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Overview

Current and Investigational Drug Strategies for Glioblastoma

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Abstract

Medical treatments for glioblastoma face several challenges. Lipophilic alkylators remain the mainstay of treatment, emphasising the primacy of good blood–brain barrier penetration. Temozolomide has emerged as a major contributor to improved patient survival. The roles of procarbazine and vincristine in the procarbazine, lomustine and vincristine (PCV) schedule have attracted scrutiny and several lines of evidence now support the use of lomustine as effective single-agent therapy. Bevacizumab has had a convoluted development history, but clearly now has no major role in first-line treatment, and may even be detrimental to quality of life in this setting. In later disease, clinically meaningful benefits are achievable in some patients, but more impressively the combination of bevacizumab and lomustine shows early promise. Over the last decade, investigational strategies in glioblastoma have largely subscribed to the targeted kinase inhibitor paradigm and have mostly failed. Low prevalence dominant driver lesions such as the FGFR-TACC fusion may represent a niche role for this agent class. Immunological, metabolic and radiosensitising approaches are being pursued and offer more generalised efficacy. Finally, trial design is a crucial consideration. Progress in clinical glioblastoma research would be greatly facilitated by improved methodologies incorporating: (i) routine pharmacokinetic and pharmacodynamic assessments by preoperative dosing; and (ii) multi-stage, multi-arm protocols incorporating new therapy approaches and high-resolution biology in order to guide necessary improvements in science.

Key words: Chemotherapy; clinical trials; glioblastoma multiforme; new agents

Statement of Search Strategies Used and Sources of Information

This paper reflects expert opinion and current literature accessed by the authors; no formal search strategy has been defined.

Introduction

Medical treatments for glioblastoma multiforme need to access and disrupt a particularly complex process. The classic cancer target, the malignant glial cell, is driven by a defined range of molecular lesions, largely shared with other malignancies [1]. However, drug penetration is only one of several major challenges. The brain is uniquely a highly structured organ and malignant glial cells effectively reprise an embryonic development programme and disseminate early. Glioblastoma is therefore an organ- and tissue-level process as much as a classic cancer cell mass. The malignant cells themselves show hierarchical and evolutionary heterogeneity, affecting both the prevalence of and the response to simple drug targets. Multiple other cell types contribute to the process, including the brain's resident macrophages, microglia. Immune and inflammatory reactions are largely ineffective or counterproductive.

The most successful drug treatments for glioblastoma have been lipophilic alkylators, classic cytotoxic agents that are able to pass through the blood–brain barrier (BBB) and deplete the cycling malignant cell population by DNA damage. The PCV schedule of procarbazine, lomustine and vincristine, established in the 1970s, remains a major component of clinical practice and as a clinical trial

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intervention. Temozolomide was not initially developed for glioblastoma, but attracted interest after observations in generic phase I trials. Results in recurrent disease were followed by the landmark demonstration of improved outcomes in combination with radiotherapy in 2005 [2], which persists as the single major advance in treatment of the last several decades.

More recently, anti-angiogenic intervention using the anti-vascular endothelial growth factor (VEGF) antibody, bevacizumab, has gained attention. Because this agent class acts on the tumour vasculature, the need for parenchymal brain access is obviated. Outside the USA, widespread adoption of bevacizumab in recurrent disease has been hindered primarily by a lack of evidence from appropriately designed trials. Anecdotal experience continues to support its enthusiastic use by some, but the combination of the high cost and a lack of direct evidence presents difficulties. In the first-line setting, two large trials have recently reported showing that bevacizumab does not improve outcomes when added to first-line temozolomide and radiotherapy [3,4].

The last decade has seen a major expansion of investigational and approved new agents in oncology. Although typically commercially developed for other cancer indications first, multiple targeted agents have been repurposed for glioblastoma in early phase clinical trials, but with limited success. Immunotherapies have progressed to phase III trials, and a number of other investigational avenues are open. This overview will describe current treatments, the status of anti-angiogenic approaches, failures and future directions with new agents and trial design in glioblastoma.

Conventional Cytotoxic Chemotherapy

Lomustine (Figure 1A) is a nitrosurea that is rapidly hydroxylated on first passage through the liver to alkylating metabolites with a half-life of 16–48 h and with good BBB penetration. Clinical dosing is 100–130 mg/m^2 on day 1 of a treatment cycle that is 6 weeks in length due to prolonged myelosuppression. Since a 1976 report [5], lomustine has typically been partnered in clinical use by procarbazine and vincristine, giving the PCV schedule. Until recently, this combination has been largely immutable due to accumulated clinical precedent and continued usage in major trials, predominantly in low-grade glioma [6,7]. However, the superiority of PCV over single-agent nitrosurea rests on limited evidence [8–10] and lomustine has shown unexpectedly high single-agent activity as a control arm in modern trials, with 6 month progression-free survival rates of 19% [11] and 25% [12].

The role of vincristine is being increasingly questioned. Disrupting microtubule dynamics is a rational strategy in glioblastoma, not only to target mitosis, but also as a way to attenuate glioma cell migration [13]. However, it is doubtful whether the central nervous system (CNS) pharmacokinetics of vincristine allow these effects to be realised: it is poorly suited to BBB penetration on account of high molecular mass, polar surface area and efflux pump liability. A Korean phase II trial is appraising the effect of vincristine omission from PCV [14] and the NOA-05 trial established precedent for the procarbazine–lomustine doublet in gliomatosis cerebri [15].

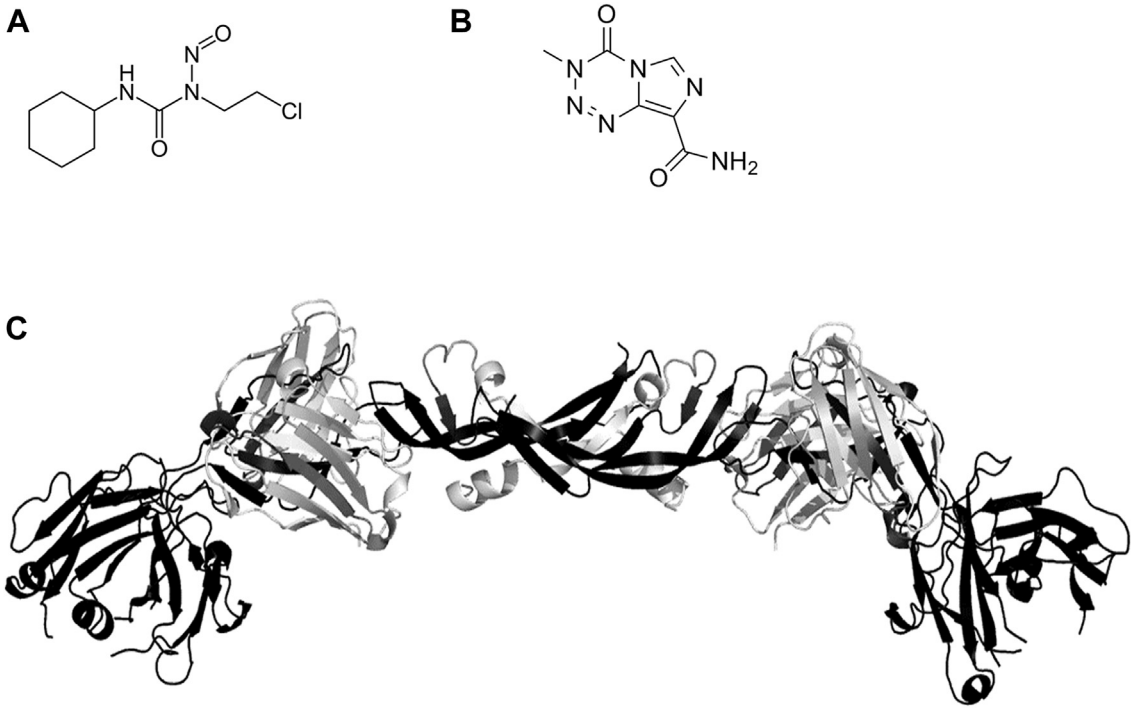

Fig 1. The structures of (A) lomustine; (B) temozolomide; and (C) vascular endothelial growth factor-A (VEGF-A) [63], the antigenic ligand of bevacizumab.

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