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ORIGINAL ARTICLE

New Horizons in the Management of Glioblastoma Multiforme: the End of the Beginning?

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ABSTRACT

Glioblastoma multiforme is a highly invasive and aggressive brain tumour. It is the most commonly seen glioma with fast-growing features, being a devastating disease with no clear causation and no means of early detection. Less than 10% of glioblastoma multiforme patients survive more than 5 years after diagnosis. Current standard treatment includes maximal safe surgical resection and adjuvant concurrent chemo-irradiation with temozolomide followed by adjuvant temozolomide. Resistance to standard therapy still develops however, suggesting that glioblastoma multiforme cells are capable of switching their dependency from one signalling pathway to an alternative. Glioblastoma multiforme is a highly vascularised disease, in which angiogenesis plays an important role contributing to its progression and deadly course. Recently, therapies with agents targeting the vascular endothelial growth factor and vascular endothelial growth factor receptor have shown clinical benefits in patients with recurrent glioblastoma multiforme. It is indeed important to identify novel angiogenic factors that play essential roles in tumour angiogenesis and glioblastoma multiforme progression. This paper gives an overview of the management of glioblastoma multiforme including new treatments that are available, touches upon potential new therapies based on the aforesaid understanding, and discusses the promise and challenges of achieving better outcomes in this patient group.

Key Words: *Angiogenesis inhibitors; Brain neoplasms; Chemotherapy, adjuvant; Glioblastoma; Neoplasm recurrent, local*

中文摘要

治療多形性膠質母細胞瘤的新角度：序幕已經結束了嗎？

曾詠恆

多形性膠質母細胞瘤是大腦最常見的膠質瘤，侵略性強、生長速度快、病情短，而且無明顯病因，亦不易及早察覺。診斷後此病的五年生存率小於10%。目前的標準療法包括在安全情況下盡可能切除腫瘤組織，同時給予同步替莫唑胺（temozolomide）結合放射治療，再施以替莫唑胺輔助化療。對這種標準療法仍會出現抗效性，證明多形性膠質母細胞瘤可以轉換利用不同的訊號途徑。多形性膠質母細胞瘤有高度增生血管，而血管增生可引致病情急速惡化。最近有研究指出利用針對血管內皮生長因子（VEGF）及VEGF受體的治療對多形性膠質母細胞瘤復發的病人有臨床幫助。找出令多形性膠質母細胞瘤形成新增血管和惡化的新的腫瘤促血管生成因子相當重要。本文介紹治療多形性膠質母細胞瘤的不同方法，包括現有的一些新療法，又提及有潛在價值的嶄新療法，並討論提升療效的展望與及需要面對的挑戰。

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INTRODUCTION

Glioblastoma multiforme (GBM) is the most common malignant primary brain tumour in adults (Figure) and carries the poorest prognosis.[1] It is a devastating disease with no clear causation and no means of early detection. Microscopic hallmarks of GBM include pleomorphism, mitotic activity, necrosis, and microvascular proliferation. The histopathological diagnosis also involves genetic evaluation of the tissue such as the DNA copy number, gene expression, selected sequencing and examination of the methylation status of methyl-guanine methyl transferase gene (MGMT). Despite an aggressive multimodal approach, median survival after diagnosis is approximately 1 year and population-based studies demonstrate even lower rates of median survival.[2]

ADJUVANT THERAPY AND CURRENT STANDARD

Neurosurgery enables not only a histological diagnosis of GBM, but also provides relief from any neurological consequences related to the mass effect of this brain tumour. Current standard definitive treatment includes maximal safe surgical resection followed by adjuvant therapy with the aim of preserving neurological function. Adjuvant radiotherapy has been the mainstay treatment for GBM in the past decades, and extended median survival to about 9 months (vs 3 months with no adjuvant therapy).[3] Current recommendations for adjuvant radiotherapy include conformal radiation with boosts delivering a total of 60 Gy by intensity-modulated radiotherapy, 3D conformal radiotherapy, or involved field radiotherapy. Other approaches to radiation therapy include: stereotactic radiosurgery, brachytherapy, doses beyond 60 Gy, and hyperfractionation. To date, however, studies evaluating these approaches have not demonstrated clinically significant benefits.

Radiotherapy with concurrent and adjuvant chemotherapy as standard of care for GBM was only established in 2005, when Stupp et al[4] demonstrated the value of concurrent chemo-irradiation with daily use of oral temozolomide (TMZ). This akylating agent was prescribed for 6 weeks, followed by 6 monthly cycles of adjuvant TMZ for 5 days, which increased median survival by a further 3 months (compared to adjuvant radiotherapy alone), and the 2-year overall survival from 10 to 26%. Moreover, the combination of TMZ plus radiotherapy was associated with a statistically significant prolongation of overall survival (from 11 to 27% at 1 year, and 2 to 10% at 5 years with a hazard ratio for death of 0.63 [95% confidence interval, 0.53-0.75]; hazard ratio here refers to the risk of adversity relative to the comparator). The outcome was particularly good in some subsets, such as those younger than 50 years, in whom the 5-year survival with combination therapy increased to 17%. Recursive

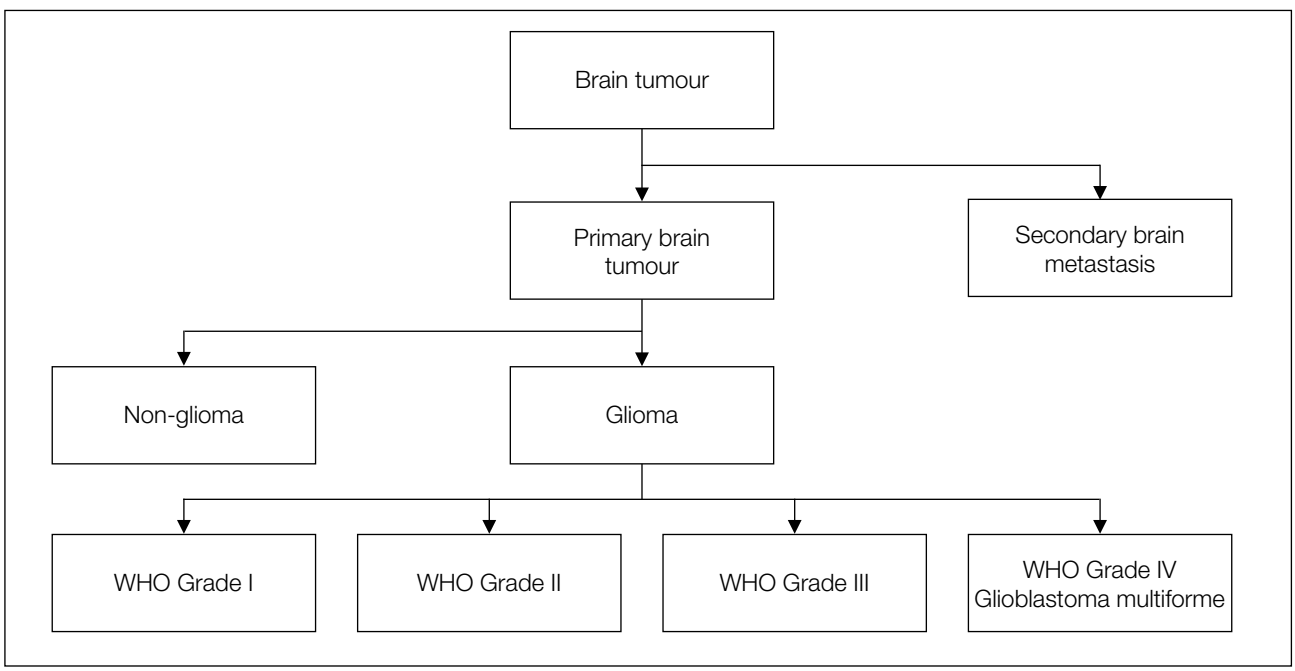

Figure. Classification of brain tumours.

partitioning analysis retains its prognostic significance overall as well as in patients receiving radiotherapy with or without TMZ for newly diagnosed GBM, particularly in classes III and IV.[5] Benefits from adjuvant TMZ were observed in all patient subsets, including those older than 60 years and those with other features of a poor prognosis, whilst the MGMT methylation status was a predictor of better treatment response and overall survival with the use of adjuvant TMZ.[6]

ANGIOGENESIS AND ANTI-ANGIOGENESIS IN GLIOBLASTOMA MULTIFORME

Despite current standard multidisciplinary treatment, most GBM patients experience early disease progression; approximately only a quarter are alive at 2 years. In patients who have recurrent GBM, treatment outcomes are poor with the median time to tumour progression being 9 weeks and the median survival being 25 weeks.[7]

Being highly vascular growing tumours, GBMs appear to respond when the existing blood supply is no longer adequate, resulting in hypoxia leading to cell death and necrosis. The vascular endothelial growth factor (VEGF) has been central to its pathophysiology, which is highly over-expressed. With hypoxia, the stability of the hypoxia-inducible factor-1 (HIF-1) is increased, and thus the HIF-1 increasingly binds to the *VEGF* gene promoter to increase VEGF mRNA transcription. High over-expression of VEGF correlates with a poorer prognosis for GBM.[1]

In the last decade, there have been breakthroughs in the management of recurrent GBM, especially due to the advent of novel therapeutic strategies, which improve the overall survival and quality of life. Anti-angiogenesis has been the centre of target for recurrent GBM in the past few years. Therapeutic agents targeting VEGF and the VEGF receptor have shown clinical benefits for patients with recurrent GBM. Bevacizumab is a humanised monoclonal antibody against the VEGF that is a potent inhibitor of angiogenesis. Based on the demonstrated improved clinical response rates compared to historical controls, bevacizumab received accelerated approval in May 2009 by the Food and Drug Administration for the first-line therapy of recurrent GBM. This was mainly based on Friedman et al's[8] finding that giving bevacizumab, either alone or in combination with irinotecan, was well tolerated and active for the treatment of recurrent GBM. Objective response rates were 28% and 38%, for bevacizumab alone and in combination, respectively; whilst respective median overall survivals were 9.2 and 8.7 months.[8] Common side-effects of bevacizumab include: mild hypertension (manageable with anti-hypertensives), fatigue, and general malaise. Rare but more serious side-effects include arterial thromboembolic events, congestive heart failure, impaired wound healing, and bowel perforation.

NEW CHALLENGES FOR ANTI-ANGIOGENESIS — THE END OF THE BEGINNING?

With the advent of anti-angiogenesis as one of the strategies for the management of patients with recurrent GBM, tumours still progress after the use of anti-angiogenic therapy and invasion seems to continue. It has been postulated that GBM is roughly separated into an angiogenic component, and an invasive or migratory component. Although the latter seems to be inert with respect to anti-angiogenic therapy, it is of major importance for disease progression and survival.[9]

Some published data support that while clinical symptoms are tempered by the anti-angiogenic treatment, tumour invasion still continues, and remains unrecognised by current standard imaging. The often robust and sustained magnetic resonance imaging (MRI) changes appearing after anti-angiogenic drug therapy may render subsequent MRI scans difficult to interpret.[10] The inhibition of angiogenesis in recurrent GBM may antagonise the efficacy of chemotherapeutic agents by normalising the blood-brain barrier function. This may restrict the distribution of drugs to the tumour cells, but more scientific evidence is needed to verify this suggestion.[11] Furthermore, while a proportion of the recurrent GBM patients do respond to anti-angiogenic therapy, matching such benefits (survival and quality of life) with cost affordability and the risks of adverse effects (arterial and venous thromboembolism, and haemorrhage) remains a challenge. At the moment, ongoing studies are investigating different combinations of anti-angiogenic therapy with other chemotherapy or newer agents with a view to achieving adequate control of GBM most cost-effectively. The findings of yet more studies aiming at newer potential therapeutic targets directed at the management of this difficult disease are therefore eagerly awaited.

CONCLUSION

GBM is indeed a devastating disease with no clear

causation nor early detection. First-line standard of care includes maximal safe surgical resection, adjuvant radiotherapy concurrent with TMZ chemotherapy and followed by adjuvant TMZ. The methylated MGMT status is an important prognostic and predictive factor for improved survival and chemotherapy response with TMZ.

There have been breakthroughs in the management of GBM including recurrent GBM. Angiogenesis plays a central role in the GBM invasion and recurrence processes, and targeting angiogenesis in the GBM progression process has shown clinical benefit for recurrent GBM patients. Single-agent bevacizumab as well as its combination with irinotecan have both shown clinical benefits in recurrent GBM patients.

Understanding the mechanisms of VEGF resistance is of paramount importance to further improve the survival of this deadly disease. Various phase III randomised, placebo-controlled trials are ongoing to further elucidate the role of anti-angiogenesis and explore new therapeutic potentials. Multidisciplinary management is the trend for further advancement of the clinical outcome of this deadly disease.

DECLARATION

The author declares that she has no conflicts of interest.

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