Therapeutic Approaches in Adult Primary Spinal Cord Astrocytoma

Subjects: Oncology

Contributor: Elena Anghileri, Morgan Broggi, Elio Mazzapicchi, Andrea Botturi

Gliomas are primary tumors arising from supporting cells of the central nervous system (CNS), usually in the brain. The 2021 World Health Organization (WHO) classifies gliomas as adult-type diffuse gliomas or circumscribed astrocytic gliomas depending on their histology and molecular features. Spinal astrocytic gliomas are very rare, and nowadays no standard of therapy is available. Treatment options are limited: surgery is often not radical, and adjuvant therapies include mostly radiotherapy (RT) or systemic chemotherapy (CHT).

Keywords: astrocytoma ; spinal cord ; therapy ; safety ; spinal cord astrocytoma (SCA) ; adult

1. Introduction

Primary spinal cord tumors are rare, representing about 4–8% of all tumors of the central nervous system (CNS) [1], that is, 10 to 15 times less common than their cranial counterparts. They are conventionally divided according to their anatomic location into three categories: extradural, intradural extramedullary, and intramedullary. Intramedullary spinal cord tumors (IMSCTs) are the rarest type, representing 20% of all intraspinal tumors. Their incidence has been reported as 0.22 per 100,000 person-years [2].

Spinal cord gliomas in adults include ependymomas and astrocytomas, representing 90% of IMCSTs. Ependymomas account for 60%; spinal cord astrocytomas (SCA) account for 30% of IMCSTs and only 3% of CNS astrocytomas [3]. The remaining IMCSTs include hemangioblastomas (3 to 8%), metastases (2%), primary CNS lymphomas, neurenteric cysts and dermoid/epidermoids and other miscellaneous tumors.

Based on the tumor location, neurological signs often deeply impact patients' quality of life. Clinical evaluation is a key point of the overall evaluation, also including the pain component [4][5][6].

The literature on SCA biology and the evolution of SCA is very poor, and any targeted therapies are lacking. Nowadays therapy is mostly derived from the brain counterpart, but "standard of care" or homogenous guidelines have not been developed yet.

The management of these lesions depends not only on the histopathological diagnosis but also on the clinical presentation and the anatomical location, allowing radical or less invasive surgery, also supported by intraoperative neuromonitoring, with minimally invasive approaches currently available.

While surgery is the mainstay treatment for grade 1 astrocytoma, and to a lesser extent for higher infiltrative-grade lesions [4], radiotherapy (RT) and chemotherapy (CHT) are of growing importance after partial removal and in recurrent and multifocal lesions. Besides the traditional alkylant drugs, targeted therapy could represent incoming promising therapy based on targetable gene mutations [7].

2. Therapeutic Approaches in Adult Primary Spinal Cord Astrocytoma

In contrast to their intracranial counterpart, the SCA still have no management consensus among clinicians but they cause even more disabling outcome and also affect younger subjects than the intracranial cases. Considering treatments, less well-defined margins between the tumor and normal spinal cord make gross total resection an extremely great challenge [8]. Treatments were most frequently surgery and RT. The effect of CHT, which like temozolomide (TMZ) was proven to be effective for intracranial glioblastoma (GBM), remains controversial on spinal cord GBM as well as in lower grade SCA. Very anecdotally targeted therapy was reported.

Recently, a systematic review study of the literature from January 2000 to June 2021, including both clinical trials and observational studies on histological SCA, with a minimum follow-up of 6 months and reporting the overall survival, progression-free survival or clinical neurological outcome after any therapeutic approach (surgery, RT or CHT) [9]. A total of 1197 citations were identified by the Medline search and additional records; based on the inclusion criteria, 18 studies were included with a total of 285 adult patients.

The available literature data are limited to series/retrospective studies, including heterogeneous patients, i.e., astrocytoma as well as ependymoma or pediatric/adult age, with scanty data on the outcomes of interest. No clinical trials have been run [9].

SCA molecular features, are still largely under-investigated, and that they could result extremely useful for therapeutic approach (i.e., BRAF–MEK inhibitors for BRAF mutant glioma).

As consequence of the difficulties of surgical exeresis, histologic grading can be challenging in SCA because of the relatively small samples obtained with surgical procedure. Therefore, grade-defining molecular biomarkers would be particularly useful for the accurate diagnostic classification of these tumors [10].

The few data available in the literature reported that molecular profile in SCA did not mirror the cerebral counterpart [11].

In 2016, Shankar et al. reported a statistically significant difference ($p < 0.001$) comparing H3F3A K27M presence in grade III and grade IV vs. grade I and grade II (mostly pediatric) astrocytomas. The most recurrent findings in grade I SCA were a BRAF-KIAA1549 translocation ($n = 3/10$) and BRAF copy number gain ($n = 5/10$). WHO grade II SCA were similarly characterized by alterations involved in the MAPK-ERK or PI3K pathways, including BRAF-KIAA1549 translocation ($n = 1/3$) and BRAF amplification ($n = 2/3$) [12]. BRAF fusion detection in grade I and grade II SCA was also confirmed by Lebrun L et al., 2020 [11] and [13], that described besides KIAA1549-BRAF fusion oncogenes, 16 new SCA-associated fusion transcripts in 31 adult SCA sample.

All of the grade III and grade IV glioma presented at least one molecular alteration, with the most frequent one being the H3F3A p.K27M mutation. The H3F3A p.K27M mutation showed a better prognosis [11]. The combination of retained H3K27me3 and negative EZH2 expression was also reported as being related to favorable overall survival ($p = 0.03$) among WHO grade II-IV cases by another group [14].

Nagashima et al., 2021 focused on the impact of Driver Genetic Mutations in Spinal Cord Gliomas and concluded that gliomas with H3F3A mutations were associated with accelerated tumor-associated spinal cord injury, leading to functional impairment. Conversely, the presence of IDH mutations, which are rarely reported in spinal gliomas, indicated a relatively favorable functional prognosis [15]. Biczok et al., 2021 identified five distinct subgroups in 26 patients (adults and pediatrics) of spinal astrocytomas based on molecular data. Histology and NGS allowed the distinction of five tumor subgroups: glioblastoma IDH wildtype (GBM); diffuse midline glioma H3 K27M-mutated (DMG-H3); high-grade astrocytoma with piloid features (HAP); diffuse astrocytoma IDH mutated (DA), diffuse leptomeningeal glioneuronal tumors (DGLN) and pilocytic astrocytoma (PA). Within all tumor entities GBM (median OS: 5.5 months), DMG-H3 (median OS: 13 months) and HAP (median OS: 8 months) showed a fatal prognosis. HAP are characterized by CDKN2A/B deletion and ATRX mutation. 50% ($n = 4/8$) of PA tumors carried a mutation in the PIK3CA gene, seemingly associated with better outcome [7]. All of them represent a targetable mutation.

Based on the rarity of adult SCA and the limited number of studies available, the literature did not provide enough data to determine a recommended treatment plan for SCA. Multicentric clinical trials, including molecular investigations, are mandatory to better manage such a rare disease.

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