CHANGES IN THERAPY PERSPECTIVE OF THE MOST COMMON AND AGGRESSIVE PRIMARY BRAIN TUMOUR

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ABSTRACT:

Glioblastoma (multiforme) is the most common and aggressive primary brain tumour. Median survival is very poor and much research is being done on innovative therapies to improve both quality of life and survival. In this review, recent articles on glioblastoma therapy are addressed and discussed. Standard therapy consists of a total tumour resection combined with radiotherapy and chemotherapy, but many new fields including gene therapy and nanomedicine may alter standard therapy in the future. However, much more investigation is needed before these innovative therapies can be implemented in patient care.

KEYWORDS: Glioblastoma multiforme, glioma, therapy, innovation, epigenetics, gene therapy, metabolic therapy, nanomedicine

Introduction

Glioblastoma multiforme or simply glioblastoma is defined as a grade IV astrocytoma, making it the most malignant form of astrocytoma. Astrocytomas are tumours derived from astrocytes, which are supporting glial cells in the central nervous system (CNS). Men are more commonly diagnosed with glioblastomas than women and present with the disease mainly between the ages of 45 to 65 [1]. Glioblastomas are the most common primary brain tumours and have an appalling median survival of less than a year. This emphasises the importance of research that explores innovative therapies [2] [3].

Symptoms and diagnosis

Glioblastoma can manifest itself in various ways. Glioblastoma can occur anywhere in the brain and symptoms depend strongly on tumour location and invasion. Therefore, specific neurological symptoms between patients differ greatly, but can sometimes point the physician towards the affected brain area. Examples of these specific symptoms are loss of vision, ataxia and aphasia. Other symptoms are less specific and can be explained by an increase in intracranial pressure as a consequence of rapid growth of the tumour. Nausea, vomiting, seizures and cognitive dysfunction are frequently reported [4]. Even after diagnosis, and unfortunately also during treatment, symptoms can change as a consequence of glioblastoma expansion, underlining the significance of frequent follow-up. Examples of these are more intense headaches, lethargy and even tonic-clonic seizures, which require critical care [5].

Diagnosis of glioblastoma consists of the aforementioned neurological examination as an initial indication, followed by a CT or MRI scan. Differentiation of primary brain tumours is virtually impossible with imaging alone and can only be confirmed using histological results. Magnetic resonance spectroscopy can provide an indication of the aggressiveness of the tumour by assessing metabolic activity [1].

Therapy

Although glioblastomas are, as a rule, malignant, they do not usually invade organs outside of the CNS. However, they do invade brain tissue [1]. If possible, therapy is primarily focused on removing the tumour source by total resection, but if not, therapy is used to reduce the speed of tumour spreading. Obviously, this is not curative and it is therefore essential to develop new therapy techniques. In this clinical review article, outcomes of recent reviews will be combined to assess the different possible therapies to beat glioblastoma.

Glioblastoma is a very invasive form of glioma and requires immediate action after diagnosis. Current standard therapy is a combination of total surgical resection, radiotherapy and chemotherapy (mostly the cytostaticum temozolomide) [6]. In the elderly, combined therapy of temozolomide and hypofractionated radiotherapy is the preferred and evidence-based method, as opposed to surgery [7]. With respect to radiotherapy in glioblastoma, physicians should be aware of pseudoprogression. An early evaluation of tumour response to radiotherapy could show an increase in tumour size that is actually oedema caused by radiation effects or therapy-induced ischaemia [8].

Regarding surgery, it has been shown that survival is improved after a radical resection. Most contemporary neurosurgeons improve their resection success rate by utilizing new techniques, varying from easy-to-use to highly complicated. One example of this is the 5-ALA technique, in which a compound of porphyrin synthesis, 5-aminolevulinic acid, is used to elicit an accumulation of fluorescent porphyrins in glioma cells. Under blue light, a used and proven method for the past ten years, the neurosurgeon can distinguish normal brain tissue from the malignant tissue, resulting in a more accurate resection and survival [9] [10].

Methods

PubMed was searched for English reviews on glioblastoma concerning humans. Because this review article addresses new, innovative therapies for glioblastoma, only articles published in 2014 or later were included. The search term "("glioblastoma"[MeSH Terms] AND (Review[ptyp] AND hasabstract[text] AND ("2014/01/01"[PDAT] : "3000/12/31"[PDAT]) AND "humans"[MeSH Terms] AND English[lang])" resulted in 37 articles, of whom 8 were included after availability selection and rigorous abstract scanning on potential and innovative character of the investigated therapy.

Changes in perspective

To improve survival, the field of glioblastoma is subject to various developments in drug therapy. First of all, there are drugs currently under investigation as an addition to the standard therapy. Talampanel, for example, is a non-competitive antagonist of the AMPA-receptor, expressed on glioma cells. In phase II trials, talampanel inhibited tumour growth by mostly unknown mechanisms; more voluminous phase III trials are planned [2]. Upregulation of MET (a receptor tyrosine kinase) is seen in glioblastoma, inducing DNA synthesis and cell proliferation. Blocking MET and/or its ligand, HGF (hepatocyte growth factor), results in less

tumour growth. Therefore, the HGF antagonist NK4 and chimeric U1snRNA/ribozyme, an inhibitor of HGF and MET expression, are examples of potential therapy targets in glioblastoma and show promising results in phase II studies [11].

Secondly, epigenetics are of increasing interest. Recent research has shown that histone deacetylase inhibitors (HDACis) inhibit oncogenes and upregulate the expression of tumour suppressor genes. In addition, they inhibit angiogenesis [12]. However, antiangiogenic therapy (especially bevacizumab) has only been shown to improve progression-free survival, without affecting survival itself [13].

Moreover, significant advances in gene therapy are being made, but the standard therapy most likely will not change in the short term, because gene therapy faces many challenges. Firstly, delivery to the tumour is often compromised by the blood-brain barrier and the high intratumorous pressure. In addition, the lack of cell selectivity remains a problem. Since recently developed oncolytic viruses and nanoparticles are not tumour specific, damage to healthy brain tissue is an important adverse effect [14].

The experimental use of metabolic therapy is uncertain and even controversial, but glioblastoma cells might be influenced by reducing glucose and glutamine intake, two important nutrients for cancer stem cells. The calorie restricted ketogenic diet (KD-R) is believed to inhibit angiogenesis, inflammation and cell survival [15].

Advancements in nanomedicine are highly anticipated, but the field has only just started to get involved and faces quite a lot problems. For instance, when magnetic nanoparticles are injected into the tumour and the patient is placed in an alternating magnetic field, the particles accumulate in the tumour and thereby ablate the malignant tissue thermally. However, overheating of the particles can occur and lead to damage of otherwise healthy surrounding tissue [3] [16].

Conclusion

All in all, the future in glioblastoma therapy seems promising. Standard therapy for glioblastoma is still the first choice and can be supplemented with novel therapies currently under investigation. These include antagonists of (over)expressed receptors (e.g. MET, HGF and AMPA) in cancer cells and antiangiogenic therapy. Although the latter does not affect overall survival, it does improve progression-free survival. Advancements in innovative fields, such as nanomedicine and gene therapy, are being made, but will most likely not alter glioblastoma therapy in the near future.

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Curious to see how the 5-ALA technique is executed precisely? Many videos are to be found on YouTube, including a video recorded at the Neurosurgical Center (NCCN), Radboudumc [10].