ALK inhibitor for Glioblastoma

Glioblastoma's lethality is derived from a number of factors including highly active pro-mitotic and pro-metastatic pathways. Two factors increasingly associated with the intracellular signaling and transcriptional machinery required for such changes are anaplastic lymphoma kinase (ALK) and the hepatocyte growth factor receptor (HGFR or, more commonly MET). Both receptors are members of the receptor tyrosine kinase (RTK) family, which has itself gained much attention for its role in modulating mitosis, migration, and survival in cancer cells. ALK was first described as a vital oncogene in lymphoma studies, but it has since been connected to many carcinomas, including non-Small-cell lung cancer and glioblastoma. As the receptor for HGF, MET has also been highly characterized and regulates numerous developmental and wound healing events which, when upregulated in cancer, can promote tumor progression. The wealth of information gathered over the last 30 years regarding these RTKs suggests three downstream cascades that depend upon activation of STAT3, Ras, and AKT [1)].

ALK targeting holds promise as a novel therapeutic approach in Glioblastoma, especially in combination schemes allowing multi-target therapy. Such schemes may incorporate detection-guided therapy and utilize next-generation inhibitory compounds with improved central nervous system penetration. Moreover, identification of ALK-mediated molecular pathway(s) related to Glioblastoma carcinogenesis/ pathology and putative therapy resistance is of high priority and warrants further exploitation [2)].

The antitumor activity of various tyrosine kinase inhibitors were tested against three humans glioblastoma cell lines (U87MG, LN229, and GSC23) in Japan, which expressed substantially low ALK levels; second-generation ALK inhibitors, alectinib and ceritinib, effectively induced Glioblastoma cell death. In addition, treatment with either alectinib or ceritinib modulated the activation of various molecules downstream of receptor tyrosine kinase (RTK) signaling and induced caspase-dependent/independent cell death mainly by inhibiting signal transducer and activator of transcription 3 activations in human Glioblastoma cells. In addition, alectinib and ceritinib also showed antitumor activity against a U87MG cell line with acquired temozolomide resistance. Finally, oral administration of alectinib and ceritinib prolonged the survival of mice harboring intracerebral Glioblastoma xenografts compared to controls. These results suggested that treatment with the second-generation ALK inhibitors, alectinib and ceritinib, might serve as potent therapeutic strategies against Glioblastoma [3)].

References

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