Secondary glioblastoma

Epidemiology

Less common than primary Glioblastoma.

Etiology

Secondary glioblastoma arise from malignant degeneration of WHO grade II or III astrocytomas.

Clinical features

Patients are younger and have a slower clinical course.

Diagnosis

The diagnosis of secondary glioblastoma requires clinical (neuroimaging) or histological (bioptic) evidence of an evolution from a less malignant astrocytoma.

Its definition continues to evolve, complicating its clinical management. Investigation of epidemiology and survival patterns may help provide needed insights.

TP53 mutations are present in > 90% of the less malignant precursors. Malignant degeneration is characterized by allelic loss of chromosome 19q and chromosome 10q. MGMT promoter methylation is more common in secondary than in primary Glioblastoma (giving a more favorable response to alkylating chemotherapy agents

Genetic sequencing of 200 glioblastomas uncovered IDH1 and IDH2 as recurrently mutated in 5% of primary glioblastoma and a majority (60–90%) of secondary glioblastomas.

Have a lesser degree of necrosis, are preferentially located in the frontal lobe, and carry a significantly better prognosis.

Histologically, primary and secondary glioblastomas are largely indistinguishable, but they differ in their genetic and epigenetic profiles. Decisive genetic signposts of secondary glioblastoma are IDH1 mutations, which are absent in primary glioblastomas and which are associated with a hypermethylation phenotype. IDH1 mutations are the earliest detectable genetic alteration in precursor low-grade diffuse astrocytomas and in oligodendrogliomas, indicating that these tumors are derived from neural precursor cells that differ from those of primary glioblastomas.

Ohgaki et al. conclude that this genetic alteration is a definitive diagnostic molecular marker of secondary glioblastomas and more reliable and objective than clinical criteria. Despite a similar histologic appearance, primary and secondary glioblastomas are distinct tumor entities that originate from different precursor cells and may require different therapeutic approaches [1].

In 2007 Ohgaki and Kleihues stated that TP53 mutations were the most frequent and earliest detectable genetic alteration, already present in 60% of precursor low grade astrocytomas. The mutation pattern is characterized by frequent G:C–>A:T mutations at CpG sites. During progression to glioblastoma, additional mutations accumulate, including loss of heterozygosity 10q25-qter (approximately 70%), which is the most frequent genetic alteration in both primary and secondary glioblastomas. Primary and secondary glioblastomas also differ significantly in their pattern of promoter methylation and in expression profiles at RNA and protein levels. This has significant implications, particularly for the development of novel, targeted therapies [2].

The age at GB diagnosis is significantly lower (46.22 vs 60.25 years) for group B. The distribution among type of GB (glioblastoma, giant cell glioblastoma, or gliosarcoma) was significantly different, with no diagnosis of giant cell GB in Group B. Compared to Group A, Group B exhibited a higher proportion of females, not married, smaller tumors, no GTR, and no radiation (all $p < 0.05$). GB-related observed survivals were comparable. Cox regression with inclusion of co-variates reveal no significant influence of GB group on observed survival. Regarding group B, mean age was 40.197 for diagnosis of initial lower grade glioma. The most common initial ICD-O-3 pathology was oligodendroglioma, NOS; astrocytoma, NOS; astrocytoma, anaplastic; and mixed glioma.

The SEER-18 registry was queried for patients with GBs. Patients were further classified into two GB groups: Group A - those with GB as the only primary tumor, and Group B - those with GB as a 2nd primary or subsequent tumor and with history of lower grade gliomas. Demographics and clinical factors were compared between group A and B. Appropriate statistics were employed to calculate incidences and differences among factors and GB-related survivals between the groups.

Overall, Group B develops GBs at an earlier age, but observed survival remains similar to those with GBs as the only primary. Moreover, this subset also exhibit different proportions of the types of GBs, and well as differences in other key clinical factors (namely, gender and tumor size at presentation). Prior treatments for lower grade gliomas likely explain some of the differences noted regarding management course after diagnosis of GB [3].

Biomarker for secondary glioblastoma

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1)
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