Glioblastoma Multiforme: A Case Study
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Citation

Abstract
A 65-year-old Caucasian woman with glioblastoma multiforme (GBM) presented to the outpatient neuro-oncology clinic. This article describes the evidence-based chemotherapy, referrals, and symptom management provided for this patient by the advanced practice nurse.

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INTRODUCTION
Advanced practice nurses (APNs) may be responsible for the initiation of chemotherapy and referral for radiation therapy for patients with glioblastoma multiforme (GBM). APNs may also be responsible for managing the symptoms created by the disease and its treatment. This case study describes the management by an APN of a newly diagnosed GBM. The encounter with the patient occurred in the outpatient neuro-oncology clinic of a medical center in a large metropolitan area.

CASE REPORT

HISTORY OF PRESENT ILLNESS
SE was a 65-year-old left-handed Caucasian woman with a history of chronic obstructive pulmonary disease (COPD) and thyroid tumor who began having problems about 6 weeks before becoming a new patient in the neuro-oncology clinic. The patient first became fatigued and short-tempered, and later developed weakness in the left extremities and slurred speech. The family was alarmed by the weakness and speech problems, so they brought the patient to the local emergency department. MRI of the brain with and without contrast showed a right fronto-parietal lesion that enhanced with contrast, and edema (Figure 1). The following day, she was transferred to the care of a neurosurgeon at a medical center. Later that day a stereotactic-guided right fronto-parietal craniotomy with radical subtotal resection of the lesion was performed. The patient was started on phenytoin (Dilantin® ) for seizure prophylaxis, but developed a rash. The medication was therefore switched to levetiracetam (Keppra® ), but she also had a reaction to this medication. She was therefore placed on valproic acid (Depakote® ).

The patient was in rehabilitation for 3 weeks after surgery; the left-sided weakness improved, and she was able to ambulate without assistance. Pathology identified the tumor as a glioblastoma multiforme (GBM). The neurosurgeon referred the patient to the neuro-oncology service for further recommendations regarding treatment of GBM. The patient continued to have fatigue, weakness in the left extremities, and trouble walking. The dysarthria and irritability had resolved. She denied headaches, hearing loss, tinnitus, visual disturbance, dysphagia, dizziness, vertigo, tingling, numbness, loss of consciousness, memory loss, and sleep disturbance.
Figure 1

Figure 1: Pre-operation MRI of the brain

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PAST MEDICAL HISTORY

History of COPD, hypercholesterolemia, thyroid tumor (benign), diverticulosis, gastroesophageal reflux disease (GERD), depression, and complex partial seizures

SURGICAL HISTORY

Significant for partial thyroidectomy, cholecystectomy, and left carpal tunnel release

MEDICATIONS

- Valproic acid (Depakote®) 500 mg oral in the morning, 500 mg oral in the afternoon, and 1000 mg oral at bedtime
- Dexamethasone (Decadron®) 2 mg oral twice daily
- Citalopram (Celexa®) 20 mg oral each day
- Rabepraxole (Aciphex®) 150 mg oral each day
- Fluvastatin extended-release (Lescol XL®) 80 mg oral each day
- Fluticasone 250 mcg/salmeterol 50 mcg inhaler (Advair Diskus®), 1 inhalation every 12 hours

ALLERGIES

- Phenytoin (Dilantin®) — rash
- Levetiracetam (Keppra®) — rash
- Penicillin — rash

SOCIAL HISTORY

Family participated in care. Patient lived with one of her five children

FAMILY HISTORY

Sister had lung cancer. No other family history of cancer and no history of diabetes, hypertension, heart disease, or stroke

PHYSICAL EXAMINATION

Height 63 inches, weight 216 pounds, body mass index 38.3, blood pressure 122/69, temperature 97.2° F, pulse 86, respirations 14, oxygen saturation on room air 98%. Significant findings were left hemiparesis, and gait disturbance with circumduction of the left lower extremity during ambulation

STUDIES REVIEWED

LABORATORY

Neutrophilia secondary to glucocorticoid therapy; valproic acid level in therapeutic range
RADIOLOGY

Post-operative MRI of the brain with and without contrast showed evidence of interval surgical resection of a right fronto-parietal lesion with a small area of residual contrast enhancement in the surgical bed (Figure 2)
Glioblastoma Multiforme: A Case Study

Figure 4
Figure 2: Post-operation MRI of the brain

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PLAN

The case was reviewed with the brain tumor board, which consisted of neuro-radiologists, neuro-pathologists, neurosurgeons, radiation oncologists, neuro-oncologists, and neuro-oncology APNs. The plan of care was presented, and the board concurred with the plan.

DISCUSSION

The prevalence of primary central nervous system tumors is 130.8 per 100,000. Of these tumors, 20.3% are glioblastoma. The incidence of GBM increases with age, with the median age at diagnosis of 64. The tumor is 1.6 times more common in males than females, and is 2.0 times more common in Caucasians than in those of African descent. The 1-year and 2-year relative survival rates for GBM are 29.3 and 8.7 respectively, with less than 4% of those diagnosed with GBM surviving more than 5 years.

Radiotherapy plus concomitant and adjuvant temozolomide (Temodar®) for newly diagnosed glioblastoma, when compared to radiotherapy alone, resulted in a 2.5 month increase in median survival, and a 16.1% increase in the 2-year survival rate. Temozolomide (Temodar®) is an alkylating agent available as oral capsules. The medication alkylates DNA bases, producing cross-links in tumor cell DNA. The cross-links cause breaks in DNA strands, interfering with DNA replication and causing cell death.

Radiotherapy plus concomitant and adjuvant temozolomide (Temodar®) is dosed at 75 mg/m²/day, started the night before the first radiation treatment, and given for 42 consecutive days. Following the completion of radiation therapy and 42 days of temozolomide (Temodar®), there is a 4 week break from treatment. Temozolomide (Temodar®) is increased to 150 mg/m²/day, and given for 5 days every 28 days. If the absolute neutrophil count remains greater than or equal to 1500 per micro-liter and the platelets greater than or equal to 100,000 per micro-liter, the dose of temozolomide (Temodar®) is increased to 200 mg/m²/day.

The potential adverse effects of temozolomide (Temodar®) include myelosuppression, gastrointestinal toxicity, and opportunistic infection. In a phase II trial of temozolomide (Temodar®), myelosuppression was the major toxicity with 88% of subjects experiencing lymphopenia. Nearly all cases of lymphopenia were asymptomatic. Thrombocytopenia and neutropenia were other common adverse effects of temozolomide (Temodar®).

Thrombocytopenia occurred in 47% of subjects and neutropenia in 18%. Alkylating agents tend to have greater effect on rapidly dividing cells. The activity of myelocytes may make them a target of temozolomide's (Temodar®) DNA cross-linking, interfering with the production of lymphocytes, neutrophils and platelets.

Elevations in alanine transaminase (ALT) occurred in 47% of subjects, and elevations in alkaline phosphatase (ALP) occurred in 26%. Elevations in liver enzymes were usually mild. A grade 1 hypocalcemia occurred in 5% of subjects, and grade 1 hypercalcemia in 2%. All electrolyte abnormalities were mild. The mechanism(s) of temozolomide’s (Temodar®) hepatic and electrolyte effects is unclear.

In a phase II trial of temozolomide (Temodar®), laboratory values were obtained on day 22 of 28 day cycles. Hepatic function panels and basic metabolic panels may be obtained every 4 weeks. However, the APN may obtain complete blood counts more frequently than once every 4 weeks to assess for trends in absolute neutrophil and platelet counts that may require intervention.

In a phase II trial of temozolomide (Temodar®), ondansetron (Zofran®) was used for emetic prophylaxis. Nausea and vomiting were still the most common gastrointestinal toxicities, with nausea occurring in 60% of subjects, and vomiting occurring in 59%. In a trial comparing the effects of radiotherapy in the treatment of
GBM to treatment with radiotherapy plus temozolomide (Temodar®), metoclopramide (Reglan®) or a 5-HT₃ serotonin receptor antagonist was given for emetic prophylaxis. No data were provided regarding the effectiveness of metoclopramide (Reglan®) and 5-HT₃ serotonin receptor antagonists at preventing nausea and vomiting. 

Metoclopramide (Reglan®), a dopamine antagonist, and phenothiazines like promethazine (Phenergan®) and prochlorperazine (Compazine®), may cause severe extrapyramidal side effects, hypotension, and sedation. 5-HT₃ serotonin receptor antagonists are less likely to cause significant adverse effects than older anti-emetics, and are more effective for moderate and highly emetic chemotherapies. 9-10 Ondansetron (Zofran®) 8 mg po, granisetron (Kytril®) 1 mg orally, or dolasetron (Anzemet®) 100 mg orally may be given 30 minutes before temozolomide to prevent chemotherapy-related nausea.

Temozolomide (Temodar®) has also been associated with the opportunistic infection Pneumocystis jiroveci pneumonia (PCP). 11-13 Lymphocytopenia is the mechanism for the development of PCP. 14 The APN should consider prescribing PCP prophylaxis for the patient on temozolomide (Temodar®). 3 Sulfamethoxazole-trimethoprim double strength (Bactrim DS®), 1 tablet orally three times a week can prevent PCP. 3,17,18

Radiation therapy may cause headache, vomiting, cerebral edema, hydrocephalus, necrosis, increased intracranial pressure, demyelination, dementia, gait ataxia, focal neurological signs, seizures, dementia, incontinence, brain atrophy, alopecia, and leukoencephalopathy. Corticosteroids can help mitigate the adverse effects of radiation therapy by reducing cerebral edema and decreasing intracranial pressure. 4 However, these medications can also irritate the gastrointestinal tract causing ulceration and hemorrhage. 19 Most patients receiving corticosteroids therefore require gastrointestinal protection with a histamine (H₂) blocker or proton pump inhibitor. 20

Craniotomy patients often receive seizure prophylaxis after surgery. The risk of seizures post-craniotomy, however, is low. 21 In children, the long-term use of anti-epileptic drugs (AEDs) for post-surgery seizure prophylaxis is not indicated, and may be discontinued a month after surgery. 22 The overall seizure rate for post-craniotomy patients restricted to 3 post-op days of an AED was 5.4% over 2.4 years. 23 The incidence of AED side effects warranting discontinuation of the drug in the post-craniotomy patient population is 12.9%. 24 AEDs may cause toxic epidermal necrolysis (TEN) or Stevens-Johnson Syndrome (SJS). For patients taking phenytoin (Dilantin®), cranial radiation increases the risk of TEN/SJS. The reasons for the increase in risk are unclear. 25 Though AEDs do not interact with temozolomide (Temodar®), phenytoin (Dilantin®) and valproic acid (Depakote®) may interact with other chemotherapeutic agents. 20-27 When an old AED is used for seizure prophylaxis in craniotomy patients, the risk of an adverse reaction may be greater than the risk of seizure. 24 Radiation therapy, however, may disturb neuron function and increase risk of seizures. 4 Many patients having craniotomy are put on a newer AED for seizure prophylaxis. Monotherapy with levetiracetam (Keppra®) is commonly used for patients who will be receiving cranial radiation and chemotherapy. 20 The best way to taper and discontinue an AED, however, is a matter of controversy. A systematic review of the literature found no reliable evidence regarding the optimal method for withdrawal of an AED. 26 The APN may choose to continue an AED during radiation therapy and for those patients with no history of seizures, gradually withdraw the AED following the completion of radiation therapy.

Patient education is another APN responsibility, and must include a detailed description of the risks and benefits of radiation therapy, chemotheraphy and other treatment-related medications. The APN also educates patients and their families regarding available support services (e.g., home health and support groups) and, if necessary, makes referrals for psychotherapy and alternative treatments.

**SUMMARY**

GBM is the most common malignant neoplasm of the central nervous system, and carries a grim prognosis. Surgical resection, followed by radiation therapy with concomitant and then adjuvant temozolomide (Temodar®) for those with GBM increases median survival by 2.5 months. 3 The APN may be responsible for prescribing temozolomide (Temodar®), monitoring its effects and the effects of radiation therapy, and managing symptoms. 5-HT₃ serotonin receptor antagonists are effective for chemotheraphy-related nausea, sulfamethoxazole-trimethoprim double strength (Bactrim DS®) is effective for preventing PCP, and corticosteroids help minimize the adverse effects of radiation therapy. Older AEDs carry a greater risk of adverse effects. The APN may prescribe a newer AED for monotherapy.
during cranial radiation, and in patients with no history of seizures gradually taper and discontinue the AED following radiation therapy. APNs also are an integral part of the health care team and are well prepared to provide psychosocial support for patients and their families, to provide education, and to make appropriate referrals.

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References
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