastoma, demonstrating promising results in this high-risk population with an event-free and overall survival of 34%±10% and 46%±11%, respectively. However, toxicity in this study was significant: 57% of patients experienced grade 3 or 4 hepatic toxicity, 8% of patients had grade 3 cardiotoxicity, and toxic mortality occurred in 13% of patients within 21 days from AHCR.[20] In spite of this high degree of toxicity, their data suggested that an aggressive retrieval chemotherapy regimen may provide long-term survival in some patients with recurrent medulloblastoma. However, benefit was confined to those patients treated with minimal tumor burden. Similarly in 2010, *Dunkel et al* demonstrated that previously irradiated patients with recurrent medulloblastoma also achieved a minimal disease state with carboplatin, thiotepa and etoposide followed by AHCR while offering a prolonged median overall survival of 26.8 months[21].

Gilman *et al* treated 32 children with recurrent brain tumors using tandem high-dose chemotherapy with thiotepa and carmustine during the first cycle and thiotepa and carboplatin during the second cycle with AHCR after each cycle.[22] This therapy resulted in prolonged time to progression and long-term survival for some of these children but toxicity was significant with a regimen-related toxic mortality rate of 25%.

Accordingly, in 1997 we embarked upon a feasibility pilot of two sequential courses of single agent thiotepa in patients with recurrent or refractory malignant solid tumors not considered appropriate for single course myeloablative regimens due to measurable residual disease. Although the dose of thiotepa per course of 600 mg/m^2 was two-thirds of the thiotepa dose of 900 mg/m^2 used in many single course multi-drug myeloablative regimens, the cumulative dose over two courses resulted in a cumulative increased dose of thiotepa by 30% (from 900 mg/m^2 to 1200 mg/m^2).

The major goal of our study was to determine the tolerability of two sequential courses of thiotepa, each with AHCR. Patients with recurrent or refractory poor prognosis malignancies were eligible to participate, thereby selecting for a patient population that had received and failed standard treatment for their disease. In this prospective study, we observed that tandem courses of thiotepa were generally well-tolerated in an already heavily-pretreated and poor prognostic patient population several of which received CSI. After it was deemed to be safe the goal would be for it to become the backbone for a transplant regimen in combination with other drugs.

The toxic mortality rate of 3.4% with this tandem regimen was clearly reduced in comparison to reported mortalities with single course regimens like that reported by Nazemi et al from a pilot study for CNS embryonal tumors in CCG99702 that preceded AHCR with craniospinal irradiation in newly diagnosed patients.[23] Other comparable studies utilizing high-dose chemotherapy and AHCR predominate in infants and young children, who tolerate high doses of chemotherapy and AHCR better than older children and adults present in our study. Additionally, non-hematologic toxicities with this tandem thiotepa regimen were less than those seen with single course multi-drug regimens. There were no reports of either ototoxicity or nephrotoxicity in these patients.

Favorable responses with durable outcomes were noted in the patients with recurrent CNS germ cell tumors and, to a lesser degree, in patients with recurrent medulloblastoma, in keeping with prior reports.[26,20] The small population size precludes us from drawing definitive conclusions regarding survival outcomes for individual malignancies. Nevertheless it is apparent that in our heavily pre-treated population, tandem thiotepa is a tolerable regimen where one-fourth of patients are able to receive their treatment entirely in the outpatient setting. The findings of our study merit further investigation into the use of tandem thiotepa in patients with CNS malignancies, given its tolerability and excellent CSF penetration. This approach may best be used in combination with other therapies such as molecularly targeted drugs or immunotherapy that work best in the setting of minimal residual disease.

Glossary

AHCR	Autologous Hematopoietic Cell Rescue
CNS	Central Nervous System
GCT	Germ Cell Tumors
CSF	Cerebrospinal Fluid
ANC	Absolute Neutrophil Count
CR	Complete response
PR	Partial response
NR	No response
PD	Progressive disease
CSI	Craniospinal Irradiation
CBC	Complete blood count

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TABLE 1.

Patient Characteristics. S: surgery, C: chemotherapy, RT: radiation therapy, AHCR: autologous hematopoietic cell rescue, DT: drug trial, AT: alternative therapy; Complete response (CR), Partial response (PR), No response (NR) or stable disease, Progressive disease (PD).

Age at Diagnosis	Sex	Diagnosis	Therapy prior to Thiotepa	Disease Status upon Enrollment	No. of Thiotepa Courses
40.1	Female	Anaplastic Astrocytoma	S, RT, C	PD	2
18	Male	Anaplastic Astrocytoma	S, C, RT	PR1	1
13.9	Male	Anaplastic Astrocytoma (Bithalamic)	RT	PR1	1
12.8	Male	Anaplastic JPA	S, RT	PR3	1
36	Male	Anaplastic Oligodendroglioma	RT, C, S	PD	2
2.1	Male	AT/RT	S, C	NR1	1
0.1	Male	AT/RT	S, C, DT, RT	PD	2
1	Female	Choroid Plexus Carcinoma	S,DT	PD	2
8.5	Male	CNS-Germ Cell Tumor	C	PD	2
9.1	Male	CNS-Germ Cell Tumor	C	PR1	2
30.7	Male	CNS-Germ Cell Tumor	C, RT	PR1	2
8.5	Male	CNS-Germ Cell Tumor	DT, RT	PD	2
19.7	Male	CNS-Germ Cell Tumor	AT, C, S	PD	1
5.4	Female	Ependymoma	S, C, RT	PD	2
7.4	Male	Ependymoma	S, RT, C	PD	2
3.1	Female	Ependymoma	S, RT, C	PR2	1
1.7	Male	Ependymoma	S, DT, RT	PD	2
15	Male	Ewing Sarcoma	S, C, DT	NR1	1
17.9	Male	Ewing Sarcoma	C, S, RT, DT	PD	2
7.6	Male	GBM	S, RT	PR1	1
28.5	Female	Leiomyosarcoma	S, RT, C	NR1	1
3.5	Male	Medulloblastoma	C	NR2	1
5.5	Male	Medulloblastoma	S, C, RT	PR1	1
4.3	Male	Medulloblastoma	C, RT	PD	1
36.3	Male	Medulloblastoma	S, C, RT	PD	2
6	Male	Medulloblastoma	S, RT, C	NR1	2
30.4	Male	Medulloblastoma	S, RT, C	PR1	2
6	Female	Medulloblastoma	S, RT, C	PR2	2
3	Female	Medulloblastoma	S, C, RT	PD	2
4	Male	Medulloblastoma	S, C, AT	PD	2
9.2	Male	Medulloblastoma	S, RT, C	NR3	2
7.8	Male	Medulloblastoma	S, RT, C	PR1	2
0.7	Female	Medulloblastoma	S, C	PR1	2
8.3	Male	Medulloblastoma	S, RT, C	PD	1
3.2	Male	Medulloblastoma	S, RT, C, AHCR	PD	2
18	Male	Medulloblastoma	S, C, RS, AHCR	PD	2

Age at Diagnosis	Sex	Diagnosis	Therapy prior to Thiotepa	Disease Status upon Enrollment	No. of Thiotepa Courses
8.8	Male	Medulloblastoma	S, C, RT	PR2	1
34	Male	Medulloblastoma	S, RT, C	PD	2
24.6	Male	Medulloblastoma	S, C, RT	PR1	2
3.3	Female	Neuroblastoma	C, S, DT, AHCR	NR1	1
5.5	Male	Neuroblastoma	S, C, RT, DT	NR2	1
4.1	Male	Neuroblastoma	C, RT, S, AHCR, DT	NR1	2
6.1	Female	Neuroblastoma	C, S, RT, AT	NR1	2
5	Male	Neuroblastoma	S, C, AHCR, DT, AT	PR1	1
6.5	Male	Osteosarcoma	RT, C	PR1	1
39.8	Female	Pineoblastoma	S, C, RT	PD	2
15	Female	Pineoblastoma	RT, C	NR1	2
15.5	Female	Pineoblastoma	S, C, RT	PR1	1
0.4	Female	Pineoblastoma	C	PD	2
1.4	Male	Pineoblastoma	C	PD	1
36.2	Female	Pineoblastoma	S, C, RT	PD	2
9	Male	PNET	RT, C	NR1	2
1.2	Male	Retinoblastoma	S, RT, C	PR1	2
4.3	Male	Retinoblastoma	C, S, RT	NR1	2
1.5	Female	Retinoblastoma	S, C	PR1	2
4	Female	Rhabdomyosarcoma (Orbital)	C, S	PD	2
26	Female	Undifferentiated Carcinoma	RT, C	PR2	2
35.5	Male	Wilms Tumor	C, S, RT	NR2	2

TABLE 2.

Patient Characteristics, Post-Thiotepa Attributable Toxicities.

	Thiotepa Course 1 (58 patients)	Thiotepa Course 2 (38 patients)
Toxicity (Number of Patients)	CNS-general Gr. III (2) Hepatic Gr. III (1) Infection Gr. III (1) Respiratory Gr. V (1) Immunosuppression Gr. V (1)	Respiratory Gr. III (1) Gastrointestinal Gr. III (1) Neurological Gr. III (1)
Days of Hospitalization		
Range	0–34 days	0–54 days
Median	6 days	4 days
Patients who were never hospitalized	13 patients (22.4%)	9 patients (23.7%)

TABLE 3.

Supportive Care Measures Administered.

Number of patients who received:	**Parenteral Antibiotics**		**Amphotericin**		**Morphine**		**Total Parenteral Nutrition**		**Transfused Platelets**	
Course #	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**	**1**	**2**
Yes	40	23	5	4	9	4	10	6	43	30
No	15	12	50	30	39	26	40	25	15	8
Unknown/NA	3	3	3	4	10	8	8	7	-	-
Total, patient#	58	38	58	38	58	38	58	38	58	38

TABLE 4.

Best Response to Therapy.

Best Response	Number of Patients	Disease Status at Study Entry
CR	5	NR1= 2, PD= 3
PR	12	PR1= 4, NR1= 2, PR2= 1, NR2= 1, NR3= 1, PD= 3
NR	22	PR1= 5, NR1= 3, PR2= 2, NR2= 2, PD= 10
PD	15	PR1= 4, NR1= 3, PR2= 1, PR3= 1, PD= 6
Not Evaluable	4	PR1= 2, PD= 2

Complete response (CR), Partial response (PR), No response (NR) or stable disease, Progressive disease (PD).

TABLE 5.

Survivor Outcomes by Disease.

Disease	Best Response	Status	Years
CNS-Germ Cell Tumor	PR	NED	4.95
CNS-Germ Cell Tumor	CR	NED	2.65
CNS-Germ Cell Tumor	CR	NED	4.68
CNS-Germ Cell Tumor	SD	NED	3.53
Ependymoma	Not eval	NED	1.94
Medulloblastoma	SD	AWD	2.65
Medulloblastoma	SD	AWD	5.70
Medulloblastoma	SD	AWD	3.08
Medulloblastoma	SD	AWD	3.13
Medulloblastoma	PR	NED	1.96
Medulloblastoma	Not eval	NED	1.35
Undifferentiated Carcinoma	PR	AWD	1.51