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Original Article

Carboplatin hypersensitivity reaction in pediatric patients with low-grade glioma

A Canadian Pediatric Brain Tumor Consortium experience

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Abstract



BACKGROUND.

Carboplatin-based regimens have demonstrated activity in pediatric patients with low-grade glioma (LGG). However, carboplatin hypersensitivity reaction (Cb HSR) represents a common and limiting factor for the continuation of therapy.

METHODS.

The objectives of this study were to describe the prevalence, characteristics, and management of Cb HSR and to detail their impact on outcome. The authors conducted a comprehensive, national, retrospective review of children who were diagnosed with LGG between 1985 and 2004 and received treatment with carboplatin.

RESULTS.

One hundred five patients from 10 Canadian centers were included. The median patient age at diagnosis was 3.5 years (range, 0.3-16.8 years), and 33 patients (31.4%) had neurofibromatosis type 1. Carboplatin was administered monthly in 46 children and weekly in 59 children. Forty-four patients (41.9%) developed Cb HSR after a median of 10.5 infusions (range, 3-39 infusions). Cb HSR occurred significantly earlier among children on the weekly schedule (4.4 months vs 9.1 months; $P = .02$). The first allergic reaction was grade I or II in 36 patients (82%). The cumulative incidence of Cb HSR increased with the number of infusions, and there was no evidence of a plateau. The only predictive factor was being a girl rather than a boy ($P = .02$). Thirty-four of 44 patients with Cb HSR were re-exposed to carboplatin, and 24 of 34 patients (70.5%) had recurrent Cb HSR. A desensitization approach did not provide any advantage compared with premedication alone for altering Cb HSR. The median number of additional Cb infusions delivered was 4 (range, 0.5-34 infusions). The effect of Cb HSR on the 5-year progression-free survival rate was not statistically significant ($P = .1$).

CONCLUSIONS.

Forty-two percent of children with LGG who received carboplatin regimens experienced Cb HSR. Most rechallenged children had recurrent Cb HSR despite Cb HSR-altering regimens. Cb HSR did not have an impact on progression-free survival. Cancer 2008. © 2007 American Cancer Society.

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Article Text

Carboplatin, a second-generation platinum compound, is used widely for the treatment of solid tumors in adults, especially for ovarian and lung cancers. Carboplatin usually is tolerated well and has moderate side effects. However, greater and prolonged use of carboplatin has resulted in an increased incidence of carboplatin-related hypersensitivity reaction (Cb HSR).^[1] The incidence of Cb HSR in patients with ovarian cancer who were treated on carboplatin-containing regimens was up to 16%.^[2-5]

In children, carboplatin is used in the treatment of various solid tumors, such as neuroblastoma, retinoblastoma, germ cell tumors, hepatoblastoma, and several types of benign and malignant brain tumors.^[6] Cb HSR has been described mostly in pediatric series of low-grade glioma (LGG), in which the reported incidence ranges from 7% to 32%; however, recent series consistently have

suggested a higher incidence of approximately 30%.^[7-10] Although the characteristics Cb HSR have been described extensively and analyzed in large cohorts of adult patients, its description in the pediatric population remains limited.

To avoid the discontinuation of carboplatin in children who have developed Cb HSR, various protocols of desensitization and/or premedication have been proposed. However, very little is known regarding the outcome of such strategies, and reports of desensitization are limited primarily to small series.^{[9][11-13]} To date, no large pediatric series on Cb HSR and its management has been described.

The primary objective of the current study was to describe the prevalence of Cb HSR in an unselected national cohort of children with LGG who received carboplatin-containing regimen. The secondary objectives were to determine predictive factors for Cb HSR; to describe the subsequent management of Cb HSR in children, including the use of premedication and/or desensitization; and to determine whether the occurrence of Cb HSR has an impact on outcome.

MATERIALS AND METHODS



This retrospective study was open to all centers in the Canadian Pediatric Brain Tumor Consortium (CPBTC), which is a group of 17 Canadian pediatric institutions that collaborate and develop research in pediatric neuro-oncology. Participating centers communicate on a monthly basis through a telemedicine system. Eligible patients were children with LGG who fulfilled the following criteria: 1) diagnosed between 1985 and 2004, 2) age <18 years at diagnosis, and 3) pathologically confirmed diagnosis of LGG except for optochiasmatic tumors with typical features of LGG on neuroimaging studies, especially in the context of neurofibromatosis type 1 (NF1). Tumors included were World Health Organization grade 1 and 2 LGG tumors, including pilocytic astrocytoma and pilomyxoid variant.^{[14][15]} Tumors that occurred anywhere within the central nervous system could be included. Exclusion criteria were previous treatments with radiation and/or chemotherapy before carboplatin-based chemotherapy. Surgical resection before carboplatin-based treatment was defined as gross total resection if there was no residual disease on postsurgical imaging studies, biopsy if <10% of the tumor was removed, and incomplete resection for all remaining patients who underwent surgery. The evaluation of tumor response to chemotherapy was based on radiology review when available and/or radiology reports. A complete response was defined as no detectable disease. A partial response was defined as a decrease >50% in tumor size, and an objective effect was defined as a decrease >25% but <50% in tumor size. Progressive disease was defined as an increase in tumor size >25%, and stable disease (SD) was used to classify all other situations.

Several different carboplatin-based regimens were used over the study period. Carboplatin was administered either monthly (median dose, 560 mg/m² per infusion) or weekly (175 mg/m² per infusion) with or without vincristine with a planned duration of treatment ranging from 12 months to 18 months.

In patients with Cb HSR, investigators were asked to describe the chronology and the pattern of symptoms and to grade the severity of the reaction according to the Common Terminology Criteria for Adverse Events (version 3.0) (see Table 1).^[16] They provided information on subsequent management (continuation or discontinuation of carboplatin, desensitization techniques) and outcome. The study was approved by the research ethics board of each participating institution.

Table 1. Allergic Toxicity Grading According to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 3.0

Grade I	Grade II	Grade III	Grade IV Anaphylaxis
Transient skin rash	Urticaria, hives	Face and neck swelling	
	Dyspnea, mild bronchospasm (=cough without wheezing)	Bronchospasm wheezing requiring parenteral medication	Respiratory distress, cyanosis, shortness of breath

Drug fever <38°C	Drug fever <38°C	Serum sickness (=arthralgia, lymphadenopathy, joint pain, myalgia)	Hypotension, tachycardia, cardiac arrest, loss of consciousness
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Statistical Analysis

To address the primary objective, the prevalence of Cb HSR was described. Cumulative incidence curves were used to describe the probability of developing Cb HSR according to the length of exposure to carboplatin and the number of courses of carboplatin administered. Potential predictors of Cb HSR were assessed by using chi-square analysis or the Fisher exact test for categorical variables and logistic regression for continuous variables. The Kaplan-Meier method was used to estimate probabilities of progression-free survival (PFS). The potential impact of Cb HSR on survival was examined by using the log-rank test. Statistical significance was considered as a *P* value <.05. All statistical analyses were performed using the SAS statistical program (SAS-PC, version 8.2; SAS Institute Inc., Cary, NC)

RESULTS



Patient Population

Ten centers participated with a total of 111 eligible patients. Two patients were excluded because of insufficient data, and 4 patients were excluded because they still were receiving carboplatin chemotherapy at the time of analysis. Therefore, 105 patients were included in this study. Table 2 illustrates the population's characteristics. Tumor locations outside the diencephalon included the spinal cord, brainstem, posterior fossa and tectal region, cerebral hemisphere, and isolated optic nerve. Of the 79 children with histologically proven diagnoses, 73 had pilocytic astrocytoma or low-grade astrocytoma not otherwise specified. Other pathologic diagnoses included pilomyxoid astrocytoma (n = 3 patients), mixed oligodendroglioma (n = 1 patient), grade 2 astrocytoma with dense desmoplastic reaction (n = 1 patient), and invasive ganglioglioma (n = 1 patients). Nine patients had documented dissemination at presentation. Of the 75 patients who underwent surgery at the time of diagnosis, 33 patients underwent a biopsy only, and 40 patients underwent an incomplete resection. Two patients who underwent an initial gross total resection eventually progressed and required chemotherapy.

Table 2. Overall Population Clinical and Treatment Characteristics

Patient characteristics	No. of patients (%), N = 105
Median age at diagnosis of low grade glioma [range], y	3.5 [0.3-16.8]
Age <12 mo at diagnosis of low grade glioma	17 (16.2)
Boys/girls	44/61
NF1	33 (31.4)
Diencephalic location	82 (78.1)
Monthly Cb administration	46 (43.8)
Median duration of treatment [range], mo	11 [1-20]
Median no. of Cb infusions [range]	12 [1-30]
Median cumulative dose of Cb [range], mg/m ²	6720 [560-13.000]
Weekly Cb administration	59 (56.2)
Median duration of treatment [range], mo	12 mo [0.7-20.9]
Median number of Cb infusions [range]	34 [4-57]

Cumulative dose of Cb [range], mg/m ²	5950 [700-9975]
Prophylactic premedication for Cb	15 (14.2)

Cb indicates carboplatin; NF1, neurofibromatosis type 1.

Carboplatin Therapy

The median time from diagnosis to the initiation of a carboplatin-based chemotherapy regimen was 1.4 months (range, 0.1-130.9 months). Carboplatin was received as a single agent by 7 patients, in combination with etoposide by 1 patient, and with vincristine by the remaining patients. Carboplatin was administered monthly in 46 patients (43.8%) patients for a median total duration of 11 months (range, 1-20 months) and weekly in 59 patients (56.2%) for a total duration of 12 months (range, 0.7-20.9 months) (Table 2). Prophylactic premedication (corticosteroid and/or antihistamine) in the absence of a history of hypersensitivity reaction was received by 15 children (14.5%).

Cb HSR

Forty-four patients (41.9%) developed Cb HSR. The median time from treatment initiation to Cb HSR was 6.5 months (range, 0.4-15.4 months) after a median of 10.5 carboplatin infusions (range, 3-39 infusions). Cb HSR occurred significantly earlier during the weekly schedule, at median of 4.4 months (range, 0.4-15.4 months), compared with a median of 9.1 months (range, 3.1-14.6 months) on the monthly schedule ($P = .02$). The occurrence of hypersensitivity reaction was not related to a specific cumulative dose of carboplatin. The cumulative incidence of Cb HSR increased with the number of infusions without any plateau effect (Fig. 1).

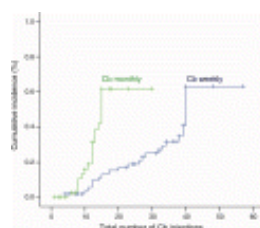


Figure 1. Cumulative incidence of carboplatin (Cb) hypersensitivity reaction according to Cb administration schedule.

[\[Normal View 14K\]](#) | [Magnified View 34K](#)

Table 3 illustrates that, among demographic factors, only sex was associated significantly with Cb HSR. Of the children with Cb HSR, 32 of 44 patients (72.7%) were girls compared with 29 of 61 girls (47.5%) among the patients without Cb HSR ($P = .02$); thus, girls had a relative risk for Cb HSR of 1.92 (95% confidence interval, 1.12-3.30). Age, NF1 status, and tumor location were not associated with Cb HSR. The schedule of carboplatin administration (weekly or monthly) did not significantly influence the incidence of Cb HSR. Five of 15 patients who received prophylactic premedication developed Cb HSR (2 patients developed grade I Cb HSR, 1 patient developed grade II Cb HSR, and 2 patients developed grade III Cb HSR). Prophylactic premedication did not prevent Cb HSR significantly and did not influence the severity of the reaction (grade III and IV toxicity; 40% vs 15.3%; $P = .22$).

Table 3. Comparison Between Carboplatin Allergic and Nonallergic Patients

Criteria	Cb HSR status: No. of patients (%)		
	Positive, N = 44	Negative, N = 61	P
Median age [range] at diagnosis of low-grade glioma, y	2.9 [0.3-16.8]	4.9 [0.4-13.2]	.3
Age <12 mo	7 (15.9)	10 (16.4)	1.0
Girls	32 (72)	29 (47.5)	.02
NF1	13 (29.5)	20 (32.8)	.9
Diencephalic tumor	33 (75)	49 (80.3)	.7

Cb weekly	25 (56.8)	34 (55.7)	1.0
Cb monthly	19 (43.2)	27(44.3)	
Prophylactic premedication for Cb	5 (11.4)	10 (16.4)	.6

Cb indicates carboplatin; HSR, hypersensitivity reaction; NF1, neurofibromatosis type 1.

Of the 44 children who developed Cb HSR, the severity of the first reaction was grade I or II in 36 patients (82%), grade III in 6 patients (13.6%), and grade IV in 2 patients (4.6%) (Table 4). Data on symptoms at the onset of Cb HSR relative to carboplatin infusion times were available in 28 patients. Most of the reactions occurred half-way through the infusion (n = 16 patients) or at the end of the infusion (n = 10 patients). One patient had symptoms at initiation of the infusion, and another patient developed delayed skin rash (grade I) >12 hours after completing the infusion. After the first episode of Cb HSR, carboplatin was discontinued in 10 patients. The reason for discontinuation was reported as the physician's decision in 9 patients without any correlation to the severity of the initial hypersensitivity reaction (3 grade I reactions, 3 grade II reactions, 3 grade III reactions, and 1 grade IV reaction). Six of those patients did not receive any further treatment, and 4 patients were switched to another chemotherapy regimen (2 patients switched to combined vincristine and etoposide; 1 patient switched to vinblastine; and 1 patient switched to combined procarbazine, carmustine [CCNU], and vincristine [PCV]).

Table 4. Severity of Carboplatin Hypersensitivity Reaction

Grade of Cb HSR	No. of patients (%)	
	First reaction, N = 44	At time of Cb re- exposure, N = 24
I	16 (36.4)	5 (20.3)
II	20 (45.4)	9 (37.5)
III	6 (13.6)	9 (37.5)
IV	2 (4.6)	1 (4.2)

Cb indicates carboplatin; HSR, hypersensitivity reaction.

Among the 44 patients who developed Cb HSR, 34 patients (77.2%) were re-exposed to carboplatin with desensitization, premedication, or both. Premedication consisted of antihistamine administration with or without corticosteroid and was initiated from 3 days to 1 hour before carboplatin infusion; in some patients, it was continued for 24 hours after carboplatin infusion. Desensitization consisted of a progressive increase in the rate of the carboplatin infusion over various periods (from 1 hour to 6 hours) according to previously described schedules.^{[11][12]} Of the 34 re-exposed patients, 21 patients initially received premedication alone without a desensitization schedule. Desensitization subsequently was added in 3 patients who continued to have signs of Cb HSR despite premedication. In total, 18 patients were re-exposed with premedication alone, and 12 patients were re-exposed with both premedication and desensitization. The 4 remaining patients were rechallenged without any premedication or desensitization and were managed symptomatically with steroid and/or antihistaminic or with a reduced infusion rate if they had recurrent symptoms.

By using premedication alone, 10 patients (55.5%) were able to complete their carboplatin treatment, including 7 patients who had no further allergic manifestations (38.8%). Among the 12 patients who underwent desensitization and premedication, only 1 patient (8.3%) was able to complete his carboplatin therapy ($P = .018$). Three of the 4 patients who were managed only symptomatically completed their carboplatin therapy. In the fourth patient, carboplatin therapy was discontinued at the request of the parents.

Twenty-four of 34 rechallenged patients (70.5%) experienced recurrent Cb HSR. Upon re-exposure, 4 of 18 patients (22.2%) who received premedication alone and 7 of 12 patients (58.3%) who received both desensitization and premedication had worsening of their hypersensitivity symptoms ($P = .05$). However, the incidence of grade III and IV symptoms at the time of carboplatin re-exposure did not differ significantly between the group that received premedication alone (44.4%)

compared with the group that received both desensitization and premedication (41.6%; $P = .4$). The median number of additional carboplatin infusions delivered with altering Cb HSR therapies was 4 (range, 0.5-34 additional infusions).

Because of recurrent hypersensitivity symptoms despite altering Cb HSR therapies, carboplatin was discontinued in 20 patients. Four patients were observed without further chemotherapy, 2 patients underwent surgical resection, and 14 received another noncarboplatin-containing chemotherapy regimen, including 7 patients who received weekly vinblastine; 4 patients who received either combined thioguanine, procarbazine, and CCNU or combined thioguanine and PCV; and 3 patients who received another line of chemotherapy. The median duration of second-line chemotherapy was 7 months (range, 2-14 months). None of the patients received radiotherapy.

Impact of Cb HSR on Outcome

With a median follow-up of 5.1 years (range, 0.3-16.7 years) after diagnosis, 57 patients (54.3%) required further treatment for disease progression or relapse at a median of 21.3 months (range, 0.6-95.9 months). Fourteen (24.5%) progressions occurred during administration of the carboplatin-based regimen.

In the entire group, the 5-year PFS and overall survival (OS) rates were $49.6\% \pm 5.5\%$ and $91.5\% \pm 3.2\%$, respectively. The 5-year PFS rate did not differ significantly between patients who did and did not develop Cb HSR ($53.9\% \pm 9.4\%$ vs $45.7\% \pm 6.8\%$, respectively; $P = .1$) (Fig. 2).

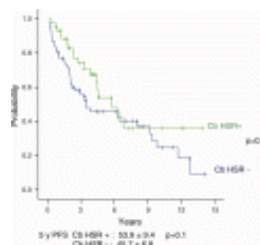


Figure 2. Progression-free survival (PFS). Cb HSR indicates carboplatin hypersensitivity reaction; +, positive; -, negative.

[\[Normal View 16K\]](#) | [Magnified View 40K](#)

In trying to understand why PFS did not differ between patients with and without Cb HSR, we compared the total duration of chemotherapy in both groups (including initial carboplatin and subsequent regimens after Cb HSR). The median total duration of chemotherapy did not significantly differ for patients who did and did not experience Cb HSR (13.2 months and 11.3 months, respectively).

DISCUSSION



The results from this retrospective, cooperative study indicated that 42% of children with LGG who were received a carboplatin-based chemotherapy regimen developed Cb HSR during the course of their treatment. Our findings are important, because, to our knowledge, this study represents the largest pediatric series to date focusing on Cb HSR in LGG and its specific management.

This prevalence of Cb HSR is greater than what was reported in other pediatric studies. In their initial reports on the carboplatin-vincristine combination, Packer et al. quoted a frequency of 7%.^[7]^[17] In a series of 29 children, Lazzareschi et al. reported 6 patients (20%) who developed Cb HSR.^[9] More recently Gnekow et al. reported the results of the German Hirntumor (HIT)-LGG 1996 protocol, in which 32% of 123 patients developed Cb HSR using a monthly schedule of administration.^[10] The lower prevalence of Cb HSR in previous reports may be related to an underreporting of mild reactions. Conversely, because Cb HSR was the focus of our attention, we may have optimized the reporting of Cb HSR.

We observed that girls were significantly more likely to develop Cb HSR than boys. To our knowledge, this finding has not been reported previously. However, the lack of such literature is not surprising, because the majority of studies that have focused on Cb HSR arose from 2 distinct adult oncology populations, patients with ovarian cancer and patients with lung cancer. Because these 2 types of cancers are strictly or relatively sex-specific, a sex effect would not be discernable in such a setting. However, Navo et al. recently analyzed the incidence of Cb HSR in 1324 patients with a variety of tumor types who received treatment with carboplatin.^[18] Fifty-seven percent of those patients were girls. The authors reported an incidence of Cb HSR of 2.6% in the total population ($n = 1324$ patients) compared with 7.9% in the ovarian cancer population ($n = 277$ patients). Although the authors mentioned that their population of patients who were treated for ovarian cancer received significantly greater numbers of cycles of carboplatin to explain the higher incidence, it is noteworthy that 91.2% of the patients in their study who developed Cb HSR were women, although the authors did not comment on this point.

The first hypersensitivity reaction, as reported previously in adult and pediatric patients, tended to occur around the 10th carboplatin infusion.^{[4][8][9][19]} It appeared to be related to the cumulative number of infusions rather than the cumulative dose of carboplatin.^{[1][20]} Throughout the treatment of these patients, the cumulative incidence of Cb HSR kept increasing with the number of infusions and did not seem to reach any plateau. Schiavetti et al. also reported a similar pattern of cumulative risk.^[8]

In contrast with the experience reported by Yu et al.,^[21] in our experience, patients who received weekly dosing had a similar incidence of Cb HSR compared with patients who received monthly dosing. However, reactions occurred 3 months earlier in the weekly dosing group (4.4 months vs 9.1 months after treatment initiation; $P = .016$).

The majority of initial reactions were mild to moderate in severity, in agreement with previous reports.^{[1][2][8]} Nonetheless, 2 patients presented initially with grade IV reactions. This potential and unpredictable adverse event certainly contributes to the subjective decision to discontinue the therapy after the first reaction regardless of its severity.^[22-24] The potential benefit of Cb HSR-altering treatments to rechallenge allergic patients remains unclear. In our experience, patients who received prophylactic premedication were just as likely to develop Cb HSR. We did not observe a significant benefit of adding a desensitization approach to premedication as a Cb HSR-altering treatment. Paradoxically, in our experience, this approach appears to be associated with a significantly lower rate of completing carboplatin treatment and higher rate of worsening allergic symptoms. This failure of desensitization differs from prospectively reported successful experiences of desensitization in women with ovarian carcinoma who developed Cb HSR.^{[19][25]} There is no clear explanation for this unexpected finding. One of the reasons may be a difference in the amount of premedication used before desensitization compared with strategies that used a premedication alone approach. In addition, because desensitization was used in only 2 of the participating centers, a center effect with a lower individual level of tolerance of recurrent symptoms may contribute toward explaining these findings. The retrospective nature of our study also may limit the interpretation of these findings.

At best, approximately 50% of patients who were rechallenged with premedication alone were able to complete their therapy, but the majority of attempts remained unsuccessful. Furthermore, the median number of 4 additional carboplatin infusions delivered (range, 1-36 additional infusions) was relatively low. It is even more noteworthy that 32% of patients presented with a more severe reaction upon re-exposure. Similar findings were reported by Rose et al.^[26]

Carboplatin-based regimens have an interesting efficacy/toxicity ratio in children with LGG. Outpatient administration enhances better quality of life. However, the development of allergic hypersensitivity may challenge the rationale of pursuing carboplatin therapy, which, although it has a proven antitumor effect in LGG,^{[7][10]} suddenly, it is associated with an adverse effect that has potential life-threatening consequences in the context of a benign tumor. Furthermore, although the exact mechanism of carboplatin hypersensitivity remains unclear, the different clinical patterns of allergic reactions suggest that several immune pathways may be involved, like type I immunoglobulin E-mediated reaction or mast cell degranulation, leading to histamine release.^[11]^[28] Theoretically, type I allergic reactions may lead to decreased half life, decreased availability, and, thus, decreased activity.^[28]

In addition, the cumulative dose for steroids suggested in successful reports of altering Cb HSR therapies may be considerable, particularly in children who are scheduled to receive weekly carboplatin for ≥ 1 year.^{[11][12][27]} This may have important short- and long-term consequences, such as mood changes, weight gain, and osteoporosis.^{[29][30]} The reported experiences of successful desensitization have required rigorous protocols, sometimes involving critical care unit availability and prolonged administration schedules.^[12] Such strategies are time consuming, costly, and add a significant burden and anxiety to the patient, family, and caregivers.

Although some authors have tried to detect predictive factors for carboplatin hypersensitivity,^{[31][32]} currently, there is no accurate predictive factor to identify which patients truly will benefit from altering Cb HSR techniques, and no definitive recommendation could be drawn from our experience. When a patient has a demonstrated response to a carboplatin-based regimen, Cb HSR-altering strategies may be justified as an attempt to salvage an effective therapy. This may be justified for patients who develop allergic reactions as a late event. However, when Cb HSR occurs early during treatment, appreciation of response may not be predictable, and the benefit of continuing carboplatin should be balanced against the risk of a more severe allergic reaction and the overall burden of desensitization strategies. Because the number of successful re-exposures was relatively low, our experience suggests that the chance to complete therapy upon re-exposure will be limited in a child with an early onset of Cb HSR. For patients with an early onset allergic reaction, alternative chemotherapy regimens that offer a good efficacy rate without evidence of long-term toxicity should

be considered instead.[33] In patients with carboplatin allergy, the current International Society of Pediatric Oncology LGG protocol discourages attempts to continue therapy by means of desensitization and suggests alternative combinations, such as vincristine plus cyclophosphamide or vincristine plus cisplatin.[34]

We did not observe a difference in PFS according to the presence or absence of Cb HSR. Such information on patients with Cb HSR is unlikely to be obtained from prospective clinical trials, because patients registered in these protocols who develop Cb HSR often are excluded from study; thus, their data may be censored or incomplete. Gnekow et al. provided some information on second-line regimens that were used for children with Cb HSR enrolled in the HIT LGG 1996 study. However no specific survival analysis was provided on that subgroup of patients.[10]

In our experience, the majority of patients who developed Cb HSR eventually discontinued carboplatin, and a significant number (18 of 44 patients) were switched to an alternative chemotherapy regimen. The 2 groups (with Cb HSR and without Cb HSR) had a similar overall duration of chemotherapy when the duration of treatment after the switch to a noncarboplatin regimen was added to the initial duration of carboplatin-based regimen in patients who developed Cb HSR. The similar duration of treatment may have contributed to the similar PFS in both groups.

In conclusion, the results from this cooperative study indicated that approximately 40% of children with LGG who received a carboplatin-based regimen developed Cb HSR. Being a girl was identified as a risk factor for Cb HSR. Altering Cb HSR strategies did not prevent worsening of recurrent allergic symptoms. We did not observe a significant benefit from desensitization/premedication approaches compared with premedication alone. The prolonged use of steroids is associated with the risk of long-term side effects, which should be taken into account in the context of a benign tumor. The effect of Cb HSR on the 5-year PFS rate was not statistically significant. Because the incidence of Cb HSR is significant, protocols and prospective studies that use prolonged carboplatin-containing regimens should include recommendations for the management of these reactions, including guidelines for discontinuation and switching to alternative chemotherapy regimens.

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