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Prospective study of selective intra-arterial cerebral infusion and intra-operative local application of carboplatin for recurrent glioblastoma multiformis

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Keywords
GBM, carboplatin, intra-arterial injection, tumoricidal, DSA

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ABSTRACT

Background. High-grade glioma is the commonest primary malignant brain tumour in adults. Intra-arterially selectively infused chemotherapeutic agents into the tumour bulk is being widely trialled recently with promising results.

Methods. This is a prospective study designed between November 2015 and November 2019. Thirty patients were diagnosed with recurrent histo-pathologically proven GBM after one surgery at least and followed by standard radiotherapy and temodal. Patients aged between 37-76 years, 18 males and 12 females were subdivided into group A of 21 patients who underwent intra-arterial delivery of carboplatinand group B of 9 patients who underwent re-surgical resection and local application of carboplatin.

Results. The mean age of the included cases was 55.4 years (range, 37-76 years). Selective intra-arterial injection was performed in 21 cases (70%), while the remaining 9 cases (30%) had local application of carboplatin in the tumour bed. Post-treatment vomiting was reported in 7 cases (23.3%). Significant and partial responses were achieved in 2 cases for each (6.7%). Time to tumour progression had a mean of 19.03 weeks (range, 3 – 30 weeks). After receiving carboplatin, the study cases had a mean survival of 26.5 weeks (range, 6 – 70 weeks). Intra-arterial injection had significantly better results compared to local tumour bed infiltration (p = 0.01).

Conclusion. Although recurrent glioblastoma multiformis has poor survival, intra-arterial delivery of carboplatin may have a slight positive impact on patient survival. The procedure however is relatively safe with manageable complications.

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Introduction

High grade glioma is the commonest primary malignant brain tumor in adults with an incidence of approximately 5 per 100,000[1].

A published phase III randomized trial showed only 9.8% 5-year survival rate for patients with high grade glioma treated by standard protocol of surgery plus radiation and temozolomide. Intra-arterially selectively infused chemotherapeutic agents into the tumor bulk is being widely trialed recently. Some of the trails showed promising results and point to more investment in the field of selective intra-arterial infusion of tumoricidal agents for treatment of malignant glioma[2].Glioblastoma multiformis which is the high-grade glioma targeted in our study like most malignant carcinoma, its cells possess replicative immortality. Normal cells that undergo DNA damage and telomere shortening have the ends of their DNA strands bind together to stop replication and apoptosis commences. Loss of P53 gene results in over expression of telomerase enzyme that is responsible in maintaining DNA strand length, repairing damage and protecting the ends of chromosomes allowing cells to continuously proliferate [3].

The protocol of maximum safe surgery of GBM followed by adjuvant chemo-radiotherapy and adjuvant chemotherapy is established as usual standard management[9]. But local recurrence is expected, with the majority of cases within 6–9 months of 1ry treatment due to resistant stem cells of GBM [10, 11].

Molecular factors such as mutation of P53,methylation of O-6-methylguanine-DNA methyltransferase (MGMT) and MIB-1 labeling index are associated with GBM recurrence [16]. Controversy exists regarding diagnosing recurrence, with histo - pathological examination of tissue as the ultimate diagnosis .On the other hand, the majority of cases having imaging finding indicative of progression could be unfit for a surgery, hindering diagnosis of recurrence difficult [12,13,17,18].

Surgery is still a significant important strategy in management of GBM. On the other hand, only few cases are recognized appropriate for a complete resection. Re-irradiation (ReRT) has improved in the last years [19]. Chemotherapy is utilized by variable groups to improve survival. Despite this , however , patients of rGBM and GBM still remain fated for poor outcomes[15].The blood–brain barrier (BBB) prevents the deliverance of the majority of the chemotherapeutic drugs [20]. On the other hand, the majority of the regimens of management surfaced via single institute retrospective analysis of phase II clinical trials, thus, there is no standard treatment for those patients non responsive to TMZ [21].

Carboplatin is the drug chosen to target recurrent glioblastoma in our study, it is an analogue of cisplatin containing a platinum atom. Once inside tumorous cells carboplatin becomes activated to produce reactive platinum complexes that form inter-strand and intra-strand cross linking of DNA molecules inhibiting DNA synthesis and replication resulting in cellular death. Its action can occur during any phase of the cell cycle (cycle non-specific). In the brain only malignant cells will be affected and normal cells are spared because they are normally non dividing stable cells [4].

Adverse effects of systemic IV Carboplatin use includes**;** Bone marrow depression usually reversible within 30days resulting in anemia 71%, febrile neutropenia18%, thrombocytopenia 25% [5].

Nausea (15%) and vomiting (64%)starts within 6-12 hours after carboplatin injection but can be limited by prior anti-emetics**[5].**Hepatotoxicity may also occur in the form of elevated alkaline phosphatase (24%), elevated AST (15%), elevated bilirubin (5%) [6].

Selective Intra-arterial Cerebral Infusion of Carboplatin involves its delivery to tumor site via balloon assisted endovascular techniques and prior focal disruption of the blood brain barrier by injecting 10cc of mannitol 20% over 2 mins[7].

Pre-infusion studies and post-infusion studies including magnetic resonance imaging with and without gadolinium to detect the effect on tumor size and magnetic resonance spectroscopy to detect the metabolic response are carried out for candidate patients [8]. IA infusion of chemotherapy refers to the regional delivery of chemotherapy to the CNS, that results in a major rise in plasma peak concentration and in the AUC associated with the 1stpass effect. This leads to a 3– 5.5-fold factor major rise in the concentration of intra-tumoral chemotherapy as theses lesions are vascular in nature[27].

The Fischer animal model [29], found that accumulation of platinum in the tumor cells nuclei was elevated by a 20-fold factor (9 ng platinum/g tissue) when infused via an IA route, when put side by side with the IV route (0.5 ng platinum/g tissue) [30].

Clinical trials incorporating patients with GBM who received cisplatin monotherapy or combined with others chemotherapeutic drugs as etoposideor TMZ documented only modest outcomes [27,28].

PATIENTS AND METHODS

This is a prospective study designed for patients have recurrent GBM between November 2015 and Novemeber2019 in Neurosurgery department, Mansoura university Hospitals, Egypt.

This study aims to evaluate the efficacy of single dose selective intra-arterial cerebral infusion and tumor bed application of carboplatin for such patients.is.

Study subject

Thirty patients were diagnosed with recurrent histo pathologically proven GBM after a one surgery at least and followed by standard radiotherapy and temodal. They were all referred from the outpatient neurosurgery clinic. Patients aged between 37-76 years , 18 males and 12 females were subdivided into two groups: Group A(21 patients who underwent intra-arterial delivery of carboplatin), Group B(9 patients who underwent re-surgical resection and local application of carboplatin).

Inclusion criteria

- Age above18 years old
- Patients with recurrent glioblastoma multiforme
- Karnofsky performance status scale 40 or above

Primary outcome measures

Evaluating response to both ways of chemotherapy delivery using imaging techniques.

Secondary outcome measure

1. Post-treatment complications.
2. Survival.

Patients consent

A written informed consent was obtained from all patients before the operation after describing and explaining the details and complications of each approach.

Procedure

Patients were admitted for a variable period of time ranging between 3-7 days. All patients were investigated by a baseline pre and post enhanced MRI and routine lab most notably serum creatinine and a baseline blood picture (CBC). History taking and baseline neurological examination was established as well for all patients. The patients were then grouped into two groups after assessment of the following:

- whether or not they require surgical decompression because of significant radiological mass effect and weather the recurrence is surgically accessible or not
- history of complications (CSF wound leakage, poor wound healing, poor scalp texture after radiotherapy, deep venous thrombosis ,pulmonary embolism severe chest infection) related to prior surgery or adjuvant chemo-radiotherapy rendering surgery high risk.

Carboplatin dosage was calculated based upon body surface area calculated using the Mostellar Formula BSA (m2) = SQRT ([height (cm) * weight (kg)] / 3600) Body surface area ($m^{2)}$ = square root ([Height (cm) * weight (kg)] divided by 3600.

The first group (Group A)

Selective Intra-Arterial Cerebral Infusion of Carboplatin was performed at a dose of 400 mg/m^2 BSA. On table, digital subtraction angiography (DSA) was done to identify the tumor vascular bed then endovascular techniques are employed to reach the vascular bed, followed by injection of 10cc mannitol 20% over to 2 minutes, DSA was redone to detect focal hyperemia indicating successful BBB disruption, after that Carboplatin infusion was commenced through a Marathon flow directed micro-catheter usually within the middle cerebral artery(MCA) or anterior cerebral artery(ACA) or one of their branches as well as a small dosage at the carotid bifurcation. Mostly, this was carried out under local anesthetic with the patient instructed to either report increasing headache, nausea, blurring of vision or increasing tingling or numbness or heaviness of an extremity.

The second group (group B)

Local application of Carboplatin during re-surgery at a dose 400mg/m2 BS. After sufficient tumor debulking a cotton pack soaked in Carboplatin solution is placed in the tumor cavity before coagulation of the walls of the cavity for 10mins; the pack is then removed and final hemostasis is

achieved and lastly the cavity is filled with the rest of Carboplatin solution.

Post-procedural follow up MRI with CE was carried out at 2 weeks and at one or two months later. Response to treatment was then determined as a significant response (SR) if CE tumor size was reduced in any of the following MRIs. A partial response PR was considered if the tumor exhibited less mass effect and edema without reduction in the size of CE tumor. A stable disease SD if no changes regarding size or mass effect occurred. A progressive disease PD was established if size or mass effect and edema were increased post procedurally.

Data Analysis

Statistical analysis of the data in this study was performed using SPSS software, version 20 (Chicago, IL). Descriptive data was expressed as means with standard deviation or medians with ranges according to data distribution.

Results

The mean age of the included cases was 55.4 years (range, 37-76 years). We included a total of 18 males (60%) as well as 12 females (Figure 1).

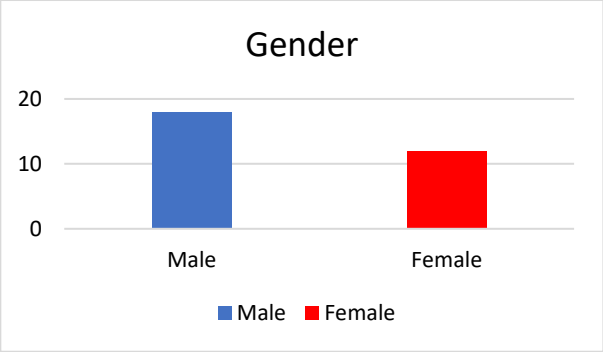

Figure 1. Gender distribution in the study cases.

The Karnofsky Performance Score (KPS) had a mean of 71.33 in the study cases (range, 50-80) (Table1).

Table 1. Analysis of KPS in the study cases

Items		*Study cases n=30*
KPS	Mean ± SD	71.33 ± 8.99
	Median (min-max)	70 (50-80)

Continuous data expressed as mean ±SD and median (range)

All study cases had been commenced on chemo radiotherapy after the first surgery. Evidence of mass effect was present in all study cases (Table2).

Table 2 Analysis of the history of the disease in the study cases.

ID	Hx of radiotherapy	Hx of chemotherapy	Previous surgery	Pre-ttt evidence of mass effect
1	Yes	Temodal	yes	yes
2	Yes	Temodal	yes	yes
3	Yes	Temodal	yes	yes
4	Yes	Temodal	yes	yes
5	Yes	Temodal	yes	yes
6	Yes	Temodal	yes	yes
7	Yes	Temodal	yes	yes
8	Yes	Temodal	yes	yes
9	Yes	Temodal	yes	yes
10	Yes	Temodal	yes	yes
11	Yes	Temodal	yes	yes
12	Yes	Temodal	yes	yes
13	Yes	Temodal	yes	yes
14	Yes	Temodal	yes	yes
15	Yes	Temodal	yes	yes
16	Yes	Temodal	yes	yes
17	Yes	Temodal	yes	yes
18	Yes	Temodal	yes	yes
19	Yes	Temodal	yes	yes
20	Yes	Temodal	yes	yes
21	Yes	Temodal	yes	yes
22	Yes	Temodal	yes	yes
23	Yes	Temodal	yes	yes
24	Yes	Temodal	yes	yes
25	Yes	Temodal	yes	yes
26	Yes	Temodal	yes	yes
27	Yes	Temodal	yes	yes
28	Yes	Temodal	yes	yes
29	Yes	Temodal	yes	yes
30	Yes	Temodal	yes	yes

Regarding the method of carboplatin delivery, selective intra arterial injection was performed in 21 cases (70%), while the remaining 9 cases (30%) had local application of carboplatin in the tumour bed (Figure2).

Post-treatment vomiting was reported in 7 cases (23.3%), whereas epilepsy was present in 8 cases

(26.7%). Additionally, hemiparesis was diagnosed only in 2 cases (6.7%) (Figure3).

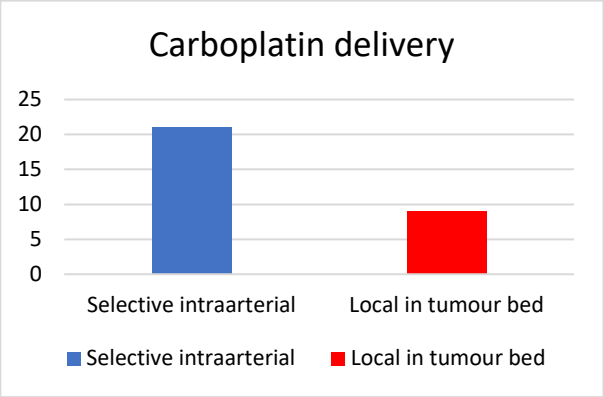

Figure 2. Method of carboplatin delivery in the study cases.

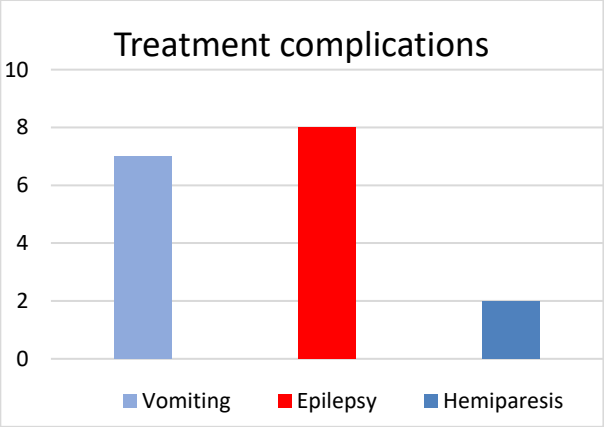

Figure 3. Treatment complications in the study cases.

More than half of the study cases had progressive disease (16 cases – 53.3%), followed by stable disease (10 cases – 33.3%). Significant and partial responses were achieved in 2 cases for each (6.7%)

Time to tumour progression had a mean of 19.03 weeks (range, 3 – 30 weeks).After receiving carboplatin, the study cases had a mean survival of 26.5 weeks (range, 6 – 70 weeks).

On dividing our study cases according to the method of carboplatin delivery, no significant difference was detected between the two groups regarding treatment complications ($p > 0.05$) (Figure 4).

Regarding treatment response, it was evident that intra arterial injection had significantly better results compared to local tumor bed infiltration ($p = 0.01$). All cases in local bed infiltration had progressive disease after treatment, while 2 cases in the other group had significant response (Table3).

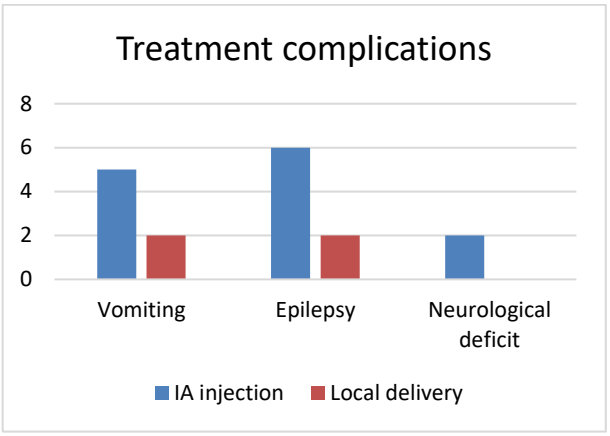

Figure 4. Treatment complications in both study groups.

Table 3. Analysis of response in the two study groups

	Groups		Test of significance
	Group 1 [Selective IA] (N=21)	Group 2 [Local in tumor bed] (N=9)	
Significant response	2 (9.5%)	0 (0%)	$\chi 2$= 11.250 P= 0.010*
Stable disease	10 (47.6%)	0 (0%)	
Progressive disease	7 (33.3%)	9 (100%)	
Partial response	2 (9.5%)	0 (0%)	

P: probability.
Categorical data expressed as Number (%)
x2= Chi-square test

Table 4. Analysis of TTP in the two study groups.

	Groups		Test of significance
	Group 1 [Selective IA] (N=21)	Group 2 [Local in tumor bed] (N=9)	
TTP (weeks)	19 (6.5 -34)	8 (7.5 -11)	t= -1.383 P = 0.178

P: probability. Continuous data expressed as median (IQR).
z= Mann Whitney U-test

There was no significant difference between the two groups regarding time to disease progression (p = 0.178) although the mean TTP was shorter in the tumor bed infiltration group (8 vs. 19 weeks in the IA group) (Table4).

Survival was significantly longer in the IA drug group (35 vs. 14 weeks in the local tumour bed group – p = 0.028) (Figure5).

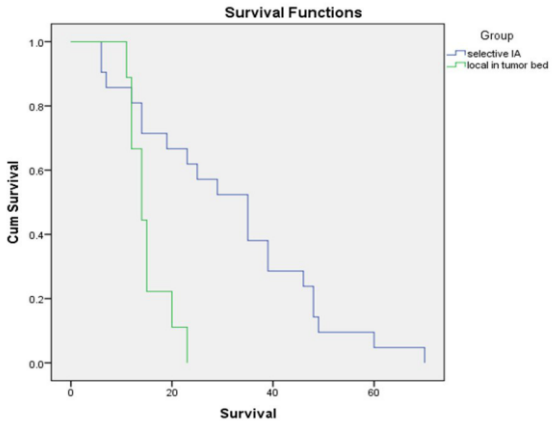

Figure 3. Survival in the study groups.

Discussion

Even with respect to all advances in aspects of treatment, patients with GBM still remain of poor prognosis[33].

During progression, salvage treatments provide highly modest efficiency. Several agents have been tested concerning this topic, providing low rates of response varying from 5 to 20% and median total survival between 5 and 7.5 months [34].

We included an overall of 30 patients in the current study, having a mean age of 55.4 (range, 37 – 76 years). We included a total of 18 males (60%) as well as 12 females.

Another study conducting similar perspective included 24 patients with recurrent GBM. The mean age of the included cases was 44.5 years (range, 26 – 67 years). Investigators comprised 13 males and 11 females in that study [25].

Another study included an overall of 25 patients whose mean age was 37.8 years (range, 22 – 68). A total of 13 males and 12 females were included in that study [26].

In our study, Karnofsky Performance Score (KPS) had a mean of 71.33 in the study cases (range, 50-80). In a similar study, at the time of initiation of therapy, median KPS was eighty. At the time of disease progression, the median KPS was sixty [35].

Another study reported that the mean KPS score was 66.8 (range, 40 – 90) [26].

In the current study, time to tumor progression had a mean of 19.03 weeks (range, 3 – 30 weeks).

Newton and his associates reported that the overall median TTP was 24.2 weeks, while for responders the median TTP was 32 weeks (range 10–174 weeks) [26].

In the current study, more than half of the study cases had progressive disease (16 cases – 53.3%), followed by stable disease (10 cases – 33.3%). Significant and partial responses were achieved in 2 cases for each (6.7%). It was evident that intra-arterial injection had significantly better results compared to local tumor bed infiltration (p = 0.01). All cases in local bed infiltration had progressive disease after treatment, while 2 cases in the other group had significant response.

IA injections depend on drug provision throughout capillary networks and finally to the perfused tissue. The tissue concentrations reached by utilizing a selective IA route are significantly greater than those reached following IV administration [36].It is assessed that above 2000 cases were managed with IA chemotherapy for GBM, most of which are parts of Phases I and II trials. There has been small evidence of considerably better results throughout the course of these trials. Numerous series state increased survival by only some weeks, with neurotoxicity or ocular toxicity appearing in 7-50% of the patients [22].In another study, volumetric analysis of serial MRIs revealed decrease in tumor mass in three out of ten cases. A rise in tumor mass in the range of 23% to 230% was detected in the other 7 cases in time extending from 2.3 to 37.7 months after starting of therapy by carboplatin [25].

Additionally, 68.29% of cases had tumor progression while the remaining cases had stable disease in another study [24].

In another study, that utilized criteria of Macdonald in order to categorize tumor responses radio logically, authors detected three full responses, twenty-two partial responses, fourteen stable disorders and twelve progressions [28].

Follézou et al. showed that carboplatin had a partial response in high grade glioma patients using a dose of 400 mg/m2[31, Clocchlatti et al. achieved a

74% response rate after 250 mg/m2 IA carboplatin infusion[32], and Cloughesy et al. increased carboplatin dose up to 1400 mg/ hemisphere in a dose-escalation study based on cerebral blood flow[37]. Other authors reported that 45 out of 57 patients evaluated with GBM (79%) experienced SD or better. Authors concluded that along with the use of standard treatment guidelines and protocols, intra-arterial chemotherapy with or without osmotic disruption of the BBB is feasible across several centers with a low incidence of catheter-related complications[23].

After receiving carboplatin, our study cases had a mean survival of 26.5 weeks (range, 6 – 70 weeks). Survival was significantly longer in the IA drug group (35 vs. 14 weeks in the local tumor bed group – p = 0.028).In another study, twenty-three patients (out of 46 cases) died after an average of 205 days; 18 were surviving at an average of 324 days from the start of intra-arterial chemotherapy [24].

Stewart et al. reported the results of intra-carotid infusion of carboplatin (200–400 mg/m^2) in 15 patients with either glioblastoma or metastatic tumors. Median survival was 9 weeks [191]. In another study, more than one year survival subsequent to start of IA therapy by carboplatin has been observed in twelve out of the twenty-three cases [25].

Furthermore, in another study, the median total survival from time of diagnosis was twenty-three months with a median survival of eleven months from start of study was detected. The progression-free survival subsequent to therapy was 6.1 months, while a free survival progression of 4.3 months was detected subsequent to the IA therapy [38].

Surgery in case of recurrent GBM may involve either biopsy (for diagnostic purposes) or repeat debulking of tumor. Only approximately 20 to 30 percent of patients with recurrent glioblastoma are candidates for a second surgery [39].

In a patient with recurrent GBM, the indications for a debulking reoperation are still to be definitely recognized. The median survival for cases submitted to operation for recurrent glioblastoma ranges from 8 to 12 months in most series [40.41] and varies from 12 to 18 months for patients with anaplastic astrocytoma [42,43,44]. There is no evidence to suggest that the results of re-surgery are more useful than could be expected with radiation and/or chemotherapy alone. However, selected patients could benefit from reoperation (eg, those with a bulky tumor exerting symptomatic mass effect). Favorable prognostic variables include patients whose age is young, a greater interval from the original operation, and the size of the recurrence as well as extent of the 2nd surgical resection [45,46].

In the current study, post-treatment vomiting was reported in 7 cases (23.3%), whereas epilepsy was present in 8 cases (26.7%). Additionally, hemiparesis was diagnosed only in 2 cases (6.7%). On dividing our study cases according to the method of carboplatin delivery, there was no major difference observed among the 2 groups regarding treatment complications (p > 0.05).Bone marrow suppression (BMS) in the form of thrombocytopenia or leucopenia was not observed in cases in this study and this can be most probably be attributed to the fact that the patients received only a single non incremented dose of carboplatin that the body eliminated too soon before BMS sets in.

In the study conducted by Stewart and his associates, three of four patients who received 400 mg/m2 of carboplatin developed retinal toxicity. Three of 9 patients who received 300 mg/m2 had decreased ipsilateral vision and one other developed worsening of a preexisting hemiparesis. Focal seizures and transient aphasia occurred in one patient each [38].

Follezou et al. described 23 patients with malignant glioma who were treated with an intra-arterial infusion of 400 mg/m2 of carboplatin every 4 weeks. One patient developed central neurotoxicity and another developed a reversible decrease in visual acuity [31].

Cloughesy et al. reported the use of escalating doses of carboplatin (up to 1400 mg/hemisphere) infused either in the supra clinoid internal carotid artery or basilar artery above the anterior inferior cerebellar artery in 21 patients with recurrent glioma. One patient had permanent neuromotor decline. The predominant complication was hemopoietic toxicity. The median survival was 39 weeks [37].

In another series of 51 cases, authors detected one grade III anemia, three grades IV and five grade III thrombocytopenia and three grade III neutropenia according to criteria of the National Cancer Institute common toxicity. These toxicities were all manageable easily. 3 cases of carotid spasms were detected and there was a asymptotic. These spasms were elicited by positioning of the catheter, and all

resolved spontaneously. No cases of neurotoxicity had been detected in this work [28].

Conclusion

Although recurrent glioblastoma multiformis has a poor survival, intra-arterial delivery of carboplatin may have a slight positive impact on patient survival. The procedure however is relatively safe with manageable complications.

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