Management of high grade primary cerebellar tumours

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Abstract

Cerebellar high-grade gliomas (cHGG) are uncommon in adults, making up only about 1% of all high-grade gliomas. These tumours differ from supratentorial high-grade gliomas (sHGG) in terms of epidemiology, molecular traits, and the age of the patients. cHGG patients are typically younger and show a higher frequency of neurofibromatosis 1 (NF1) mutations, atypical RAS mutations, and H3K27M mutations. Standard treatment includes surgical resection followed by chemotherapy and radiation. Recent studies emphasize the genetic differences between cerebellar and supratentorial tumours, with new treatments targetting specific molecular abnormalities. Immunotherapy has shown limited effectiveness due to the unique tumour environment in cHGG, and further research is required to improve treatment strategies for these rare tumours.

Keywords: Cerebellar glioma, high-grade glioma, molecular therapies, immunotherapy.

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Introduction

Cerebellum is a common site of primary brain tumour in children but much rare in adults, accounting for approximately 1% of all high-grade gliomas.[1] Approximately 43% of these are isocitrate dehydrogenase (IDH) wild type glioblastoma, 30% are high-grade astrocytoma with piloid features, 8% diffuse midline glioma, and the rest include IDH mutant high-grade gliomas.[2]

The epidemiology of cerebellar high-grade gliomas (cHGG) differs from that of supratentorial high-grade gliomas (sHGG), with cHGG patients typically being younger on average. Data from the US based Surveillance, Epidemiology, and End Results (SEER) registry that includes the largest adult cohort of these tumours, reveals that 36% of cHGG patients are over 65 years of age, while 24% are under 40 years. In contrast, the respective figures for sHGG patients are 46% and 7%. Additionally, there are several genetic distinctions between the two groups; cHGG shows a higher prevalence of neurofibromatosis 1 (NF1) mutations, atypical RAS mutations, and a greater proportion of tumours with H3K27M mutations, commonly classified as grade 4 diffuse midline gliomas (DMG). While verified protocols exist for management of their supratentorial counterparts, limited information regarding cerebellar high-grade gliomas is available.[3]

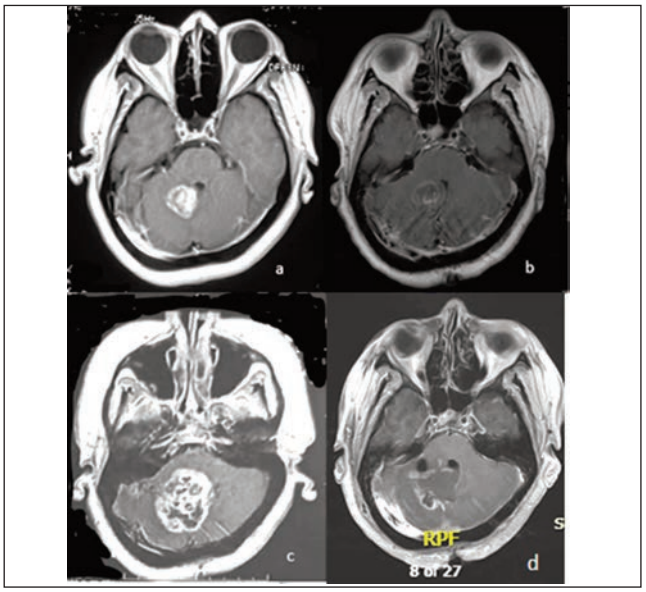

Figure: a) and b) show the first pre-op, post-op MRI post-contrast axial images of middle aged lady with cerebellar HGAP (High-Grade Astrocytoma with Piloid features). c) shows progression of disease 8 months after first surgery (pre 2nd op). d) shows second post op MRI post-contrast axial image (post 2nd op).

Literature Review

Surgical resection remains the primary treatment for high-grade gliomas, considering factors such as patient age, comorbidities, the extent of disease, and proximity to critical brain areas. The goal is to minimize surgical morbidity while achieving effective tumour debulking. Recent advances have emphasized the importance of adjuvant therapy in managing high-grade tumours. Following initial surgery, patients typically receive fractionated external beam radiation therapy, usually delivering 59.4 to 60Gy in 1.8Gy fractions for grade IV astrocytoma and glioblastoma. The preferred concurrent chemotherapy is Temozolomide, administered initially at 75 mg/m^2, followed by 150-200 mg/m^2 for five days each month for six months. Additionally, stereotactic

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radiosurgery has emerged as a novel treatment method, allowing high-dose radiation to be targeted precisely at tumour sites while minimizing exposure to surrounding healthy tissue.[4]

The largest study on the topic included a total of 23,329 patients with a mean age of 58±16 years diagnosed with intracranial glioblastoma. Of these cases, 208 (0.9%) were in the cerebellum. There was a slight predominance of males (58.7%). Nearly 82% patients underwent surgical intervention (28.8% gross total resection, 26% subtotal resection, 12.5% biopsy only). The median survival of patients who underwent gross total resection was 16 months compared to 6 and 7 months for patients who underwent subtotal resection or biopsy only. The overall median survival of patients with cerebellar glioblastoma was 8 months, with 1, 2 and 5 year survival rates of 21%, 13%, and 2% respectively. Patients who did not undergo surgery had a mean survival of 4 months only. Of the total, 72.1% patients with cerebellar glioblastoma received radiotherapy with an overall survival of 11 months in comparison to 2 months for those who did not receive radiation.[5]

The national oncology database sponsored by the American College of Surgeons and the American Cancer Society provides the updated population-based analysis of the treatment trends and outcomes since the standardization of glioblastoma treatment. A total of 665 patients with cerebellar glioblastoma were studied from 2005-2015 and a comparison was made with their supratentorial counterparts with attention to the effect of adjuvant therapy on outcome. According to this study the overall median 1 and 2 year survival rates for cerebellar glioblastoma were 42.6% and 20% respectively. Overall median survival was 9.3 months. Outcomes with surgical management were also studied and the 1 year survival for patients undergoing no surgery, biopsy, subtotal resection, and gross total resection were 33.9%, 40.2%, 35.2%, and 52.4%. The 2 year survival rates were 14.3%, 22.5%, 15.4%, and 27.8% respectively. Among patients who got radiation as part of adjuvant therapy, relative to those not getting any radiation, the 1 and 2 year overall survival were 51.2% vs 25.1% and 23.5% vs 13.7% (p<0.001) with median survival of 12.4 months.[6] There is still no agreement on whether radiotherapy should be administered locally, to the entire brain, or with a craniospinal approach. Some researchers argue that craniospinal treatment is crucial for reducing metastasis. It has been suggested that radiotherapy is especially significant for cerebellar high-grade gliomas (cHGG) due to the high occurrence of unamplified EGFR. This claim is based on the link between radio-resistance and EGFR positivity in supratentorial high-grade gliomas (sHGG) and the anecdotal observation that cHGG patients treated with radiotherapy and lacking EGFR tend to have longer survival rates.[2]

A case report regarding diffusely infiltrating anaplastic astrocytoma of cerebellum shows the role of Bevacizumab as concomitant therapy. According to this report the patient initially underwent partial resection of cerebellar lesion diagnosed on pathology as anaplastic astrocytoma. After which the patient was started on the standard concomitant chemo-radiation therapy (CCRT). But in 5 days of starting therapy the patient experienced worsening of dysarthria so a repeat MRI was done which showed significant enlargement of T2 enhanced area with extension in cerebellar peduncle and a new gadolinium enhancing lesion in midbrain, and the patient had to be switched to Bevacizumab at a rate of 10 mg/kg every 2 weeks. A repeat MRI was done which showed a decrease in T2 enhanced lesion and improvement in the neuronal symptoms. After finishing the concomitant chemo-radiation therapy, patient was discharged with adjuvant Temozolomide and Bevacizumab every 2 weeks. Even at 2 years follow up, the cerebellar lesion remained static on MRI, and no enhancement in midbrain indicating that Bevacizumab can be used as a part of treatment.[7]

A retrospective review comparing various combinations of concomitant chemoradiation on outcome of cerebellar glioblastoma in 21 patients shows that patients who took adjuvant chemotherapy had longer progression free survival (10.1 months) than those who did not receive any chemotherapy (2.5 months). A further subgroup analysis was performed on those patients receiving concurrent Temozolomide versus concurrent therapy with non-Temozolomide agents like Procarbazine, Vincristine and those that had radiation therapy followed by chemotherapy. The median overall survival was 20.4, 17.6 and 19.1 months respectively, whereas the median progression free survival was 7.6, 6.7 and 16.6 months. In case of first recurrence, 8 patients underwent re-do surgery with radiation while 2 patients underwent stereotactic radiosurgery.[3] Emerging treatments for cerebellar glioblastoma show differences from those for supratentorial gliomas, with cerebellar tumours having less EGFR amplification and more CDKN2A/B loss and PDGFRA amplification. PDGFR inhibitors are more effective in cerebellar high-grade gliomas, while EGFR inhibitors are less so, indicating the need to tailor therapies based on these molecular differences.[2]

HGAP (High-Grade Astrocytoma with Piloid Features) is a newly identified subtype of IDH-wildtype glioma that primarily originates in the cerebellum and shares molecular features with pilocytic astrocytoma (PA). Characterized by

alterations in the MAPK pathway, including BRAF fusions and mutations in NF1, FGFR, and KRAS, HGAP is a candidate for targetted therapies like MEK inhibitors, RAF inhibitors, and FGFR inhibitors. Additionally, the presence of ATRX mutations and CDKN2A/B deletions in many HGAP cases suggests potential efficacy for DNA-damaging agents, ATR inhibitors, and CDK inhibitors, particularly when combined with radiotherapy, highlighting the need for further clinical studies focussed on these therapies.[6] A phase-II clinical study failed to demonstrate benefit of palbociclib (CDK inhibitor) in recurrent HGG, but in the light of pre-clinical evidence that concurrent radiotherapy is required for efficacy, further clinical study is warranted, including in HGAP-cHGG.[2]

Diffuse midline glioma (DMG-H3K27M) is driven by abnormal histone modifications leading to epigenetic disruptions, with therapies targetting these changes, including histone deacetylase and demethylase inhibitors, currently in early clinical trials. CAR T-cell therapy targetting GD2, highly expressed in these tumours, shows promise, especially in brainstem and spinal cord locations. Additionally, inhibiting the upregulated STAT3 pathway with the kinase inhibitor WP1066 has shown potential in slowing tumour growth, highlighting new avenues for treatment.[2]

Immunotherapies have had limited success in treating cHGG due to their "cold" tumour microenvironment, which lacks sufficient T-cell infiltration and is further complicated by the use of lymphotoxic treatments and significant tumour heterogeneity. Strategies to overcome these challenges involve converting HGG into "hot" tumours with active immune responses and using combination therapies, such as oncolytic immunotherapy with viruses, which can enhance the effectiveness of other immunotherapies. Despite mixed results from clinical trials of immune checkpoint inhibitors (ICIs) in HGG, combining them with oncolytic viruses may improve outcomes. Understanding the unique immunology of CGB and HGAP is essential for developing effective immunotherapy strategies, as these tumours may require specific approaches due to differences in their microenvironments.[2]

Conclusion

The cerebellum is viewed as a unique region with a lower likelihood of HGG. cHGG possess different molecular features than sHGG. Current standard of care remains surgical resection followed by concurrent chemo-radiation therapy. It is essential to gain a better understanding of the pathogenesis of these tumours and to create targetted therapies that focus on specific molecular drivers and immune environments.

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