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RESEARCH ARTICLE

CURRENT MANAGEMENT OF BRAINSTEM GLIOMAS.

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Abstract

Brainstem gliomas (BSGs) which have extremely poor prognosis represent up to 20% of all pediatric brain tumors, while only for 1-2% of adult brain tumors. Because of high mortality and morbidity rates of biopsy or any surgical excision, treatment decisions are usually based on MRI findings alone and not include a histopathological diagnosis. However, technologic advances in recent years made it possible to surgically approach BSGs with reduced mortality and morbidity, and therefore, surgery became a more commonly practiced treatment modality than before in such patients. Accessible evidence suggest the conventionally fractionated total dose of 54-60 Gy (1.8-2.0 Gy per fraction) RT as the standard of care for BSG patients, however, it should be noted that treatment response is almost always transient and followed by inevitable fatal recurrences. For this reason, studies focusing on molecules that may enhance the effectiveness of RT may potentially play an important role in changing the poor fate of BSG patients, but, this can only be achievable by cooperative studies targeting tumor biology to determine the genetic characteristics and molecular markers of BSG.

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Introduction:-

Brainstem gliomas (BSGs) are glial tumors with dismal prognosis emerging in the medulla oblongata, pons, or the mid-brain. BSGs represent up to 20% of all pediatric- and 1-2% of all adult brain tumors (1,2). Nearly 75% of all BSG are diagnosed under the age of 20 with the main age peak between 5 and 8 years pursued by a relatively smaller second peak between ages 36 to 45 years (3,4). Since biopsies are seldom rehearsed due to complication concerns, the magnetic resonance imaging (MRI) is the commonest radiologic examination method utilized to classify BSGs: (1) diffusely infiltrative (diffuse intrinsic) low-grade BSGs, (2) enhancing focal malignant BSGs, (3) tectal gliomas, and (4) exophytic gliomas (2). As indicated by the World Health Organization's (WHO) classification, the most common of diffuse intrinsic BSG subtype is the anaplastic astrocytomas (grade 3) which accounts for 80% of all BSGs that is trailed by glioblastoma multiforme (grade 4) and or diffuse infiltrative astrocytomas (grade 2) (5-8). Neuraxial dissemination is uncommon during the diagnosis, though such dissemination is reported approximately in 5 to 25% patients during the autopsy (6,7). Dorsal exophytic, focal and cervicomedullary tumors usually present as grade 1 tumors such as pilocyticastrocytomas or

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gangliogliomas followed by diffusely infiltrative astrocytomas (8,9). Hemangioblastomas can likewise occur in the brainstem in adolescents and young adults with Von Hippel-Lindau disease (10).

Clinical Presentation

Patients with BSG usually present with classic brainstem symptoms such as ataxia, long tract signs, cranial nerve deficits, or any blend of them. Even though symptoms may vary upon the tumor localization, typically, presence of any cranial nerve dysfunction with accompanying long tract signs is usually considered suggestive of a BSG. Patients may also present with headaches and signs of increased intracranial pressure if the cerebrospinal fluid drainage is obstructed by the tumor, which may cause hydrocephalus in up to one-fourth of all cases. Despite most patients have high-performance status at diagnosis, rapid clinical deterioration is unavoidable in practically all patients, if not intervened earlier.

Biology

Though the exact etiology and genetic profile of BSGs are not fully understood yet, still, the accessible limited autopsy and biopsy series gave some clues about the molecular biology of these tumors (11-15). One important reason for the rarity of such studies is the biopsy-related excessive severe toxicity concerns. However, in a recent meta-analysis of 1480 BSG patients reported by Kickingeder et al. (16), encouraging excellent rates of overall morbidity (7.8%), permanent morbidity (1.8%), and mortality (0.9%) were noted with stereotactic biopsy. As exhibited in recent investigations, increased utilization of biopsy procedures may uncover several key molecular targets which may hopefully open potential new windows for targeted therapies (14,17- 20).

Neuroimaging

High-quality MRI is the current imaging choice for a description of the exact location of the tumor and discrimination of diffuse BSGs from their focal counterparts. Focal BSGs appear as highly contrasted and well-demarcated lesions occupying <50% of the pons in MRI examinations, whereas diffuse BSGs appear as poorly contrasted and less or un-demarcated lesions those occupy >50% of the pons with often encasement of the basilar artery (21). Additionally, perfusion MRI, diffusion tensor imaging and proton MR spectroscopy (MRS) may prove useful for the areas of concern where biopsy is judged to be risky (22-26). Although each imaging method provides useful information, MRS has precedence over the others as it informs us about the tumor metabolism (26). In this setting, N-acetyl aspartate (NAA), creatine, lactate, and choline are the most commonly used metabolic indicators. Typically, contrasting with the low NAA levels, the levels of choline (a byproduct of cell membrane turnover) are high in BSGs. Similarly, creatine and phosphocreatine levels are lower than or equal to the levels in normal tissues contrasting with the high lactate. These findings are particularly important for neurofibromatosis type 1 (NF-1) patients. High levels of NAA are interpreted as a sign of NF-1 involvement, whereas low levels indicate a BSG (27). Because so-called “undifferentiated bright objects” are frequently encountered in cases with NF-1 (T2 hyperintensities in the brainstem) MRI should be carefully interpreted to differentiate such lesions from true tumors (28).

18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET), due to the high basal FDG involvement in the surrounding normal brain tissue, is used to identify changes in relapse and post-treatment periods, rather than in the primary imaging of BSG. The higher FDG avidity than the surrounding tissues indicates progressive or relapsed BSGs, whereas none/lower FDG avidity implies necrotic tissues. The current limited role of PET in primary diagnosis and response assessment in BSGs and other brain tumors will undoubtedly be broadened with the implementation of novel PET tracers specific to brain imaging. Of note, cystic structures and possible intra-tumoral hemorrhage following radiation therapy (RT) are the situations to be distinguished from tumor progression, where pulse sequence gradient echo or computed tomography (CT) scans might prove beneficial (22).

Prognostic Factors

Short life expectancies complicate the identification of factors those may influence the course of disease in BSG patients, therefore, only a limited number of studies have been reported to specifically address this issue. Albright et al (29) reported cranial nerve palsies and higher mitotic index as indicators of poorer prognosis, whereas the presence of intratumoral calcification and/or Rosenthal fibers as relatively better prognosticators. In other studies, the presence of long-tract signs (30), age under 3-years (31), and short symptom duration (32) was reported to indicate a poorer prognosis. Although the exact relationship between cranial nerve damage, long-tract signs and BSG prognosis not known, they are accepted as signs of an aggressive tumor phenotype. Compared to other types,

diffuse BSG has a distinctly poor prognosis (21). Since the NF-1 patients have a favorable disease course and longer life expectancies, such patients must be managed as a distinct group (33).

Treatment

Surgery

Treatment decisions for BSGs are generally grounded on MRI findings alone with no histopathological verification as a result of the high morbidity and mortality concerns, although the diagnostic accuracy of MRI has not been affirmed at this point by histopathological findings (34). Several studies have demonstrated that the histopathological findings might reveal different pathological entities apart from diffuse gliomas, such as the primitive neuroectodermal tumors (PNET), malignant teratoidrhabdoid tumors, pilocyticastrocytomas or brainstem infections including the pontine tuberculoma or histiocytosis (35-39). This differentiation may serve vital in particular cases: the chemoradiotherapy is a reasonable treatment option for PNETs (36), while pilocyticastrocytomas may stay stable for long periods even without any treatment (5,8).

Surgery might be performed for tissue diagnosis in the form of biopsy or resection, but, meaningful resection is often not possible. On the other hand, in some tumors, such as the tectal gliomas, even partial resection may relieve symptoms for long durations and may eliminate the need for any further adjuvant treatment (40). Technologic advances in the recent years rendered it conceivable to surgically approach BSGs with reduced mortality and morbidity rates. Consequently, surgery turned into a more generally rehearsed treatment modality than before in such patients. Surgery may really be beneficial in some patients' groups, however, it is hard to solidly remark whether these surgical results speak to an improvement over those reported in modern RT series or not, in absence of comparative studies.

Chemotherapy and Immunotherapy

The data on combination or single-agent chemotherapy are scarce and till now, neither of randomized phase 3 studies could report results favoring the addition of neoadjuvant/concurrent/adjuvant chemotherapy to standard RT. The unrevealed tumor biology, resistance chemotherapeutics, and poor penetration of drugs hamper the efficacy of single- or multi-agent chemotherapy regimens (41). In contrast to adult glioblastoma multiforme, unfortunately, addition of temozolomide (TMZ) to RT did not result in any survival advantage with median survival of 9 to 10 months (42-44). Various cytotoxic and non-cytotoxic radiosensitizers have also been investigated in BSG patients but no success has been reported yet (45-49).

Immunotherapy-based enhancement of the antitumor immunity is another area of research to increase the efficacy of other treatments in BSGs. One of the most popular topics in this field is the interferon, which unfortunately yielded limited and problematic results. Wakabayashi et al (50) who added interferon- α to chemotherapy and RT reported 3 complete and 9 partial responses in a cohort of 16 diffuse BSG patients, and the responders had a median survival times better than the frequently reported <10 months period. In contrast, Packer et al (51) was not able to confirm this promising outcome in a further phase I/II study in 32 BSG patients, rendering the role of immunotherapy questionable.

Radiotherapy

Radiotherapy (RT) is the only treatment modality that proved to improve survival to the range of 7-16 months (52). Moreover, despite being transient, RT improves neurologic functions and patients' quality of life measures. RT which has been standard utilized for all BSGs previously is currently more selectively practiced and reserved for progressive stages in patients with better prognosis. Conduction of randomized studies in BSGs was judged to be an impossible mission for many years because of the relative rarity of new cases. Despite of this fact, radiation oncologists from 13 centers within the Pediatric Oncology Group (POG) decided to share their experiences in 1983 in order to reach meaningful results. As a result of this first commendable effort, data of 62 BSG patients treated between January 1972 and December 1981 were collectively analyzed, and Freeman et al (53) reported 3-year survival rate as 23%. No matter how disappointing the results were, they influenced the future clinical studies in a significant manner: First, surgery was proved to be useless in such patients other than the diagnostic and tumor debulking purposes. Second, RT was discovered and accepted as the choice of treatment for BSG patients. Third, focal RT was recognized as the adequate radiation portal regarding the rarity of BSG dissemination along the craniospinal axis in absence of local progression. And finally, both the power and vital importance of multicenter studies in achieving conclusive remarks for such rarely diagnosed tumor groups stimulated the other investigators for further collaborative studies. Consequently, as depicted in Table 2, many studies have been designed to

investigate optimal treatment options for BSG patients (30, 53-65). As a result, conventional RT of 54-60 Gy (1.7-2 Gy/fraction, in 6 weeks) became the accepted standard treatment diffuse infiltrative BSG. Although later higher RT doses up to 64.8-78 Gy was tested by using hyperfractionation, unfortunately, such higher doses were found to increase treatment related severe complications such as steroid addiction, vascular events, changes in white substance, loss of hearing, seizures, and hormonal disorders (55-65), without any remarkable survival advantage.

Concurrent use of TMZ with RT has been rapidly adapted for BSG patients based on the promising results reported by Stupp et al. in newly diagnosed glioblastoma multiforme patients (66). In a recently published phase I study by the Children's Oncology Group, 63 patients diagnosed with diffuse intrinsic BSG were treated with 59.4 Gy (1.8 Gy) RT and concurrent doses of TMZ 90 mg/m² /day followed by 200 mg/m²/day to be a total of 10 cycles (42) and the outcomes were compared with the outcomes of Children's Cancer Group (CCG) 9941 protocol. The primary purpose of the study was defined as 1-year event-free survival. Tragically, the 1-year event-free survival rate was found to be 14% which was significantly lower than the 21.9% obtained from CCG-9941. Furthermore, median survival time of 9.6 months was demonstrative for inefficacy of TMZ in BSGs. The reason behind the ineffectiveness of TMZ was hypothesized to be associated with failure of the epigenetic silencing of methylguanine methyltransferase (MGMT) enzyme. However, in a recent study Zarghooni et al. (67) refuted this hypothesis as no expression of MGMT was found in the molecular analysis of 11 patients.

Targeted therapy in this patient group is another potential treatment modality and several agents have been introduced, but unfortunately, yet none of the tested agents could demonstrate a meaningful improvement in the prognosis of BSG patients compared to standard RT. It has been shown that EGFR is highly expressed in diffuse infiltrative pontine gliomas patients with significant gene amplification (68). Pediatric Brain Tumor Consortium (PBTC) used gefitinib during and after RT in 43 patients (69). Respective 56.4% and 19.6% overall survival rates reported for 1- and 2-years were superior to other PBCT studies. Haas-Kogan et al. (70) in a phase II study of 40 BSGs tested the farnesyltransferase inhibitor tipifarnib concurrent with and after RT. However the median 6.8 months progression-free and 8.3 months overall survival times were not different from the historic RT series. Thalidomide, an antiangiogenic agent, did not demonstrate any increase in survival as a single agent or as a component of multi-agent chemotherapy protocols (71-73). Platelet derived growth factor (PDGFR), VEGFR, c-KIT inhibitors, and imatinib are also widely interested agents, however neither of them could demonstrate any survival benefit to date (74,75).

Brachytherapy and stereotactic radiosurgery have been tried on selected patients but did not demonstrate any advantage over conventional RT. Besides, their negative effects on patients' quality of life, unacceptable life threatening risks of such RT techniques limited related studies (76-79). The major causes of RT failures following such restricted field RT techniques are attributed to the diffuse infiltrative nature of the tumors (21).

Although the accessible evidence suggest 54-60 Gy RT as the standard treatment for BSGs, yet, it should be remembered that treatment the treatment response is almost always transient and followed by inevitable fatal recurrences. For this reason, studies focusing on molecules that may enhance the effectiveness of RT may play an important role in changing the poor fate of BSG patients, but, this can only be achieved by conduction of future cooperative studies targeting the tumor biology to determine the genetic characteristics and molecular markers of this tumor type.

Brainstem Gliomas Associated with Neurofibromatosis-1

Although the optic glioma is the most common type of brain tumors in NF-1 patients, other tumors can be seen all through the neuraxis including the BSG. Despite its relative rarity, BSG can represent a treatment challenge when diagnosed in such patients. In NF-1 patients BSG progress relatively slower than those diagnosed in patients without NF-1 (80). For example, in a series of 21 patients, Pollack et al. (81) demonstrated that only 9 patients presented with symptoms, only 4 of which required intervention. Further, in long-term, disease stabilization or regression was reported in 7 out of 10 patients, who previously showed signs of progression. In another study, Molloy et al. (33) reported that 15 of 17 patients with radiographic and symptomatic presentation survived beyond 52 months; further confirming the indolent course of NF-1 associated BSG. Therefore, in patients with NF-1 all patients should better be evaluated carefully with a conservative treatment approach regarding that close observation may be sufficient in asymptomatic patients. However, for patients with radiographic progression and symptomatic presentation, treatment should be planned as for the other BSGs.

Brainstem Gliomas in Adults

BSG are rare in adults and constitute only 2% of all primary CNS tumors (82). In contrast with BSG diagnosed in children, adult BSG follow a relatively slower clinical course and a better prognosis even if they have the same grade according to WHO classification. However, it should be noted that usual median progression-free and overall survival times after treatment are respectively 11 and 16 months, which are still far less than being satisfactory (83). Because only limited data are available for adult BSGs, they are treated in a similar manner with childhood BSGs. Same conventional fractionation scheme and doses of 54-60 Gy RT are considered to be the present standard of care, and the role of chemotherapy and other treatment modalities remain to be experimental.

Radiotherapy Volume, Dose and Techniques

Standard RT for BSGs is 54-60 Gy (1.8-2 Gy per fraction); escalated doses and alternative fractionation schemes did not reveal any further benefit as discussed previously. Target volumes should necessarily be determined on MRI, and, since gross tumor extension is determined best by T-2 or FLAIR MRI sequences, same sequences should be preferred for gross tumor volume (GTV) delineation. Clinical target volume (CTV) is usually created by giving GTV a margin of 1-1.5 cm, but to prevent unnecessary toxic events, margins should be adjusted by accounting for the tumor location and anatomical barriers. Planning target volume (PTV) is usually determined by adding 0.3-0.5 cm to CTV. Craniospinal RT should be avoided in BSG cases since brainstem is the primary location of recurrence with only <5% exclusive neuroaxis dissemination. Two dimensional treatments should be avoided. Three-dimensional treatment including conventional intensity-modulated RT techniques should be utilized to reduce the incidence of potential acute and/or late toxicities. PTV must be covered by 95% and 107% of the prescribed dose, and hot spots must carefully be kept away from critical organs. In order to prevent acute and late complications, doses of spinal cord, brain stem, optic chiasm, optic nerve, cochlea, hypothalamus, pituitary and temporal lobes should be kept within the related tolerance limits accordingly. Excluding the surgically managed cases, RT should start as soon as possible.

Management of Recurrent Brainstem Gliomas

Although BSGs often shrink in response to RT with a resultant improvement in patients' symptoms (85), median time to disease progression is still only 5-6 months. Despite various phase II studies specifically addressing the recurrent BSGs have been conducted (86-89), it is difficult to rely on these results in absence of historical control data. In a recent study from MD Anderson Cancer Center, response to various chemotherapeutics and/or low-dose RT, survival and possible prognostic factors were evaluated in a group of 31 recurrent BSGs (85). Seven patients underwent re-irradiation of 18-20 Gy (2 Gy/fr) to the primary tumor region. However, complete response was achieved in none of the re-irradiated patients, and most common response type was stable disease with only 2 months of progression-free interval. This interval was found to be correlated to prior progression-free interval but not to the number of previous treatment attempts. Interestingly, despite of the low RT dose utilized, highest response rate (57%) and longest progression-free survival was achieved in re-irradiated patients. This data which suggests a beneficial role for re-irradiation of primary tumor site in recurrent BSGs should be interpreted as hypothesis generating and tested in further phase III randomized trials.

Conclusion:-

The results of two respective recent meta-analyses of the published studies between 1984 and 2005 by Hargrave et al. (52), and between January 2005 and March 2011 by Jansen et al. (90) have shown that the current 5 to 9 months median progression-free- and 8 to 11 months overall survival times in BSGs were not different from those results achieved 30 years ago. Therefore, it is imperative to point out that, unfortunately, despite the significant advances in the diagnostic and treatment tools, no clear improvement in survival has been achieved in BSG patients. Since then the current standard RT for BSGs constitute 54-60 Gy (1.8-2 Gy per fraction) with systemic therapies still being experimental In order to improve results, studies should focus on the biology of the tumor, more efficient chemotherapeutics, and targeted agents in concurrent with and/or adjuvant RT settings. Given the low incidence of the disease, this goal can only be achieved by cooperative group study designs.

Table 1:-Clinical, radiological, and histological characteristics of brainstem gliomas

Type of tumor	Diffuse intrinsic	Focal midbrain	Dorsal exophytic	Cervico /Medullary junction
Frequency (%)	75-85	5-10	10-20	5-10

Symptoms and signs	Short symptom duration Ataxia Long track sign Multiple cranial nerve deficits	Increased intracranial pressure Ataxia Isolated cranial nerve deficits	Increased intracranial pressure Nystagmus Isolated cranial nerve deficits	Cranial nerve deficits Apnea Sensory disturbances Long track sign Torticollis Hydrocephalus
MRI findings	Diffuse pons enlargement Minimal contrast enhancement Hypointensities T1 Hypointensities T2	Small, well demarcated Variable contrast enhancement No edema Hypointensities T1 Hyperintensities T2 Ventricle enlargement	4 th ventricle location Hypointensities T1 Hyperintensities T2 contrast enhancement	Cervicomedullary location Extension to 4 th ventricle Hypointensities T1 Hypointensities T2
Histology	Astrocytoma (Grade II-IV)	Astrocytoma (Grade II-III) Ganglioglioma	Pilocytic Astrocytoma Astrocytoma (Grade II)	Low-grade astrocytoma Ganglioglioma

Table 2:-Clinical studies of brainstem gliomas

	Patients (N)	Median survival (month)	Survival (%)		
			1-y	2-y	3-y
Freeman et al. 36-60 Gy (53)	62		50	29	23
Guiney et al. 20-55 Gy (54)	32	34			49
POG 8495 HFRT (30, 55, 56)					
66 Gy (1.1 Gy/fr bid)	38	11	48	6	3
70. Gy (1.17 Gy/fr bid)	57	10	40	23	21
75.6 Gy (1.26 Gy/fr bid)	39	10	39	6	6
SJCRH (57)					
70.2 Gy (1.17 Gy/fr bid) + EP	9	11	44	11	
POG 9239 (58)					
54 Gy (1.8 Gy/fr + Cisplatin)	130	8	31	7	4
70.2 Gy (1.17 Gy/fr bid) + Cisplatin			17	7	5
POG 8495 (59)					
70.2 Gy (1.17 Gy/fr bid)	131	10	40		
CHOP/NYU (60,61)					
64.8 Gy (1.2 Gy/fr bid)	16	11	48		
72 Gy (1.0 Gy/fr bid)	35			28	
CCG 9882 (61-63)					
72 Gy (1 Gy/fr bid)	53	9	38	14	8
78 Gy (1 Gy/fr bid)	66	9.5	35	22	11
UCSF(64, 65)					
72 Gy (1 Gy/fr bid)	20	13			
78 Gy (1 Gy/fr bid)	39	10.8			

Abbreviations: CCG: Children's Cancer Center, CHOP/NYU: Children's Hospital of Philadelphia/New York University, fr: Fraction, POG: Pediatric Oncology Group, RT: Radiation therapy, SJCRH: St. Jude Children's Research Hospital, UCSF: University of California, San Francisco.

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