PRIMEVIEW

MEDULLOBLASTOMA

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Medulloblastoma (MB) is one of the most common childhood malignant brain tumours. It originates within the brainstem or the cerebellum, which are located in the posterior fossa. Although many patients now survive MB, these individuals can develop chronic health complications as a direct result of the tumour and its treatments, in addition to secondary malignancies.

EPIDEMIOLOGY

MB comprises ~63% of childhood intracranial embryonal tumours and has an annual incidence of ~5 cases per million individuals. In some individuals, MB manifests later in adolescence or in adulthood. Heritable factors are currently the only well-established risk factors for MB and include pathogenetic mutations in genes coding for proteins that have a role in developmental signalling pathways and DNA repair.

DIAGNOSIS

Imaging using brain and spinal MRI is required for MB diagnosis. However, other paediatric brain tumours are radiologically similar to MB and are also located in the posterior fossa; thus, histopathological and molecular analyses are essential to confirm a diagnosis. Results from imaging and cerebrospinal fluid cytology can be used for MB staging. DNA methylation profiling is the current gold-standard technique for determining the subgroup of MB.

Many clinical manifestations of MB are non-specific, such as headache, nausea and fatigue. More-specific symptoms include ataxia and difficulties with motor skills.

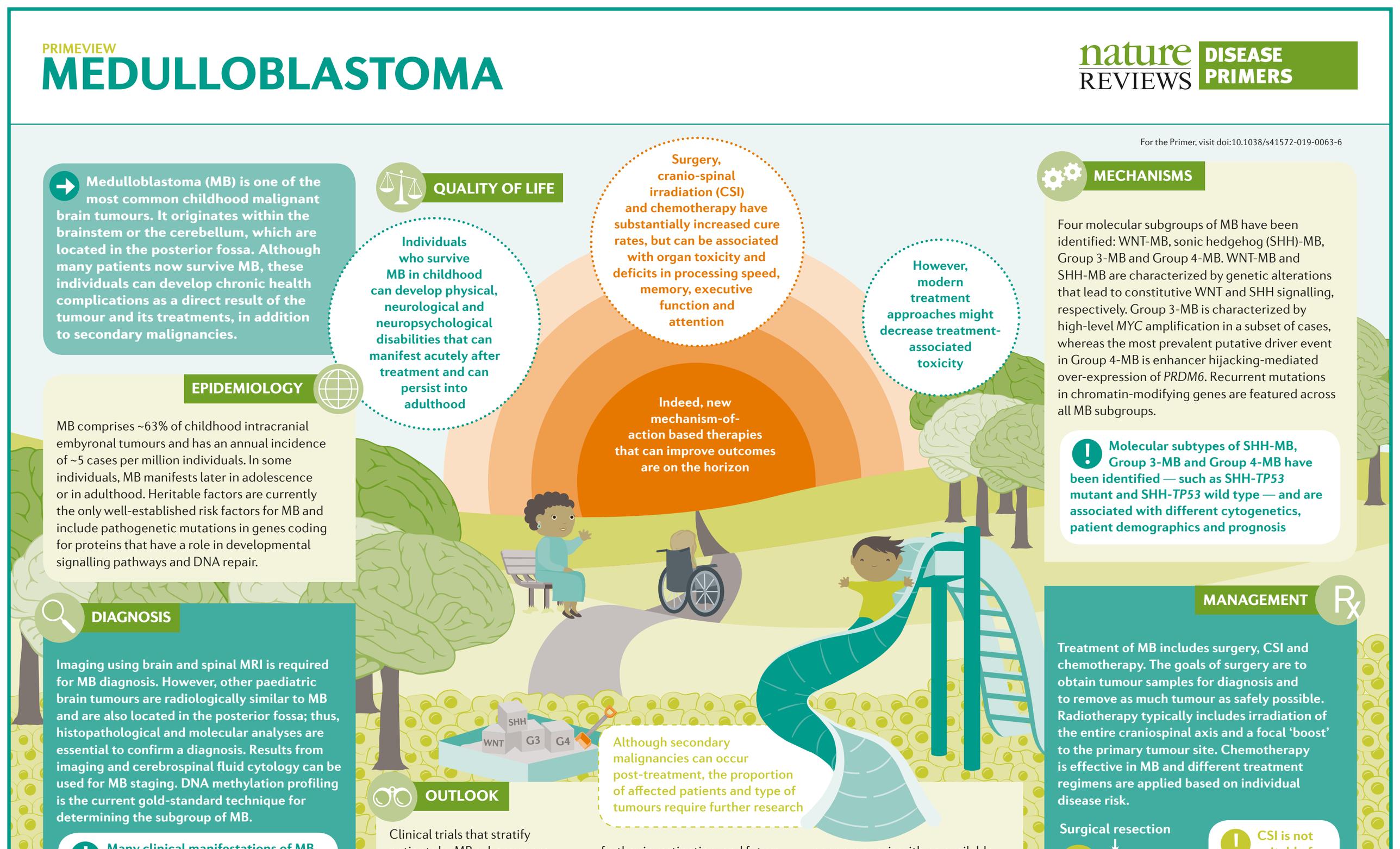
QUALITY OF LIFE

Individuals who survive MB in childhood can develop physical, neurological and neuropsychological disabilities that can manifest acutely after treatment and can persist into adulthood

Surgery, cranio-spinal irradiation (CSI) and chemotherapy have substantially increased cure rates, but can be associated with organ toxicity and deficits in processing speed, memory, executive function and attention

However, modern treatment approaches might decrease treatment-associated toxicity

Indeed, new mechanism-of-action based therapies that can improve outcomes are on the horizon



Although secondary malignancies can occur post-treatment, the proportion of affected patients and type of tumours require further research

OUTLOOK

Clinical trials that stratify patients by MB subgroup are required to evaluate relative treatment efficacies. Moreover, the emergence of MB subtypes within each subgroup requires further investigation, and future trials should also stratify patients based on molecular subtype and underlying cancer predisposition. Some patients with MB have a poor prognosis with no available gold-standard treatment, and integrating new treatment options into the clinic is desperately needed for these patients.

MECHANISMS

Four molecular subgroups of MB have been identified: WNT-MB, sonic hedgehog (SHH)-MB, Group 3-MB and Group 4-MB. WNT-MB and SHH-MB are characterized by genetic alterations that lead to constitutive WNT and SHH signalling, respectively. Group 3-MB is characterized by high-level *MYC* amplification in a subset of cases, whereas the most prevalent putative driver event in Group 4-MB is enhancer hijacking-mediated over-expression of *PRDM6*. Recurrent mutations in chromatin-modifying genes are featured across all MB subgroups.

Molecular subtypes of SHH-MB, Group 3-MB and Group 4-MB have been identified — such as SHH-*TP53* mutant and SHH-*TP53* wild type — and are associated with different cytogenetics, patient demographics and prognosis

MANAGEMENT

Treatment of MB includes surgery, CSI and chemotherapy. The goals of surgery are to obtain tumour samples for diagnosis and to remove as much tumour as safely possible. Radiotherapy typically includes irradiation of the entire craniospinal axis and a focal 'boost' to the primary tumour site. Chemotherapy is effective in MB and different treatment regimens are applied based on individual disease risk.

Surgical resection
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CSI
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Adjuvant chemotherapy

CSI is not suitable for patients <3 years of age owing to high toxicity

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