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Review

Complete response to bevacizumab plus irinotecan in patients with rapidly progressive GBM: Cases report and literature review

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common and aggressive malignant primary brain tumor in adults. The etiology of GBM is not known, and the prognosis is usually very poor. Despite new diagnostic techniques and treatment methods, the management of patients with GBM is difficult.

Currently, the standard of care for the treatment of GBM is surgical resection, followed by concurrent RT with temozolomide, completed by adjuvant CT with temozolomide. Despite the survival benefit associated with these treatments, the majority of patients relapse following initial therapy. Unfortunately, optimal management for patients with recurrent or progressive GBM is unclear.

In general, treatment for recurrent GBM may involve repeated resection, focal irradiation, and systemic therapies. When considering in terms of chemotherapy regimen, bevacizumab and irinotecan combination therapy for the progressive GBM may be used a suitable regimen. Also complete response in case of recurrent GBM is very rare.

We present two cases with GBM who had complete response with bevacizumab plus irinotecan as second-line CT regimen, which rapidly progressed after surgery, chemoradiotherapy (CRT) and first-line temozolomide therapy.

Signs of rapid proliferation in the pathologic specimen of both cases were recorded. During follow-up both cases developed recurrent tumor within a month after first three cycles first-line temozolomide CT.
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Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults.[1] Initially treatment of GBM is surgery. Other members of trimodality treatment are concurrent RT with temozolomide, and completed by adjuvant CT with temozolomide.[2] However, aggressive trimodality treatment approaches, the prognosis for GBM is poor.

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults.[1] Initial treatment of GBM is surgery. Other members of trimodality treatment are concurrent RT with temozolomide, and completed by adjuvant CT with temozolomide.[2] However, with aggressive trimodality treatment approaches, the prognosis for GBM is poor.

Median survival of patients with GBM is usually 15 months and less than a 10% 5-year survival rate.[3] Despite an aggressive multimodal approach, the median survival time after diagnosis is approximately a year with population-based studies demonstrating even lower median survival rates. Furthermore, the prognosis for recurrent GBM is very poor, and median overall survival (OS) is usually 4–6 months, 5 years survival rate is less than 5%.[3–7]

The optimal management for patients with recurrent or progressive GBM is unclear. In general, treatment for recurrent GBM may involve repeated resection, focal irradiation, and systemic or experimental therapies.

CT as standard of care for GBM is applied as daily temozolomide combined with RT followed by adjuvant temozolomide treatment.[2] The role of CT in gliomas has historically been disappointing, with adjuvant therapy extending longer-term survival in the minority of GBM patients.[8–10] When disease progression occurs, salvage CT is usually unsuccessful, and in this case 6-month progression-free survival (PFS) is usually lower than 15%.[5]

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GBM is hypervascular in nature and growth has been shown to be angiogenesis-dependent.[11,12] Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). It binds and inactivates VEGF, thereby inhibiting angiogenesis, endothelial cell activation and tumor proliferation. It was the first anti-angiogenic inhibitor approved as an anti-tumor therapeutic agent. Since 2004, mainly metastatic colorectal cancer patients, the FDA approved bevacizumab for cancer patients.[13–16]

The use of bevacizumab in treatment of recurrent GBM was firstly reported about ten years ago.[17] Due to the good response rates after this trial, bevacizumab was used in GBM treatment.[18,19] In addition to its clinical benefits, bevacizumab-based therapies provided symptomatic relief and improvement in patients with recurrent malignant glioma.[20]

After bevacizumab monotherapy study,[18] combinations of bevacizumab with chemotherapeutic agents such as temozolomide, irinotecan, carboplatin, nitrosoureas, etoposide and erlotinib have been used in GBM patients. Reports showed that, patients had more benefit especially after bevacizumab plus irinotecan therapy.[21–28] In these studies PFS was generally obtained in approximately 2–4 months, and OS was 4–6 months.

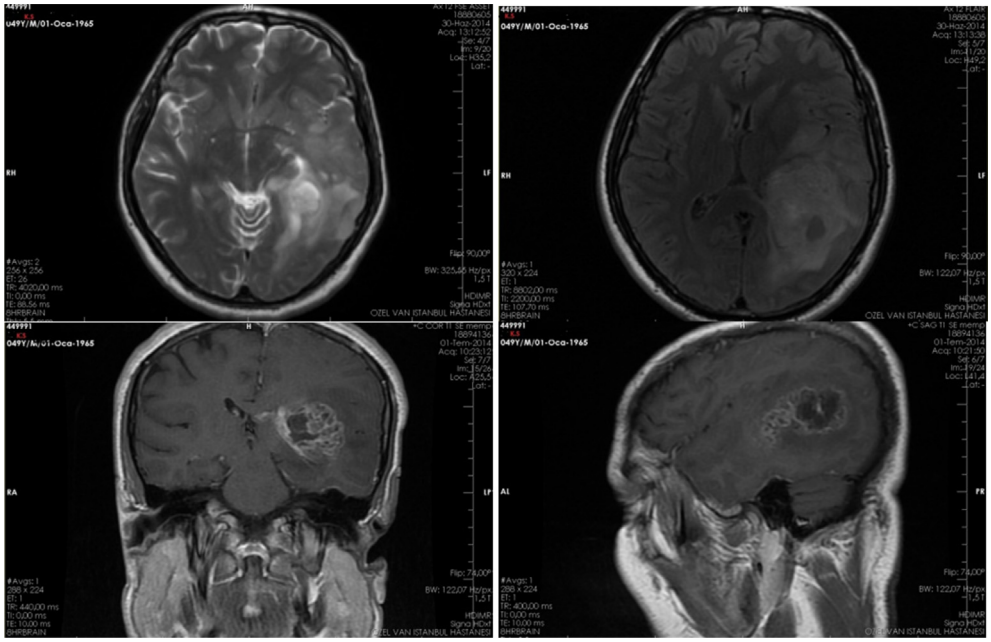

Fig. 1. 50 years-old man with GBM. Pretreatment MRI demonstrates that axial T2WI, T2 flair and contrast-enhanced T1WI irregüler peripheral enhancement tumor and edema in the left temporoparietal region

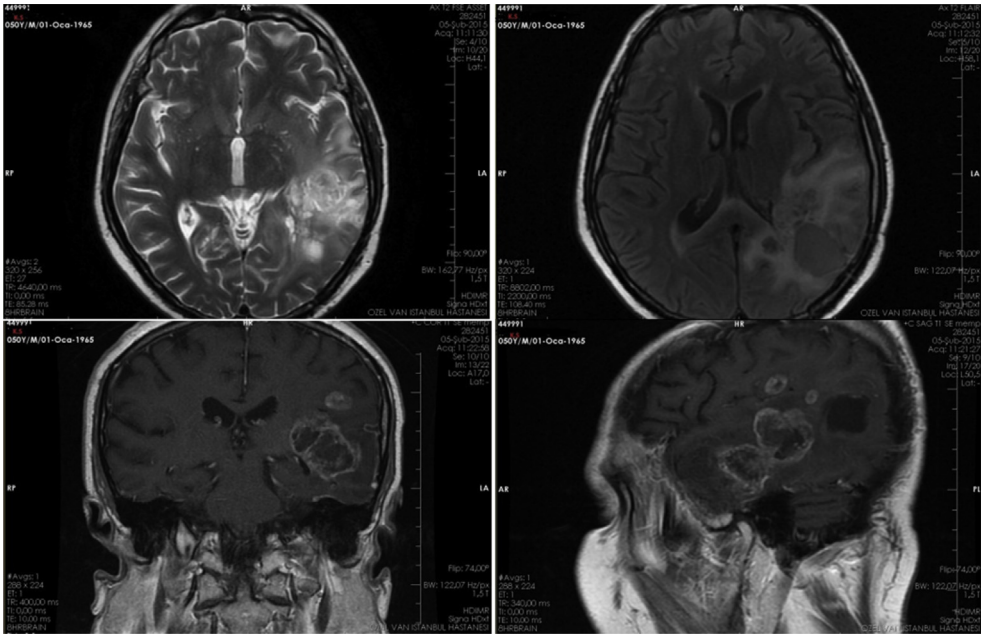

Fig. 2. MRI after temozolomide treatment. Enlargement of the temporoparietal tumor was seen. It's seemed to progression. Also MRI of brain with gadolinium shows satellit nodül

To date, no standard therapy has proven itself to be superior to other treatments when combined with bevacizumab for the treatment of recurrent GBM. Bevacizumab monotherapy was used in patients with GBM who progressed after initial treatment. But utility of irinotecan in combination with bevacizumab has not been established yet.[29,30]

In the treatment of recurrent GBM patients some times re-irradiation is another treatment options.[31] But re-irradiation is very low efficacy method in GBM patients.

Bevacizumab appears to be an effective agent for recurrent GBM. In patients with recurrent GBM who progressed on either bevacizumab monotherapy or combination therapy were then subsequently treated with an alternate bevacizumab containing regimen. Often, adding a cytotoxic agent or switching the companion cytotoxic agent is attempted, but the efficacy is unclear.[32]

Both of our cases had rapid progression of disease. Surgery, RT and first-line adjuvant CT therapy were missed at early period. We started a combination therapy with bevacizumab plus irinotecan in these patients. After six-cycle therapy a complete response was ensued. In recurrent GBM patient complete response is extremely rare. Taking into consideration, we recommend starting this combination therapy at an early period in patients with rapidly progressive disease.

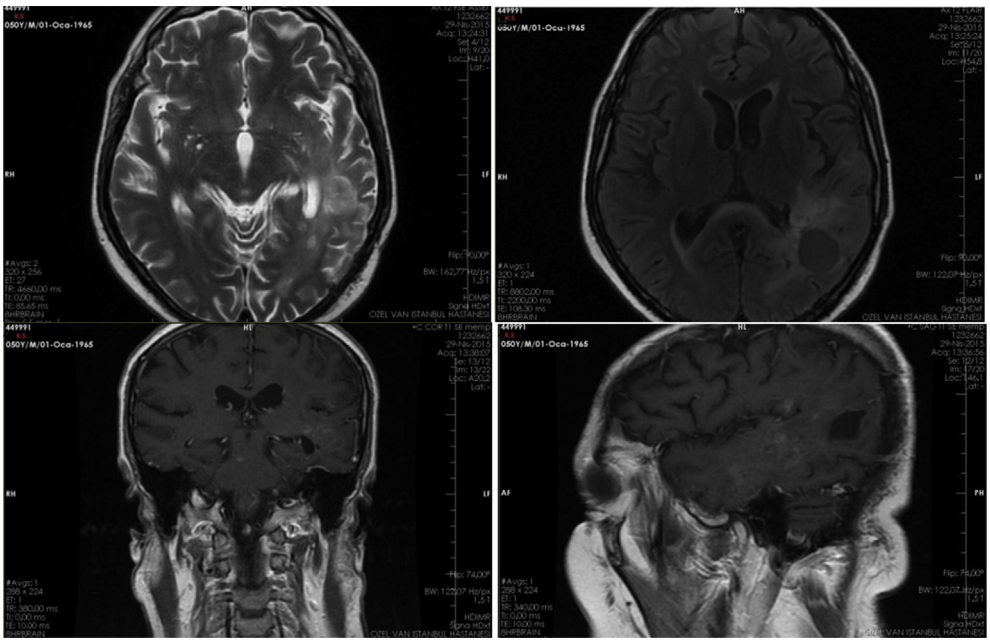

Fig. 3. T1W1 post gadolinium and T2WI-T2 flair shows a marked decreased in the enhancing portion of the lesion the surrounding abnormal hyperintense edema and cystic component on T2WI were noted 6 cycles after administration of bevacizumab plus irinotecan. It was obtained near complete response

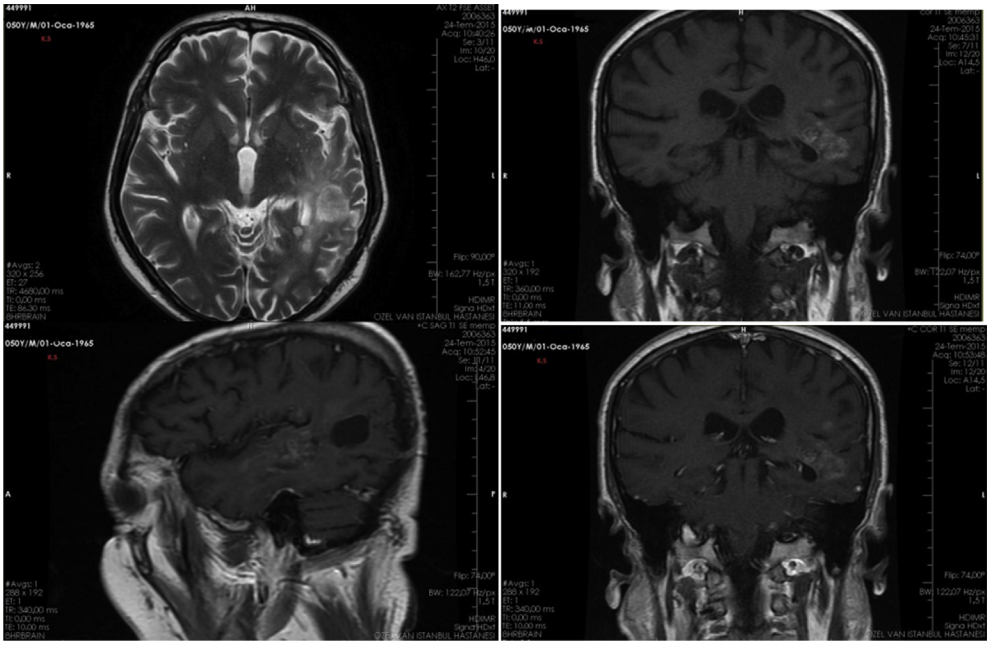

Fig. 4. After 12 cycles bevacizumab plus irinotecan treatment. MRI reveals no enhancement after i.v gadolinium injection. It was obtained complete response

First case

The patient is a 50-year-old man who had been operated in April 2014. Then the patient took concurrent RT with temozolomide. Afterwards the patient was admitted our clinic. The patient had got headache, weakness in both legs and dizziness.

Magnetic resonance imaging (MRI) was performed, and revealed irregular peripherally enhancing tumor and surrounding edema in left temporoparietal region (Fig. 1). We started temozolomide 200 mg/m^2/d for five days every 28 days. After three cycles a control MRI was performed. MRI demonstrated enlargement of the temporoparietal tumor with an accompanying newly developed satellite nodule compatible with disease progression (Fig. 2). After these findings we decided to change our treatment regimen.

We were started bevacizumab 10 mg/kg and irinotecan 125 mg/m^2 one day every 14 days. After 2 cycles all symptoms disappeared. After 6 cycles, at the end of the third month, MRI was performed. MRI shows nearly complete response (Fig. 3). After 12 cycles a complete response was obtained. At the end of the sixth month MRI was again performed demonstrating a complete response (Fig. 4). The patient had been well for the next 3 months following to CT (Fig. 5).

The patient was using lamivudine 100 mg/day due to chronic hepatitis-B. No disease other than hepatitis-B, was found in the history of the patient. Previously used, dexamethasone therapy was withheld but levetiracetam was continued as 1000 mg/day.

After the third cycle of therapy, grade 2 nausea and grade 2 vomiting were observed. Hematologic toxicity was not observed. Liver function tests remained above normal only after the third cycle of treatment, but returned to the normal level after two weeks.

Levetiracetam was withheld after 12 cycles. The patient had been followed up every 4 months and serial MRIs of the brain had shown no recurrence of the tumor. To date, it has been one and a half years after the patient's last dose irinotecan and bevacizumab for recurrent GBM. Thus he is considered to be in remission. We planned a MRI control 6 months later. The patient is followed with full healing.

Second case

The patient is a 23-year-old wheelchair-dependent woman with right side paralysis and speech impairment findings. The patient had been operated in October 2014. Then the patient took concurrent RT with temozolomide. After 2 cycles adjuvant temozolomide 200 mg/m^2/d for five days every 28 days treatment, clinical findings progressed. MRI performed at this period demonstrated an inoperable mass (Fig. 6). Revealing a too fastly progressed tumor we decided to change the treatment regimen.

We were started bevacizumab 10 mg/kg and irinotecan 125 mg/m^2 one day every 14 days. After 3 cycles, wheelchair-dependency and speech impairment symptoms disappeared. After 6 cycles, at the end of the third month, MRI was performed. MRI revealed complete response (Fig. 7). After 12 cycles, complete response signs were continuing. At the end of the sixth month MRI was performed again. MRI showed that complete response was still ongoing. (Fig. 8).

The patient was using levetiracetam 2000 mg/day, dexamethasone 12 mg/day, oxcarbazepine 1800 mg/day, diazepam 10 mg/day, lansoprazole 30 mg/day. Other than that, there was no history of any disease.

After all cycles of therapy, grade 2 nausea was observed. She did not experienced any other side effects. Hematologic toxicity was not observed. Liver function tests were slightly higher above normal only after the ninth cycle of treatment. But after two weeks in the next control the liver function tests began to decline and after eleventh cycle control returned to their normal level. After 6 cycles, levetiracetam dosage was reduced to 1000 mg/day, and went on same dosage. Oxcarbazepine, dexamethasone, and diazepam were withheld after 6 cycles. After 6 cycles, the patient was enrolled in the physical therapy program for right side paralysis.

The patient had been followed up every 4 months and serial MRIs of the brain had shown no recurrence of the tumor. To date, it has been one year after the patient's last dose irinotecan and bevacizumab for recurrent GBM. Thus she is considered to be in remission. We suggested MRI control 6 months later. The patients are followed with full healing.

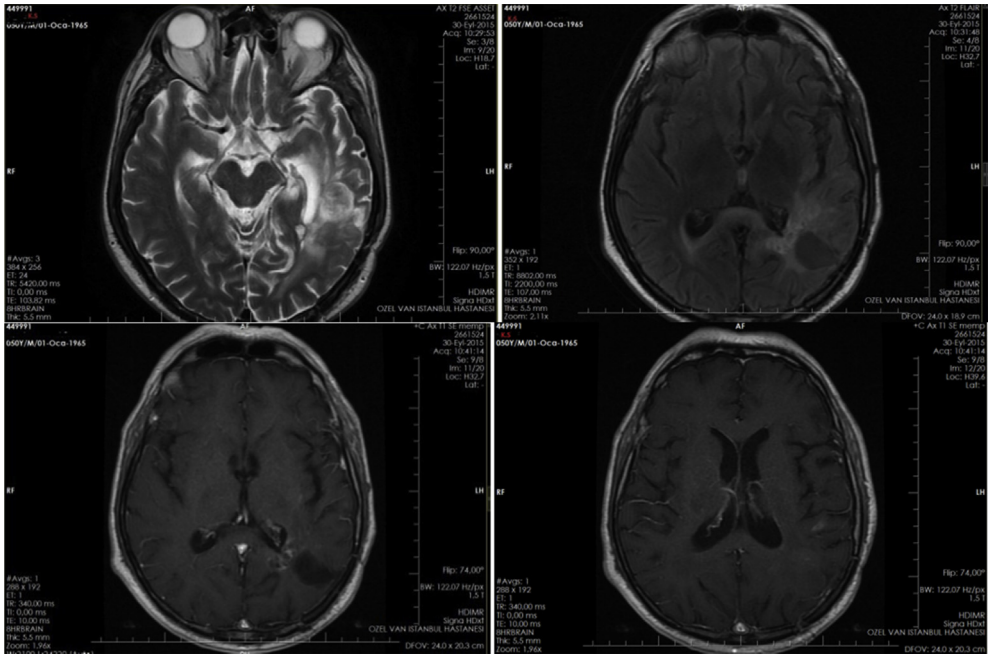

Fig. 5. T1W1 post gadolinium and T2WI-T2 FLAIR shows on T2WI were noted 6 months after administration of bevacizumab plus irinotecan treatment. Post-contrast enhanced T1WI illustrates no obvious enhancement in lesion area. It's continue complete response

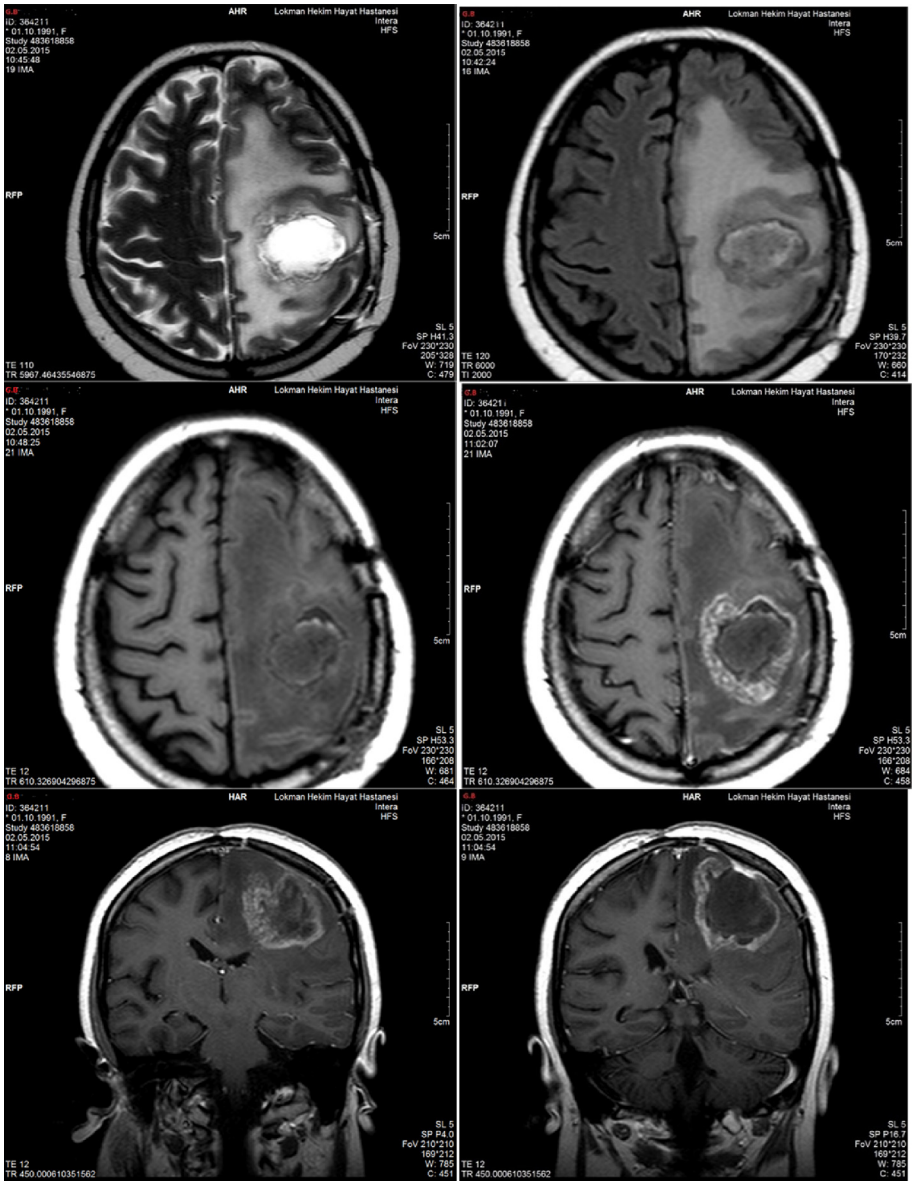

Fig. 6. 23 years-old woman with operated brain tumor receiving therapy with temozolomide. MRI of the brain on T2 weighted images showing operation area in the left parietal lobe. Post-contrast enhanced T1WI illustrates peripheral heterogenous enhancement that point out progression. Note significant amount of tumor associated vasogenic edema

Discussion

GBM is a rapidly progressive brain tumor. Treatment methods are multimodal. Surgical resection, adjuvant postoperative RT with concurrent CT, and adjuvant CT are best choice treatment methods. Despite of multidisciplinary aggressive treatment the prognosis of patients with GBM is still dismal. Remission is not achieved in majority of the patients. Relapse is common in patients who achieved remission. Despite the use of a combined modality approach, most patients eventually die.

Cancers of the brain and nervous system are relatively rare. GBM continues to be the most common and lethal malignant primary brain tumor in adults.[33]

When we look at recurrent or progressive GBM, optimal treatment for these patients is unclear. Re-intervention or best supportive care are two different methods in these patients. Usually, management of locally recurrent GBM includes re-resection, and/or re-radiation, and CT. Best supportive care (BSC) is a choice method in patients with poor performance status. In one trial re-intervention or BSC was evaluated. Patients undergoing re-intervention were better PFS than BSC patients. One year alive patients ratio was better than re-intervention group.[34] For re-intervention, pre-treatment performance status is the most important prognostic factor. Other factors that contribute to the benefit from second-line therapy include the volume of residual disease, the histologic grade (both at initial therapy and at recurrence), the relapse-free interval, and recurrence pattern (local versus diffuse).[35–38]

Re-surgery for recurrent GBM is another important choice. Re-operation provides a 3–5 month median survival.[39] Surgery allows histological diagnosis and can provide relief for neurological deficits related to mass effect. Surgery, however, is not curative due to the infiltrative nature of the disease. While only retrospective data are available to evaluate survival benefit, extent of resection correlates with better prognosis.[40–43] Performance status is the most important prognostic factor for prolongation of survival time

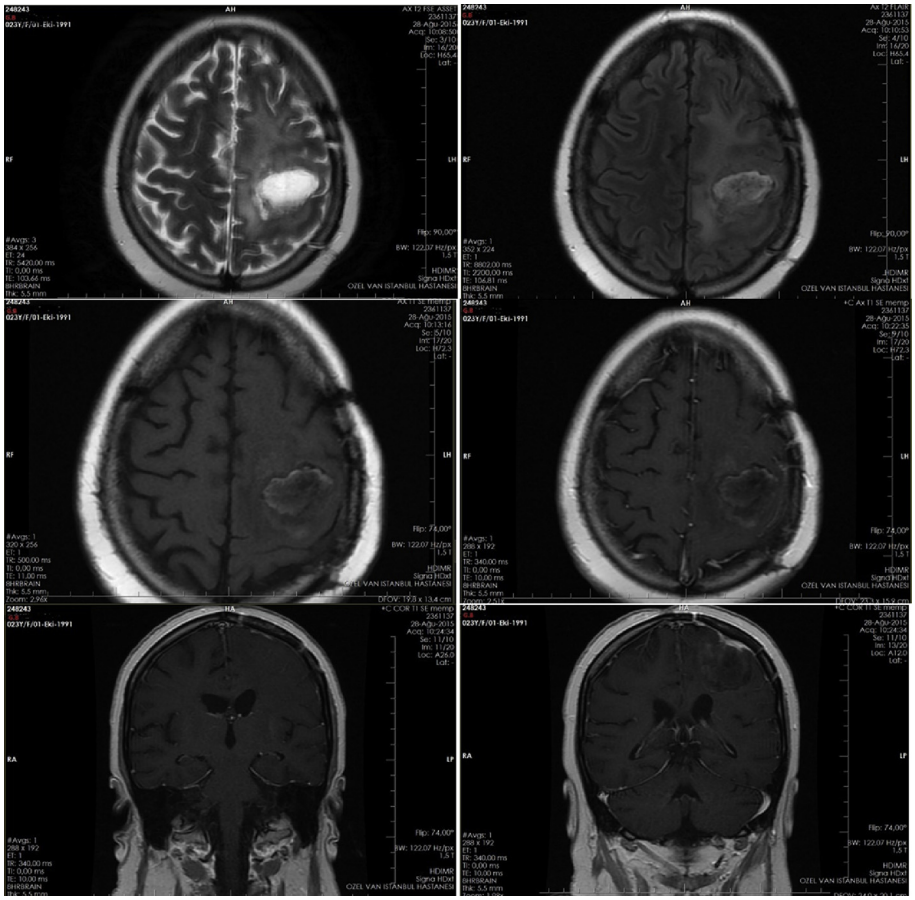

Fig. 7. After 3 cycles bevacizumab plus irinotecan therapy, MRI scan of the brain. T1-weighted and T2 weighted images showing operation area in the left parietal lobe. This area was noted to be peripheral hemorrhagic rim and surrounding edema, but no enhancement. Also decreased edema. It was considered complete response

after re-operation. Other favorable prognostic variables include younger than 50 age, a longer interval since the original surgery, and the extent of the second surgical resection.[34,43]

Re-radiation for recurrent GBM is another method. Re-radiation again provides a 3–5 month median survival. Re-radiation also is not a curative method. Many RT techniques have developed in recent years. Some methods such as brachytherapy and cyber-knife are of these methods. Despite the increase in response rates they are used in the limited cases.[44–49]

CT is other choice in relapse GBM. But blood–brain barrier renders many conventional chemotherapeutics ineffective.[50] This barrier could be overcomed if combined drugs are used.

Often used chemotherapeutic drug is temozolomide. Temozolomide is used in both adjuvant and recurrence cases.[2] Benefit from the temozolomide is primarily to patients with a tumor with a methylated promoter of methyl-guanine methyl transferase.[43]

Irinotecan is a topoisomerase-1 inhibitor with excellent penetration into the central nervous system.[51] It has a different mechanism of action than alkylating agents such as temozolomide, carmustine, and lomustine and has demonstrated modest activity in recurrent GBM.[30,52–54]

Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor (VEGF). It binds and inactivates VEGF, thereby inhibiting angiogenesis, endothelial cell activation and tumor proliferation.[13–16]

The pathognomonic features of GBM are the presence of necrosis and vascular proliferation. VEGF, which is strongly expressed in GBM tumor cells. Although this overexpression is associated with a poor prognosis, it also provides a target that can be blocked by bevacizumab. Bevacizumab as a single agent or combination other chemotherapeutic agents for patients with GBM was used patients with progressive disease despite treatment with other therapies. Bevacizumab plus irinotecan study revealed almost nine months overall survival.[19]

In patients with recurrent GBM patients who were heavily pretreated or had bevacizumab plus irinotecan therapy with different dosage and different day schedule regimen, were found to have almost seven months overall survival. If trials evaluated for side effects, almost didn't seen any important side effect.[5,21,23,55–57]

Conclusion

GBM is the most common primary malignancy of the central nervous system and is a very aggressive malignancy. With improvements in surgery, CT, and RT, a prolonged survival time is observed, although the outcomes are still fatal. There is a dismal prognosis despite combined treatment modalities. The recurrence is inevitable; its management is often unclear. Case dependent recurrence management is often. Treatment decisions for patients with recurrent or progressive disease must be individualized, since therapy is not curative.

As mentioned above, studies have revealed that the maximum median overall survival for patients with recurrent GBM is about 6–10 months. But we obtained a complete response with irinotecan plus bevacizumab therapy in two patients with GBM with fast disease progression.

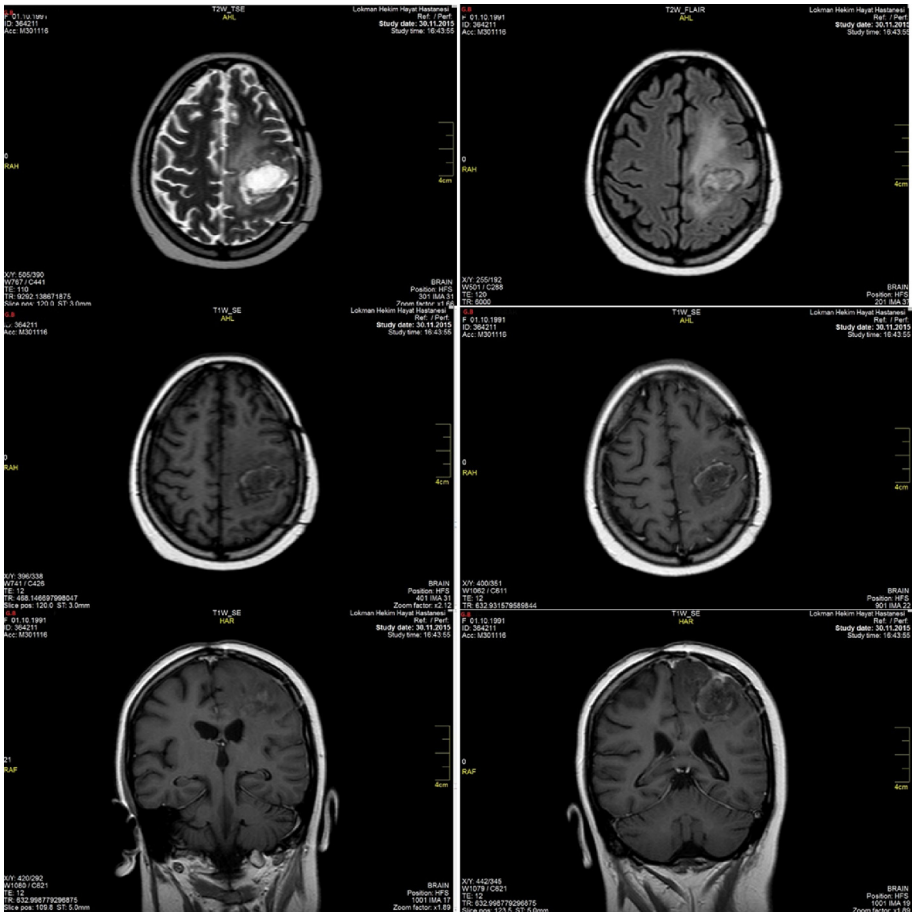

Fig. 8. MRI control assessed sixth month after treatment. Post-contrast enhanced T1WI illustrates no obvious enhancement in lesion area. MRI findings are similar compare to before examination. Complete response was continued

It is unclear if irinotecan or bevacizumab might be used alone in GBM. But when two drugs are combined, an optimal treatment regimen could be achieved in patients with recurrent high grade and fast growing GBM.

It is reported that, in patients with quickly progressed disease and in surgery, RT and CT resistant patients death will be seen very quickly. Non of the treatment regimens could provide complete response in such patients.

Our cases had quite rapidly progressive disease. Bevacizumab plus irinotecan combination therapy provided clinical response after two cycles, and we achieved complete response after six cycles.

Treatment of the patients was completed in 12 cycles. At the end of the first year brain MRI findings of both patients were free of relapses.

We recommend initiation of bevacizumab plus irinotecan combination therapy as early as possible in patients with findings of rapid disease progression. However, we believe that other studies are also needed to keep in mind about it.

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