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The effect of ophthalmic artery chemosurgery on immune function in retinoblastoma patients: A single institution retrospective analysis

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Abstract

Background—Ophthalmic Artery Chemosurgery (OAC) is associated with grade 3 and 4 neutropenia, however the effect on T-cell number and function is unknown. The purpose of this retrospective review was to confirm that patients treated with OAC do not develop immunosuppression warranting PCP prophylaxis.

Procedure—IRB approval was obtained for a single center retrospective review of immune function tests in retinoblastoma patients who received OAC.

Results—Twenty-three patients received 3 cycles of OAC and had immune function testing (absolute CD4 count) performed at a median of 34 days post-completion of therapy (range 15-63 days). Only one patient had a low absolute CD4 count of 189 cells/mL (normal 359-1570 cells/mL) two and a half months after IV carboplatin and 28 days after their third dose of OAC. This patient was found to have co-existing hypogammaglobulinemia. Repeat immune function testing normalized through continued OAC treatment.

Conclusion—Clinically significant immune suppression appears rare following OAC alone, but patients previously treated with IV chemotherapy may be immunosuppressed and may benefit from pneumocystis pneumonia prophylaxis until the CD4 count recovers.

Keywords

Ophthalmic artery chemosurgery; intra-arterial chemotherapy; Pneumocystis Pneumonia prophylaxis; retinoblastoma

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Introduction

Retinoblastoma is the most common primary pediatric intraocular malignancy, with an incidence of 8,000 new diagnoses per year worldwide, and approximately 300 per year in the United States.^{1, 2} At Memorial Sloan Kettering Cancer Center (MSKCC) we see approximately 90 new cases of retinoblastoma each year.

The treatment of retinoblastoma has evolved dramatically over the past ten years. Ophthalmic Artery Chemosurgery (OAC) has transformed our treatment algorithm, and is now standard first line therapy for most children at our center. This has eliminated the need for systemic chemotherapy, with the exception of infants < 3 months of age or < 7 kg in weight, who receive single agent intravenous (IV) carboplatin as a “bridge” therapy until they are old enough for OAC, and for those children with high-risk enucleation pathology features or metastatic disease. OAC has eliminated 90% of the enucleations we performed just 5 years ago.³

OAC allows for smaller doses of chemotherapy to be delivered directly to the tumor, in higher concentrations than that delivered by conventional IV chemotherapy. OAC doses are titrated using patient age for an approximation of eye size and arterial territory (Table I).⁴ These small doses of chemotherapy result in minimal clinically significant systemic toxicity. While most patients experience some degree of neutropenia, fewer than 1% of patients develop febrile neutropenia or require transfusions. Grade 3 or 4 neutropenia occurs in 29% of cycles, and is associated with melphalan doses greater than 0.4 mg/kg.⁵

Although OAC is known to have an effect on the immune system, as evidenced by neutropenia, the effect on T-cell number and function is unknown. The low doses of OAC are not believed to be T-cell suppressing, there are no known cases of *Pneumocystis* pneumonia (PCP) in patients receiving OAC for retinoblastoma, and we do not prescribe PCP prophylaxis for OAC treatment alone. However there is a lack of documented evidence validating this practice. The purpose of this retrospective review was to confirm that patients treated with OAC do not develop immunosuppression warranting PCP prophylaxis.

Methods

Ophthalmic Artery Chemosurgery

OAC is a surgical procedure performed in an interventional radiology suite; cerebral angiography with anticoagulation is performed under general anesthesia to guide a microcatheter (1.5 Fr) via the femoral artery to the orifice of the ophthalmic artery. Then, small total body doses of melphalan, topotecan, and/or carboplatin are slowly administered in a pulsatile manner. The catheter is withdrawn, a pressure dressing applied, and the child is observed for 4-6 hours in the PACU before being discharged home the same day.

Patients

Ophthalmic artery chemosurgery treatment for retinoblastoma began at our institution in 2006, and as of the time of review in 2014 we had treated 274 patients with OAC. We performed a single center IRB approved retrospective review of retinoblastoma patients who

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were treated with OAC and had immune function testing performed at MSKCC from 2006 to 2014. Immune function was assessed by determination of absolute CD4 count (with flow cytometry immunophenotyping) and T-cell function via mitogen response to phytohemagglutinin (PHA). Available medical records were reviewed for each patient and a de-identified database was created, with 62 initial patients.

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While 274 patients had OAC from 2006 to 2014, immune function testing was not standard for patients receiving OAC alone as it was not believed to be T-cell suppressing. The 62 patients who had OAC and immune function testing were tested in recent years as part of informal clinical evaluation to confirm normal immune function before resuming vaccinations or required immune function testing after receiving IV chemotherapy.

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Thirty-five patients had immune function tests performed > 2 months after completion of OAC and their data was deemed inevaluable because immune reconstitution may have occurred as a process of natural time. Twenty-seven patients (median age 12 months, range 4-94 months) had immune function testing performed 2 months (maximum of 63 days) after treatment with OAC. They received a median of 3 consecutive cycles of OAC (range 2-7). Four patients received < 3 consecutive cycles of OAC and their data was deemed inevaluable because patients who received less than the median of 3 cycles may have had normal immune function because they received less treatment.

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Twenty-three patients received 3 consecutive cycles of OAC (median 3 cycles, range 3-6), had immune function testing performed 2 months after completion of OAC, and were considered evaluable (Figure. 1). Ten received OAC alone; 13 received IV chemotherapy prior to OAC, with the majority receiving 1-3 cycles of IV carboplatin +/- vincristine and etoposide, all completing at least one month prior to starting OAC. Immune function testing was performed at a median of 34 days post OAC treatment (range 15-63 days). All twenty-three received melphalan, with a median cumulative dose of 12mg, range 6-33mg. Eighteen received topotecan, with a median cumulative dose of 3.5mg, range 1-10mg. Twenty received carboplatin, with a median cumulative dose of 135mg, range 50-450mg.

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Five patients who did not fit the inclusion criteria were noted to have low PHA specific mitogen levels and their data was included in the mitogen group, for a total of 28 patients with evaluable mitogen results. Four received IV chemotherapy prior to OAC, consisting of 2-5 cycles of carboplatin +/- vincristine, all completing at least one month prior to starting OAC; one received OAC alone. Three were patients who had immune function testing completed >3 months (one at 7 and two at 12 months) from completion of therapy and two were patients who had < 3 cycles of OAC.

Results

CD4 counts

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Twenty-three patients had evaluable CD4 counts (Table II). They received a range of 3-6 cumulative cycles of OAC. Ten received OAC alone and had normal CD4 counts; thirteen received IV chemotherapy prior to OAC, and one had a low CD4 count. Twenty-two had normal CD4 counts ranging from 386-2688 cells/ μ L (normal range 359-1570 cells/ μ L). The

patients whose data were not reported were outside the inclusion criteria and all had normal CD counts.

Only one of the 23 (4%) evaluable patients (1.6% of the 62 patients who had immune function testing at any time during OAC) was found to have a low CD4 count (189 cells/ μ L). The patient received 2 cycles of “bridge” chemotherapy, consisting of IV carboplatin (18.7mg/kg/dose), immediately followed by 3 consecutive cycles of OAC. Cumulative doses of OAC at the time of low CD4 count were melphalan 9mg (1.3mg/kg) and carboplatin 80mg (11.6mg/kg). Testing was performed 117 days after completion of IV chemotherapy and 28 days after the third cycle of OAC. PCP prophylaxis had been initiated at the start of IV chemotherapy and was ongoing. This patient experienced more protracted neutropenia than usual during treatment. The patient was evaluated by a pediatric immunologist, diagnosed with hypogammaglobulinemia, and subsequently treated with IVIG. Throughout the immunology work-up and management the patient continued receiving OAC. Repeat immune function tests during OAC treatment demonstrated a normal CD4 count of 1302 cells/ μ L, 165 days post IV chemotherapy and 42 days after the fourth cycle of OAC. Cumulative doses of OAC at the time of normalized testing were melphalan 9mg (1.3mg/kg), carboplatin 140mg (20.2mg/kg), topotecan 0.4mg (0.05mg/kg). The patient went on to receive two additional cycles of OAC, for a total of 6 cycles over a 6 ½ month period, consisting of cumulative doses of melphalan 16mg (2.3mg/kg), carboplatin 240mg (34.8mg/kg), and topotecan 1.4mg (0.2mg/kg). A normal CD4 level of 1068 cells/ μ L was documented 48 days after the final OAC treatment.

Mitogen tests

Twenty-eight patients had evaluable mitogen results, including the 23 patients who fit the inclusion criteria and the 5 patients who were outside the inclusion criteria but had abnormal results. The patients whose data were not reported were outside the inclusion criteria and also had normal PHA specific mitogen levels. Seventeen of the 28 patients had normal PHA specific mitogen test results, ranging from 118360-244406 CPM (normal range: 109576-256486 CPM). Eight received chemotherapy prior to OAC, 9 received OAC alone.

Eleven (39%) of the 28 patients (18% of the 62 patients who had immune function testing at any time during OAC) had low PHA specific mitogen test results (Table III). Ten patients had marginally low PHA results (ranging from 74678-105703 CPM) while only one patient had a very low PHA result of 7272 CPM with a normal CD4 count of 619 cells/ μ L, 109 days after completion of 9 cycles of IV chemotherapy (vincristine, carboplatin, etoposide, cyclophosphamide, and doxorubicin, doses unknown) and 15 days after the third cycle of OAC. Nine patients had received prior IV chemotherapy, with a range of 1-9 cycles. The two patients who did not receive systemic chemotherapy received the highest cumulative doses of OAC out of the 11 patients with low PHA results, however, they did not receive the highest cumulative doses of OAC in the entire cohort. Repeat PHA specific mitogen tests were within normal range for 7/7 patients who were available for repeat testing; normal levels occurred 1½ - 8 months after the initial low test was performed. Four patients were unavailable for repeat testing, including the patient with the lowest PHA result.

Discussion

Prior to this publication there was evidence that retinoblastoma patients receiving OAC develop neutropenia but a lack of data regarding the effect of OAC on T-cell number and function. The low doses of OAC are not believed to be T-cell suppressing, and currently we do not prescribe *Pneumocystis pneumonia* (PCP) prophylaxis for OAC treatment alone. There is no evidence in the literature that any patients receiving OAC for retinoblastoma have developed PCP and to date none of our patients receiving OAC for retinoblastoma have developed PCP.

Pneumocystis carinii was first identified as an opportunistic pathogen in 1973, in 51 children treated for malignancies.⁶ The HIV epidemic in the 1980s increased the investigation of PCP pneumonia prevention. Research revealed host specificity and it was found that the pneumocystis species responsible for human infection was *Pneumocystis jiroveci*. Over time, the pneumonia was then referred to as *Pneumocystis jiroveci* pneumonia, or PJP.⁷ The terms PCP and PJP are both acceptable acronyms for pneumocystis pneumonia.

Several known risk factors for developing PCP have been identified. There is strong evidence that patients have a significant risk of developing PCP with a prolonged CD4 positive T-cell level less than 200, long term administration of glucocorticosteroids, a diagnosis of acute lymphoblastic leukemia, or are the recipient of an allogenic hematopoietic cell transplant. The risk status is not conclusive for patients with prolonged neutropenia (defined as a neutrophil count less than 500 for 7 days or longer), acute myeloid leukemia, or for those receiving treatment with R-CHOP, BEACOPPesc, high dose cytarabine, or temozolomide with concurrent radiation therapy.^{8, 9} Children who develop PCP often have compromised T cell-mediated immunity as their primary risk factor. In neutropenic patients who develop PCP, lymphopenia is typically also present. Therefore, PCP prophylaxis is not necessarily required for neutropenic patients who do not also have lymphopenia.

A lack of data on the baseline incidence of PCP without prophylaxis in non-HIV immunocompromised patients makes it difficult to determine which patients definitely require prophylactic therapy.¹⁰ Children receiving known immunosuppressive therapy affecting T cell mediated immunity should receive prophylaxis for PCP.^{10, 11} Once PCP prophylaxis is initiated it should continue until there is laboratory documented evidence of recovery of T cell-mediated immunity, with a CD4 value > 200.

This retrospective review found 22 of 23 patients (96%) had normal CD4 counts following OAC treatment. Only one patient had a documented CD4 count < 200 during OAC. This patient had received IV chemotherapy four months prior, and was diagnosed with hypogammaglobulinemia during OAC treatment as part of a work-up for prolonged neutropenia. Repeat testing of this patient during and after three additional cycles of OAC demonstrated normal CD4 levels, allowing the patient to stop PCP prophylaxis. Therefore, clinically significant immune suppression appears rare following OAC alone. Patients previously treated with IV chemotherapy may remain immunosuppressed and may benefit from PCP prophylaxis until they have documented immune reconstitution with a CD4 level > 200.

The degree of clinical significance of abnormal PHA specific mitogen test results is uncertain. Eleven out of twenty-eight patients had below normal results. A limitation to this study is that we may have overestimated the risk of low mitogen/PHA levels by including patients with abnormal results who did not fit the eligibility criteria. We felt that overestimating the incidence of low mitogen/PHA levels was more conservative than underestimating the incidence.

Below normal PHA results may indicate impaired T cell function, and an impaired ability for T cells to respond to antigens. Although it had been general practice in our center to test mitogen function after treatment, we were unable to find any evidence to suggest PHA specific mitogen test results should be used to start or stop PCP prophylaxis. Additionally, mitogen tests are time consuming, cost prohibitive, and do not have formal pediatric reference values.¹² The data was included in this report because it could be of future research or clinical benefit. Currently mitogen testing is no longer used by our team.

The implication of the CD4 test results in regards to vaccination during and after OAC treatment is an area of further interest for this patient population. Currently there are no standard guidelines directing vaccination during OAC or revaccination after OAC. Our practice is to hold vaccines during treatment and resume a catch-up schedule when the patient is 3 months post completion of therapy, however the argument could be made for continuing non-live vaccines during treatment, as the patients would likely have a response.

In conclusion, the incidence of a low CD4 count is rare following OAC, and PCP prophylaxis is most likely not necessary in patients receiving OAC alone. Patients who receive immunosuppressive IV chemotherapy may require continued PCP prophylaxis during OAC until an appropriate CD4 count is documented. Further research is needed to fully define the degree of PCP risk in specific populations such as retinoblastoma patients receiving OAC with various agents.

Limitations to this study included the small sample size, single institution, and retrospective review. Following this review we continue our current policy of not initiating PCP prophylaxis for patients receiving OAC alone.

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Abbreviations

MSKCC	Memorial Sloan Kettering Cancer Center
OAC	Ophthalmic artery chemosurgery
IV	Intravenous
PCP	<i>Pneumocystis</i> pneumonia
PHA	Phytohemagglutinin
PJP	<i>Pneumocystis jirovecii</i> pneumonia
CD4	Cluster of differentiation 4
CPM	Counts per minute

Figure 1. Patient Sample Flow Diagram

Table I
Current OAC Drug Doses via Age Algorithm

Intra-arterial Drug Doses				
Age	3-6 months	6-12 months	1-3 years	>3 years
Melphalan	2.5mg	3mg	4mg	5mg
Carboplatin	30mg	40mg	50mg	50mg
Topotecan	0.5-2mg	0.5-2mg	0.5-2mg	0.5-2mg

Gobin, et al, 2011, updated with personal communication, 2016

Table II
CD4 Counts (n=23)

<u>Above lower limit of normal:</u>	
<ul style="list-style-type: none">• n = 22, CD4 count range 386-2688 cells/μL• Test performed a median of 34 days after OAC• Received 3-6 cumulative cycles of OAC• 12 received IV chemotherapy prior to OAC	
<hr/>	
<u>Below normal:</u>	
<ul style="list-style-type: none">• n = 1, CD4 count 189 cells/μL after IV chemotherapy and during OAC• Prior treatment: 2 cycles of IV carboplatin and 3 cycles of OAC at time of testing (cumulative melphalan dose 9mg or 1.3mg/kg, cumulative topotecan 0mg, cumulative carboplatin 80mg or 11.6mg/kg)• CD4 count and abnormal mitogen level normalized through continued OAC treatment and remained normal at completion of OAC treatment	

Table III

Low PHA specific mitogen test results

Patient	PHA results	Prior IV chemo cycles	Days s/p IV chemo	Cycles OAC	Cumulative Melphalan	Cumulative Topotecan	Cumulative Carboplatin	Days s/p OAC
	Normal range (109576-256486 CPM)							
1	7272	9	109	3	14mg (1.16mg/kg)	3mg (0.25mg/kg)	50mg (4.13mg/kg)	15
2	74678	2	118	3	9mg (1.3mg/kg)	0mg (-)	80mg (11.6mg/kg)	28
3	79694	2	127	3	8.5mg (1.21mg/kg)	3mg (0.43mg/kg)	0mg (-)	34
4	91442	2	134	2	6mg (0.83mg/kg)	0mg (-)	0mg (-)	63
5	93897	1	120 [*]	3	11mg (1.15mg/kg)	3mg (0.33mg/kg)	170mg (17.71mg/kg)	23
6	94344	5	146	4 ^{**}	unknown	unknown	unknown	22
7	96072	none	n/a	5	23mg (1.53mg/kg)	9mg (0.6mg/kg)	260mg (17.33mg/kg)	7 months
8	101926	none	n/a	5	20mg (1.33mg/kg)	5mg (0.33mg/kg)	170mg (11.33mg/kg)	57
9	102803	3	16 months	2	0mg (-)	0mg (-)	90mg (13.8mg/kg)	12 months
10	103275	3	122	5	15.5mg (2.15mg/kg)	4mg (0.55mg/kg)	52.5mg (7.29mg/kg)	20
11	105702	3	10 months	3	6mg (1mg/kg)	2mg (0.33mg/kg)	40mg (6.67mg/kg)	7 months

^{*} Date of IV chemotherapy unknown, maximum of 120 days based on day of diagnosis

^{**} Received 3 cycles of OAC in China, doses unknown, immediately prior to 1 cycle of OAC at MSKCC and immune function testing