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New perspectives in the treatment of adult medulloblastoma in the era of molecular oncology

Alba A. Brandes[a,*], Marco Bartolotti[a], Gianluca Marucci[b], Claudio Ghimenton[c], Raffaele Agati[d], Antonio Fioravanti[e], Maurizio Mascarin[f], Lorenzo Volpin[g], Franco Ammannati[h], Barbara Masotto[i], Marina Paola Gardiman[j], Dario De Biase[k], Giovanni Tallini[k], Girolamo Crisi[l], Stefania Bartolini[a], Enrico Franceschi[a]

[a] *Department of Medical Oncology, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS Institute of Neurological Sciences, Bologna, Italy*
[b] *Department of Biomedical and NeuroMotor Sciences (DiBiNeM), University, of Bologna, Section of Pathology, M. Malpighi, Bellaria Hospital, Bologna, Italy*
[c] *Pathology Department, Verona Hospital, Verona, Italy*
[d] *Department of Neuroradiology, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS Institute of Neurological Sciences, Bologna, Italy*
[e] *Department of Neurosurgery, Bellaria Hospital – IRCCS Institute of Neurological Sciences, Azienda USL, Bologna, Italy*
[f] *Department of Radiotherapy Unit, CRO, Aviano, Italy*
[g] *Department of Neuroscience and Neurosurgery, San Bortolo Hospital, Vicenza, Italy*
[h] *Department of Neurosurgery I, Careggi University Hospital, Firenze, Italy*
[i] *Section of Neurosurgery, Department of Neuroscience, University of Verona, Verona, Italy*
[j] *Surgical Pathology & Cytopathology Unit, Department of Medicine (DIMED), University Hospital, Padova, Italy*
[k] *Department of Medicine (DIMES) – Anatomic Pathology Unit, Bellaria Hospital, University of Bologna, Bologna, Italy*
[l] *Department of Neuroradiology, Parma University Hospital, Parma, Italy*

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* Corresponding author at: Department of Medical Oncology, Bellaria-Maggiore Hospitals, Azienda USL – IRCCS Institute of Neurological Sciences, Via Altura 3, 40139 Bologna, Italy. Tel.: +39 051 6225697; fax: +39 051 6225057.
E-mail address: alba.brandes@yahoo.it (A.A. Brandes).

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Abstract

Medulloblastoma is the most common central nervous system tumor in children, while it is extremely rare in adults. Multimodal treatment involving surgery, radiotherapy and chemotherapy can improve the prognosis of this disease, and recent advances in molecular biology have allowed the identification of molecular subgroups (WNT, SHH, Groups 3 and 4), each of which have different cytogenetic, mutational and gene expression signatures, demographics, histology and prognosis.

The present review focuses on the state of the art for adult medulloblastoma treatment and on novel molecular advances and their future implications in the treatment of this disease.

Keywords: Medulloblastoma; Adults; Treatment; SHH; WNT

1. Introduction

Medulloblastoma, a malignant, invasive, embryonal tumor of the cerebellum with a preferential manifestation in children and a marked tendency to cerebro-spinal fluid (CSF) metastatization [1], is found in 15–30% of all childhood primary tumors of the central nervous system (CNS). About 70% of the cases occur in patients under 15 years of age, the incidence peak being 3–6 years [2]. In adults, medulloblastoma is much less frequent, accounting for less than 3% of primary CNS tumors. A recent US registry analysis from the Surveillance, Epidemiology, and End-Results (SEER) database [3] found that the incidence of medulloblastoma was 1.5 cases per million in the general population, children being ten times more likely to develop the disease than adults (6.0 vs. 0.6 cases per million). Males are 1.58 times more likely than females to be diagnosed with medulloblastoma during childhood, but this difference is not maintained in adulthood [3].

2. Histopathology and biology

The exact cellular origin of medulloblastoma is a matter of debate. It has been suggested that the disease might arise from two distinct embryonal cell groups: cells from the ventricular zone (VZ), which differentiate into Purkinje cells, basket cells, and other glial and neuronal cells of the cerebellum, and cells from the external germinal layer (EGL) that produces cerebellar granule cells. These cell groups are related to different molecular subtypes of medulloblastoma: it widely known that VZ cells give origin to the wingless (WNT) subtype, while sonic hedgehog (SHH) medulloblastomas derive from EGL cells [4].

The latest 2007 WHO classification [1] of CNS describes five histopathological subtypes of medulloblastoma: classic (80% of all medulloblastomas in children, 70% in adults), desmoplastic (15% in children, 30–40% in adults), anaplastic (10–20%), large-cells (2–4%), and extensive nodularity (3%). Differences between children and adults have been found for histological subgroups, which are of prognostic significance: desmoplastic and nodular subtypes are associated with a better prognosis in children <5 years of age whereas anaplastic and large-cells are associated with poor prognosis in all age patients [5]. Medulloblastoma, typically having a median localization in children, is more commonly lateral in adults [6].

3. Clinical and radiological presentation

Because medulloblastoma arises in the posterior fossa, a frequent complication is hydrocephalus due to the compression of ventricle IV, with a consequent increase in intracranial pressure. Common symptoms are vertigo, vomiting, ataxia and headache. Patients with a tumor localized in the mid-cerebellum may have symptoms (nystagmus,