The Effect of Chemotherapy on Optic Pathway Gliomas and Their Sub-Components: A Volumetric MR Analysis Study

Ben Shofty, MD,1,2* Michal Mauda-Havakuk, MD, PhD,1,3 Lior Weizman, PhD,4 Shlomi Constantini, MD, MSC,1,2 Dafna Ben-Bashat, PhD,5 Rina Dvir, MD,6 Li-Tal Pratt, MD,1,3 Leo Joskowicz, PhD,4 Anat Kesler, MD,1 Michael Yalon, MD, PhD,7 Lior Ravid, BSc,1 and Liat Ben-Sira, MD,1,3

Background. Optic pathway gliomas (OPG) represent 5% of pediatric brain tumors and compose a major therapeutic dilemma to the treating physicians. While chemotherapy is widely used for these tumors, our ability to predict radiological response is still lacking. In this study, we use volumetric imaging to examine in detail the long-term effect of chemotherapy on the tumor as well as its various sub-components. Procedure. The tumors of 15 patients with OPG, treated with chemotherapy, were longitudinally measured using our novel, previously described volumetric method. Patients were treated with up to five lines of chemotherpayy. Sufficient follow-up imaging data, and patient’s numbers, allowed for analysis of two treatment lines. Volumetric measurements of the tumors were segmented into solid-non-enhancing, solid-enhancing, and cystic components. Outcome analysis was done per specific treatment line and for the overall follow-up period. Results. An average reduction of 9.7% (±23%) in the gross-total-solid volume (GTSV) was noted following treatment with vincristine and carboplatin. The cystic component grew under therapy by an average of 12.6% (±39%). When measured over the course of the whole study period, the cystic component grew by an average of 35% (±100%) and the GTSV increased by 12% (±35%). Conclusion. Initial treatment with vincristine and carboplatin seems to have a minimal initial effect, mostly on the solid components. The cystic component in itself seems to be unaffected by chemotherapy, and contributes to the subsequent growth of the total volume. During the overall treatment period, both solid and cystic components grew regardless of combined treatment methods. Pediatr Blood Cancer © 2015 Wiley Periodicals, Inc.

INTRODUCTION

Optic pathway gliomas (OPG) are the most common primary neoplasm of the optic pathway in children, comprising 5% of brain tumors in this population [1]. These tumors are especially prevalent among neurofibromatosis I (NF1) patients. OPG are mostly low-grade gliomas (WHO I), diagnosed according to their typical MR appearance and rarely require biopsy [2–4]. Over the long follow-up period, these tumors tend to have an erratic natural history. While some progress, and require multiple treatment modalities, others remain stable for many years [5]. A minority of these tumors spontaneously regresses [6]. Long-term management of these patients is based upon frequent MR studies, together with clinical and neuro-ophthalmological evaluations when possible [7]. The timing of follow-up is adjusted (slowly reduced or intensified) based on clinical and radiological findings. Treatment is initiated only if there is clear-cut radiological progression or deterioration in vision [8,9]. Treatment is currently based on chemotherapy, with vincristine and carboplatin (VCR/CRB) most commonly serving as first-line agents [10–12]. Other treatment options, frequently used in case of carboplatin allergy or failure of the first line treatment, are weekly vinblastine [13], and other multi-agent regimes [14]. Temozolomide which was used in the past is no longer recommended [15].

Management decisions regarding treatment initiation and efficacy are based on visual ability, when available, and the change in tumor size as evaluated by the radiologist. When considering the benign nature of these tumors and the severe functional (visual) impairment that they may cause, it seems that the main challenge of treatment is stabilization or improvement of visual ability. Unfortunately, visual preservation using chemotherapy has been shown in recent studies to be less successful than once thought [16–19]. In addition, perhaps due to the fact that the young age of these patients makes the periodic assessment of vision a challenging task at times, studies attempting to assess functional response to treatment have failed to demonstrate a correlation between the radiological changes of the tumor and the visual outcome [16,20]. This lack of correlation may very likely be due to the fact that to date, most management decisions of OPG patients are based on radiological-linear measurements of the tumor that are neither accurate nor reproducible. Due to these factors it is crucial to introduce more accurate response assessment methods that may bridge the gap between visual changes, and radiology in OPG.

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site.

Abbreviations: CRB, carboplatin; DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; FSE, fast spin echo; FSPGR, fast spoiled gradient echo; NF1, neurofibromatosis I; OPG, optic pathway gliomas; RAP, rapamycin; TAR, tarceva; TMZ, temozolomide; VBL, vinblastine; VCR, vincristine; VNR, vinorelbine

1The Gilbert Israeli Neurofibromatosis Center, 2Pediatric Neurosurgery Dana Children’s Hospital, 3Pediatric Radiology Unit, 4Functional Brain Center, The Wohl Institute for Advanced Imaging, 5Pediatric Hematology-Oncology, all at the Tel-Aviv Medical Center and The Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel, 6School of Engineering and Computer Science, The Hebrew University of Jerusalem, Jerusalem, Israel, 7Pediatric Hematology Oncology, Sheba Medical Center, Tel-Hashomer, Israel

Grant sponsor: Israeli Cancer Research Foundation (ICRF); Grant sponsor: Gilbert Israeli Neurofibromatosis Center (GINFC)

Conflict of interest: Nothing to declare.

Shofty Ben and Mauda-Havakuk Michal contributed equally to this study.

*Correspondence to: Dr. Ben Shofty, Department of Neurosurgery, and The Gilbert Israeli Neurofibromatosis Center, Tel-Aviv Medical Center, 6th Weizmann St., Tel-Aviv 64239, Israel. E-mail: shoftyben@gmail.com

Received 8 December 2014; Accepted 26 January 2015

© 2015 Wiley Periodicals, Inc.
DOI 10.1002/pbc.25480
Published online in Wiley Online Library (wileyonlinelibrary.com).
patients, enabling better identification of patients that may benefit from treatment.

In this study, we retrospectively investigated the effect of chemotherapy on OPG, including assessing the value of tumor sub-segmentation, utilizing a volumetric measurement method that we developed and described previously [21,22]. Using these methods we attempted to identify sub-groups of patients that may respond better to chemotherapy.

METHODS

This study was approved by the institutional ethics committee at the Tel-Aviv Medical Center. All OPG patients under follow-up care of the Israeli Pediatric Neuro-Oncology Program and the Gilbert Israeli NF Center over the years 1990–2013 were considered for this study. Inclusion criteria were: a hypothalamic/chiasmatic tumor (Dodge II/III), treatment with chemotherapy, and at least three MR imaging studies, with at least one MRI done before initiating treatment. Patients with tumors epicentered outside of the hypothalamic/chiasmatic area, and patients with insufficient follow-up data, were excluded.

Volumetric Measurements

Volumetric measurements were done utilizing a method previously described by us [21,22]. The procedure applies our own pre-processing algorithm, followed by total volume and sub-segmentation measurement completed using Analyze (Version 9.0, Mayo Clinic, Rochester, MN). This process, illustrated in Figure 1, is described briefly in this section.

Measurement Methodology

Step 1. Intra-scan co-registration: Registration of the different sequences of a single MR study (baseline or follow-up exam) is done using the rigid registration tool of the Statistical Parametric Mapping software package (SPM, Institute of Neurology, University College of London, UK). This enables an accurate comparison between T1 and T2 slices for each patient. Step 2. Measurement: Using the Analyze Direct Software (Version 9.0, Mayo Clinic), in a semi-automated fashion we measure the tumor volume and segment the tumor into three components: solid, non-enhancing; solid, enhancing component, and cystic. Step 3. Inter-scan registration and comparison: Sequential registration is performed, matching various consecutive MRI studies of the same patient to the baseline exam using the SPM software package. This enables accurate monitoring of changes in the tumor. Step 4. Tumor delineation and segmentation updates: To minimize inter/intra-observer variability, we overlay the patient’s previous tumor border demarcation markings on the new imaging study. This enables immediate detection of subtle changes in tumor size and components. The tumor border delineation and its internal classification are updated according to the data of the current scan.

Fig. 1. Graphical representation of our preprocessing and measurement algorithm. Bracketed numbers correspond to the technical step described in the text.

Pediatr Blood Cancer DOI 10.1002/pbc
Using this semi-automated co-registration and internal classification method, we reviewed the MR images acquired during routine oncological follow-up for each patient in the study group. All measurements are routinely done by a trained technician, verified and corrected by the radiology resident (M.M.H.), and approved by an experienced pediatric neuro-radiologist (L.B.S.).

Treatment Evaluation

We performed three different analyses to evaluate the effect of treatment on tumor volume. The gross-total volume of the tumor was analyzed as well as the changes in its sub-components.

Overall treatment analysis effect. This analysis begins with the first chronological MR study, acquired before initiation of treatment (3–0 months prior to initiation of chemotherapy). This MR is defined as the base-line study (X1). The last available imaging study served as an outcome study (X2). Percentage of change during the entire follow-up period, for each component separately as well as for the total solid volume, was calculated (X2-X1/X1). Overall treatment in this context refers to all chemotherapy and radiation treatments administered during this period. The effects of surgical resections were excluded from this analysis. A change of more than ±20% in tumor volume was set as the threshold in order to define response or progression.

Single line analysis. This analysis focused on the effect of a single, specific line of treatment on the volumetrics of the tumor. For this calculation we included the first chronological MR study acquired before initiation of treatment as the base-line study (X1). As the outcome study we included an imaging study done following completion of the treatment protocol. The patient must have received at least 6 months of treatment, and the outcome MR must have been completed less than 6 months following treatment termination (X2). This analysis was performed for two individual treatment lines: vincristine/carboplatin (VCN/CRB) and vinblastine (VBL).

Growth rate evaluation. In an experimental attempt to establish an objective standard for follow-up of low-grade tumors, we developed a novel approach to calculating tumor growth rate. These evaluations were completed only when the necessary imaging data were available: at least two imaging studies done prior to treatment initiation (Pre1, Pre2), and at least two following termination of treatment (Post1, Post2). The tumor growth ratio was calculated according to this formula: pre-treatment growth ratio = (pre2-pre1)/delta time in months. The same formula was applied to the post-treatment measurements. Thus the growth ratio in mm³/month was calculated, and the pre-treatment rate was compared to post-treatment rate.

In an attempt to identify patients that may respond better to treatment, the complete patient cohort was divided into two groups according to tumor type at presentation: Group A were patients with a cystic component, and Group B were patients without a cystic component. Treatment effect was also analyzed according to NF1 status (patients with or without NF1) and treatment indications (radiological, visual, or both).

RESULTS

Patient Population

A total of 17 patients (12 males, 5 females) met the inclusion criteria. Two patients were excluded for insufficient follow-up data.

Treatment Effect on OPG Patients

We conducted an overall treatment analysis on the entire group, and a first-line analysis to assess specific treatment efficacy. Figure 3 illustrates the average group response for each type of analysis. It is clear that response is minimal for the first line of treatment and nearly non-existent for the overall treatment period. Note that the cystic component is consistently unaffected by treatment, growing by 12% and 35% over the first line and overall treatment periods respectively. During the first line treatment
period, 3 out of 15 treated patients experienced a response to treatment, 8 patients displayed stabilization/no change in their tumor, and 4 patients experienced progression. During the overall treatment period, three patients (same responders from first-line analysis) responded to the various modalities, seven patients remained stable, and five experienced tumor progression. Demographics and response rate for the different analysis groups can be seen in Table I.

Single Treatment Line Analysis

In order to evaluate response to individual treatments, we isolated individual lines of treatment and calculated tumor volumetrics before and after each specific treatment. This section focuses on the single line of treatment analysis for VCR/CRB, for which data were available for all 15 patients. In addition, we calculated a tumor growth rate for four patients treated with VCR/CRB for whom we had more extensive pre- and post-treatment imaging records.

Figure 4A summarizes tumoral changes for first line analysis (A), and for overall treatment period analysis (B), dividing the patients between patients with, and without a cystic component at presentation (Fig. 4A). Several other risk factors (NF status, treatment indication, tumor grade at presentation) were examined also. Results are presented in Supplementary Table S1, as no significant difference was found using this parcellation.

Tumor Growth Rate Analysis

Tumor growth rate data (for the VCR/CRB treatment period) was available for four patients. Two of these had a cystic component at presentation (patients 3 and 4), and two did not (patients 1 and 2). For these four patients, the tumor grew by an average of 63 mm³/month before starting treatment with VCR/CRB. When measured following treatment, we noted a decline in growth rate to 30 mm³/month. In the two patients with a cystic component at presentation, growth was accelerated following treatment. In the two patients without a cystic component at presentation, the growth rate was reduced (Fig. 5).

Vinblastine

To evaluate the effect of VBL on OPG, we grouped together all patients that received VBL either as 2nd or 3rd line and had sufficient follow-up data during the treatment period. Complete data were available for five patients. Mean time on treatment was 7.8 months (range 5–10 months). During this period, three patients displayed a massive increase of approximately 200% in tumor solid component at presentation (patients 3 and 4), and two did not (patients 1 and 2). For these four patients, the tumor grew by an average of 63 mm³/month before starting treatment with VCR/CRB. When measured following treatment, we noted a decline in growth rate to 30 mm³/month. In the two patients with a cystic component at presentation, growth was accelerated following treatment. In the two patients without a cystic component at presentation, the growth rate was reduced (Fig. 5).

Table I. Demographics, Follow-Up, and Response Rate for Each Analysis Subset

<table>
<thead>
<tr>
<th>Analysis</th>
<th>N</th>
<th>Follow-up time (months)</th>
<th>Number of NF1 patients</th>
<th>Avg. age at first imaging (years)</th>
<th>Responded</th>
<th>Stabilized</th>
<th>Progressed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall analysis</td>
<td>12</td>
<td>53</td>
<td>10</td>
<td>6.5</td>
<td>3</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>VCR/CRB</td>
<td>15</td>
<td>19.6</td>
<td>10</td>
<td>6</td>
<td>3</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>5</td>
<td>7.8</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

n, number of patients; NF1, neurofibromatosis I; Avg., average; VCR, vincristine; CRB, carboplatin.

Pediatr Blood Cancer DOI 10.1002/pbc
In this study, we have evaluated the use of our volumetric measurement methodology on a group of patients with long-term follow-up. We looked into the effect of single-line chemotherapy treatment as well as the long-term changes that occur following various oncological treatment modalities.

Accurate, evidence-based assessment of treatment efficacy is difficult for OPG patients, given the rarity of patients, significant clinical diversity, and radiological heterogeneity of OPG. Discrepancy between functional visual outcome and radiological changes further complicates this foggy picture [16,17]. In current clinical practice, these tumors are usually assessed anatomically using linear measurements. These measurements are error-prone and highly user-dependent, especially when comparing multiple recurrent imaging studies in which changes are subtle. Considering all these factors, it is clear that traditional radiological response evaluation methods are simply not sensitive enough to accurately assess treatment effect on OPG. Because vision is not assessable in some OPG patients due to their young age or limited cooperation, alternative, more sensitive radiological-response-evaluation methods are needed.

Volumetric measurements, although slowly gaining popularity, are still not routinely used in most studies, or in routine clinical follow-up of these patients. Our method [22] utilizes publicly available software tools and provides an affordable, easy to use solution for volumetric measurements and sub-segmentation of OPG. In the current study, we demonstrate a useful application of volumetric-based analysis. Specifically, we characterized sub-groups of OPG patients according to their different sub-components, and looked for a correlation between these groups and response to chemotherapy. We also divided our patients into two morphological groups, patients with (Group A) and without (Group B) a cystic component at presentation, in an attempt to identify a radiological tumor phenotype that correlates with response to treatment. We utilized two different methods of analysis: overall analysis of the tumor course during the entire follow up period, and analysis of tumor changes induced by a single first-line type of chemotherapy. In addition, we introduced a novel concept of response assessment, via tumor growth rate measurements.

The efficacy of chemotherapy for OPG has been questioned in recent literature [16,18,19]. Original data dealing with the effect of standard therapeutic lines on these tumors is nearly 25 years old [10–12]. While the accepted first line of VCR/CRB chemotherapy has been widely used for more than two decades, no careful re-assessment was done during this period following obvious advances in imaging technology. Data from several case series-based publications argued that the value of chemotherapy in these patients, when focusing on vision, is not satisfactory, and that visual response does not correlate with radiological response [16,19,25]. In a larger, multi-center study published recently, one third of the patients experienced some visual improvement following first-line chemotherapy; however, once more, a poor correlation between radiographic and VA outcomes was noted [20]. This anatomical–functional dissociation, coupled with disappointing results from other studies, clearly shows that better radiological outcome assessment measures are needed.

Our results demonstrate that following first-line chemotherapy treatment with VCR/CRB, approximately 73% of the patients demonstrated either stability or a positive response to treatment when evaluating the solid tumor components. The tumoral cyst, however, did not seem to be affected by first line treatment with VCR/CRB. Following first-line treatment, approximately 66% of our patients required at least one more treatment modality. Despite the fact that 73% (11 patients) either stabilized or responded...
following initial treatment, 66% of these patients (6 out of the 11) required second-line treatment (for a total of 10/15 patients requiring second-line treatment). The reason for additional treatment was either functional visual deterioration (n = 3), or due to further tumor progression noted on MR images following the stabilization period (n = 3). This high second-line treatment rate highlights the short-term effect of the accepted first-line protocol. This high percentage of clinical and radiological deterioration is consistent with evidence from other clinical series [16,26].

Our overall treatment period analysis results are also disappointing, with average enlargement of approximately 12% in the volume of the solid components following various types of chemotherapy and radiation (excluding surgical resections). The fact that despite multiple types of treatment protocols (average 2.3) the overall solid radiological outcome is marked growth challenges the efficacy of the available treatments. The large standard deviation of the volumetric changes in our study may imply that more than one biological group exists in this cohort. Unfortunately due to the small number of patients we did not find any significant radiological biomarkers for this.

When looking at the response rate, only three patients responded to overall treatment. These were the same responders from the first-line analysis. The other patients all eventually progressed. In all patients that presented with a cystic component, the cystic component showed marked enlargement despite various treatment lines, growing an average of 35%. An interesting finding is evident from this group, for patients that presented with a cyst, the solid components of the tumor are more likely to respond to treatment, even as the treatment seems to have no impact at all on the cystic component.

Tumor growth rate is a novel concept that relies on accurate volumetric measurements in order to assess the baseline tumor growth rate, measured in cubic centimeter per time unit. A baseline measurement can be compared to growth rate during and after treatment in order to assess an individual patient’s response. This concept may help us understand the initial biology of the tumor, and assist in making treatment decisions for patients in which the response, when measured in volume alone, is unclear. Four patients in this study provided sufficient data to evaluate tumor growth rate. While a small benefit from therapy can be seen on average for this group, this average value is misleading. In reality, two of the patients displayed significant immediate response to the first-line treatment, while the other two patients displayed a marked increase in their tumor growth rate following treatment. Interestingly, the two patients that responded had a cystic component at presentation, while the two non-responders did not have a cyst.

We are aware of the methodological problems associated with this small, proof-of-concept study. Our series represent a highly selected group of patients that were referred to a tertiary referral center, with a strong neurosurgical orientation, receiving multiple types of treatment and MR studies. These patients, however, clearly represent those that pose a difficult therapeutic dilemma for the multidisciplinary team. In addition, our study suffers from the known shortcomings of a retrospective study. This paper should be considered as a motivation for more extensive volumetric follow-up, including analysis of different treatment models.

In the future, with the technological advances that are now publicly available, we believe that careful volumetric measurements with assessment of tumor growth rate will become widely used for OPG and other low-grade tumors. Isolation of the cystic component from the solid bulk of the tumor is important, especially for patients in which there is enlargement of the cyst without significant change in the solid component. In these patients, cyst management procedures may be considered instead traditional chemotherapy.

CONCLUSIONS

Sub-segmentation of treated OPG may aid in identifying patients who may benefit from chemotherapy. From our limited series, it appears that patients presenting with a cystic component may respond better to treatments in general and to treatment with VCR/CRB in particular. Careful volumetric measurements done on our limited group demonstrate disappointing overall results for patients with progressive OPG. Larger, prospective clinical trials utilizing volumetric measurements are needed to better evaluate the effect of chemotherapy on OPG.

ACKNOWLEDGMENTS

This study was supported by a grant from the Israeli Cancer Research Foundation (ICRF) to SC and BS and by the Gilbert Israeli Neurofibromatosis Center (GINFC).

REFERENCES

16. Shofty B, Ben-Sira L, Freedman S, Yalon M, Dvir R, Weintraub M, Toledano H, Constantini S, Kesler A. Sub-segmentation of treated OPG may aid in identifying patients who may benefit from chemotherapy. From our limited series, it appears that patients presenting with a cystic component may respond better to treatments in general and to treatment with VCR/CRB in particular. Careful volumetric measurements done on our limited group demonstrate disappointing overall results for patients with progressive OPG. Larger, prospective clinical trials utilizing volumetric measurements are needed to better evaluate the effect of chemotherapy on OPG.

Pediatr Blood Cancer DOI 10.1002/pbc


