Facing the Future of Brain Tumor Clinical Research

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Abstract

This edition of CCR Focus provides critical reviews of several important areas in the field, including the application of findings from genomic investigations of brain tumors to improve diagnosis, clinical trial design, and ultimately optimizing individual patient treatment. Another article is a critical review provided by experts in the field that discusses the recent clinical trials using angiogenesis inhibitors, possible explanations for the results, and how to move forward. There is a concise discussion of the application of immunotherapy to brain tumors by key investigators in this field, reflecting the potential opportunities as well as the disease-specific challenges. Finally, leading pediatric brain tumor investigators provide an overview of the field and insights about the recent seminal discoveries in two pediatric brain tumors, supporting the paradigm that laboratory investigations lead to more precise diagnosis, prognosis, and ultimately better treatment. Herein, an overview of the recent advances and challenges in the area of clinical and translational brain tumor research is provided to set the stage for the contributions that follow.

See all articles in this CCR Focus section, "Discoveries, Challenges, and Progress in Primary Brain Tumors."

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Introduction

Malignant primary brain tumors remain an important area of clinical research. Most of these cancers remain incurable despite decades of laboratory and clinical investigation. These tumors are somewhat unique in that they rarely spread outside the central nervous system (CNS). Despite this finding, surgery is not curative even in low-grade (WHO grade 2) tumors because of their infiltrative nature (1). However, the extent of tumor resection is important as it has prognostic significance in many CNS cancers, and in some tumors, such as medulloblastoma and low-grade glioma, dictates subsequent therapies (2). Following surgery, radiotherapy remains the cornerstone of most brain tumor treatment regimens (3). Enhancing tumor targeting with new radiation modalities such as intensity-modulated radiotherapy or alternative radiation sources such as heavy particle therapy (i.e., proton, carbon ion) may improve the risk to benefit ratio in brain tumors (4).

The progress in developing effective chemotherapy regimens for primary brain tumors lags behind that of other cancers. For the most common and most aggressive brain tumor, glioblastoma (WHO grade 4), the only systemic chemotherapy that has proven survival benefit is temozolomide, an oral alkylating agent. Even with the first-line use of temozolomide, the survival benefit is only measured in months (5). Over the past several decades, many novel treatment agents have been tested; some of these studies are listed in Table 1. These included established and novel cytotoxic chemotherapy agents, antiangiogenic agents, signal transduction modulators, biologic agents, and immunotherapies (6). Early studies recognized that drug delivery across the blood–brain barrier may limit the efficacy of many therapeutic agents; novel routes of delivery have been tried. These include direct tumor injection, intra-arterial delivery, tumor perfusion using convection-enhanced delivery, and implantation of slow release vehicles (i.e., polifeprosan 20 with carmustine wafer; refs. 7, 8). Despite all of these efforts, the portfolio of effective agents remains quite limited.

The challenges that exist in finding effective treatments for patients with brain tumors stem from inherent heterogeneity and continual genomic transformation of the cancer, the unique microenvironment consisting of glial cells, microglia, and others, and the variable integrity of the blood–brain barrier, leading to issues with drug delivery. Furthermore, although preclinical testing often demonstrates high rates of efficacy for new agents, this has not yet translated to more effective treatment regimens. Although preclinical models are improving, they do not fully recapitulate the challenging aspects of the human disease such as genomic heterogeneity and tumor invasiveness (9). The testing of new regimens in clinical trials in this patient population is further complicated by limitations in...
current assessment of treatment efficacy. Standard imaging technologies, such as MRI, can be used to quantify the area (or volume) of abnormality. However, treatment may evoke reactions within the brain parenchyma that emulate tumor and may be incorrectly interpreted as treatment failure (pseudoprogression, Fig. 1). Conversely, some therapies, such as agents that target angiogenesis, may alter blood–brain barrier permeability, decreasing diffusion of the imaging contrast agent leading to an ‘improvement’ in imaging that may not reflect an overall improvement or decrease in tumor burden (pseudoresponse, Fig. 2). In addition, incorporating measures of patient outcomes such as neurocognitive function, symptom burden, and quality of life have been successfully done, but now need to be integrated into the overall metrics of treatment efficacy.

Although progress has been made, particularly in our understanding of the complex biology of malignant brain tumors, these advances in tumor biology have not been translated into the clinic. Many studies in both newly diagnosed and recurrent brain tumors have been completed; some of the key studies are listed in Table 2. However, these efforts have only led to a few therapeutic successes that have resulted in new standards of care. Nonetheless, even the negative studies have helped to create clinical trial platforms that set the stage for the next generation of multifaceted studies that can include mandatory tumor tissue with real-time analysis for patient selection and stratification as well as incorporation of measures of patient outcome with successful longitudinal assessment of quality-of-life measures, symptom burden, and formal neurocognitive testing. The articles in this edition of *CCR Focus* highlight some of the advances that will be incorporated into the next generation of clinical and translational research. It is through these collaborative efforts, integrating the cutting edge scientific discoveries with novel clinical trial designs, that the therapeutic advances will occur.

**Advances in Brain Tumor Molecular Profiling**

The past two decades have been remarkable for a dramatic increase in our knowledge of the tumor biology of these cancers. Using advanced molecular testing platforms, collaborative groups such as the one organized by The Cancer Genome Atlas and others have yielded important insights into the heterogeneity of these tumors (10–12). Classical histopathology provides a tumor grading system that has been traditionally used for classification and prognosis, but a variety of molecular markers have been described that are increasingly being used to modify and subtype tumors within each of the tumor grades. The article by Huse and Aldape (13) in this *CCR Focus* section provides a concise overview of the recent molecular findings and how these are affecting disease classification and, more importantly, how these markers are being used in prospective clinical trials. These authors offer extensive supporting data that molecular testing provides a critical advance in disease classification and at the current time should be used in conjunction with classical histopathology. These enhanced classification efforts may also provide potential therapeutic targets and better patient selection for specific treatments.

**Clinical Trial Challenges**

As with advancing treatment for other cancers, the foundation of determining efficacy continues to be the successful completion of robust clinical trials. These studies in brain tumors are proven to be challenging for several reasons. Malignant primary brain tumors are relatively uncommon. Even the most common, glioblastoma, has fewer than 15,000 patients diagnosed in the United States annually (14). Most patients do not participate in clinical trials either because of limited interest or access or ineligibility due to their poor performance status. Increasingly, however, these accrual issues are being circumvented by collaborations among the major cooperative groups and/or centers. Clinical trials will need to incorporate molecular profiling into the study design to account for differences in tumor prognosis or likelihood of response to specific treatments (predictive factors). Although molecular subtyping may make fewer patients eligible for a trial and make accrual issues even more challenging, these factors may be offset by the use of efficient clinical trial designs that provide such robust and tumor-specific treatment effects that smaller numbers of patients will be required to determine a measurable improvement.

Molecular classification of most primary brain tumors has identified many potential targets (Text Box 1); to date none have translated into specific treatments. This situation may improve with the implementation of clinical trials that incorporate mandatory tumor profiling and study designs.

![Figure 1. Pseudoprogression: an example of spontaneous improvement of imaging findings after completion of concurrent temozolomide and radiotherapy for glioblastoma. A, before surgical resection. B, after surgery. C, after concurrent temozolomide and radiation. D, after three cycles of adjuvant temozolomide (4 months after completion of radiation). E, after nine cycles of temozolomide.](image-url)
that are hypothesis driven, based on assessing the presence of the target and tumor response. For many targets, it is not known whether if the target was present in the newly diagnosed tumor, it will still be present at progression. This has important implications for patient management and targeted therapies and may require resampling tumor.

Drug delivery in the presence of a variably intact blood–brain barrier remains a challenge. Increasingly, preclinical testing has evaluated drug delivery and some agents have undergone early clinical testing that included measuring drug concentrations within tumor samples (pharmacokinetics) and the impact on the drug target (pharmacodynamics). These studies, however, require extensive resources and have been difficult to complete.

**New Clinical Trial Designs for Brain Tumor Studies**

Accrual issues, the increasing portfolio of possible treatment agents, and the recognition that combination regimens will likely be required have led to increasing interest in developing novel trial designs that can efficiently screen for efficacy. Unfortunately, the results from single-arm phase II trials, particularly in patients with newly diagnosed tumors, have been difficult to interpret; therefore, randomized studies are being increasingly used (15). An overview of many of the currently used designs in brain tumor clinical trials was recently published (16). One of the novel designs, called the factorial design, permits simultaneous evaluation of multiple permutations of combinations of a set of agents. A study has been successfully completed in patients with glioblastoma that evaluated three experimental agents in combination with temozolomide during the adjuvant phase of treatment. For this trial, only 20 patients per arm were required to provide adequate power to determine the impact of each individual agent and to determine whether there was improved benefit of triplet therapy (temozolomide plus two experimental agents) compared with doublet treatment regimens (17).

The adaptive randomized design begins by completely random allocation of patients to each of the arms, but the weighting of randomization is altered by efficacy data (18). Treatment arms with the most success get a higher rating.
and are more likely to get patients. If there is a real efficacy difference, the randomization weighting will continue until one treatment is declared the winner. This design may reduce accrual needs while maintaining the structure of a randomized trial. Adaptively designed trials are in progress for brain tumors, but no results have been reported to date.

The randomized discontinuation design has not been used in brain tumor trials but may be particularly well suited for the brain tumor patient population as the design focuses on patients with "stable disease." All patients are treated with the new regimen for a set period of time. Treatment responders continue therapy and patients with disease progression or unacceptable toxicity stop. Patients with no significant change (stable disease) are then randomized to active agent or placebo. At a set time later, a comparison of the progression-free survival (PFS) rate is made between agent and placebo. An improvement in PFS rate with the experimental agent is a strong evidence of treatment efficacy. This strategy, which requires far fewer patients than a traditional randomized phase II or III study, has been successfully used in a clinical trial in renal cell carcinoma (19).

Outcome Measures for Brain Tumor Clinical Trials

Assessment of treatment response in brain tumor clinical trials has been challenging. The irregular and infiltrative nature of these cancers makes traditional measures often difficult and creates variability of quantitation and interpretation. There are ongoing discussions regarding the optimal endpoint measures with each of the conventional cancer clinical trial measures as described below.

Overall survival (OS) is definitive and universally recognized as a robust endpoint. However, crossover or salvage treatments may alter the ability to assess efficacy if a variety of treatments are used in salvage among the study patients at

### Table 1. Single-agent targeted therapies for recurrent glioblastoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Target</th>
<th>Trial phase</th>
<th>Number of patients</th>
<th>6-month PFS (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib (50)</td>
<td>PDGFR, c-kit, and c-ABL</td>
<td>II</td>
<td>51</td>
<td>16</td>
</tr>
<tr>
<td>Gefitinib (51, 52)</td>
<td>EGFR</td>
<td>II</td>
<td>53 and 28</td>
<td>13 and 14</td>
</tr>
<tr>
<td>Erlotinib (53, 54)</td>
<td>EGFR</td>
<td>II</td>
<td>110 and 38</td>
<td>11 and 3</td>
</tr>
<tr>
<td>Pazopanib (55)</td>
<td>VEGFR and PDGFR</td>
<td>II</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td>Tipifarnib (56)</td>
<td>Farnesyltransferase</td>
<td>II</td>
<td>67</td>
<td>12</td>
</tr>
<tr>
<td>Temsirolimus (57)</td>
<td>mTOR</td>
<td>II</td>
<td>65 and 41</td>
<td>8 and 3</td>
</tr>
<tr>
<td>Cediranib (58, 59)</td>
<td>VEGFR</td>
<td>II and III</td>
<td>31 and 131</td>
<td>26 and 16</td>
</tr>
<tr>
<td>Bevacizumab (60, 61)</td>
<td>VEGF-A</td>
<td>II</td>
<td>85 and 48</td>
<td>36 and 29</td>
</tr>
<tr>
<td>Aflibercept (62)</td>
<td>VEGF-A</td>
<td>II</td>
<td>42</td>
<td>8</td>
</tr>
<tr>
<td>Clengitide (63, 64)</td>
<td>αvβ3,αvβ5 integrins</td>
<td>II and III</td>
<td>81 and 26</td>
<td>15 and 12</td>
</tr>
<tr>
<td>Vorinostat (65)</td>
<td>HDAC</td>
<td>II</td>
<td>66</td>
<td>15</td>
</tr>
<tr>
<td>Enzastaurin (66, 67)</td>
<td>PKC</td>
<td>II and III</td>
<td>72 and 174</td>
<td>7 and 11</td>
</tr>
<tr>
<td>Cabozantinib (68)</td>
<td>EGFR and C-MET</td>
<td>II</td>
<td>124</td>
<td>21</td>
</tr>
</tbody>
</table>

Abbreviations: c-kit, stem cell factor receptor; C-MET, met-protooncogene.

Adapted and updated from ref. (69); Seminars in Oncology, Volume 38, Supplement 4, Gilbert MR, pp. S21–33, Copyright 2011, with permission from Elsevier.

Text Box 1. Potential molecular targets in glioblastoma

**Cell surface growth factor receptors**
- Epidermal growth factor receptor (EGFR)
- Platelet-derived growth factor receptor (PDGFR)
- Fibroblast growth factor receptor (FGFR)
- Transforming growth factor receptor (TGF)
- Vascular endothelial growth factor receptor (VEGFR)
- Insulin-like growth factor receptor (IGFR)

**Signaling transduction pathway and downstream effectors**
- PI3K/Akt
- Ras/mitogen-activated protein kinase (MAPK)
- Mammalian target of rapamycin (mTOR)
- Protein kinase C (PKC)
- TP53
- MET (hepatocyte growth factor, Met-protooncogene)
- Janus kinase/signal transducer and activator of transcription (JAK/STAT)
- Smoothened
- Notch
- Retinoblastoma (Rb) signaling
- Farnesyltransferase

**Angiogenesis**
- VEGFR
- Vascular endothelial growth factor (VEGF)
- Integrins
- Angiopoietin 1/2

**Other targets**
- Histone deacetylase (HDAC)
- Isocitrate dehydrogenase mutations (IDH1 and IDH2)
- Poly (adenosine-diphosphate-ribose) polymerase (PARP)
disease recurrence. This is most germane for the lower-grade gliomas in which effective salvage regimens have been developed that may, therefore, affect OS independent of the protocol treatment. In addition, survival studies require long follow-up for some brain tumors, for example in patients with low-grade (WHO grade 2) and some anaplastic (WHO grade 3) gliomas (20–23).

PFS has the advantage of not having the potential problem of crossover or varied use of salvage regimens. However, the definition of disease progression as determined by conventional imaging may be confounded by treatment-related changes. Concurrent assessment of clinical status may improve the determination of disease status, but as described below, there is no consensus on the optimal outcomes measures.

Table 2. Recent randomized trials for adult primary brain tumors

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Disease type</th>
<th>Treatment(s) tested</th>
<th>Trial phase</th>
<th>Outcomes; Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>EORTC 26981 (5)</td>
<td>Newly diagnosed GBM</td>
<td>Temozolomide-radiation vs. radiation</td>
<td>III</td>
<td>Temozolomide radiation with improved OS, PFS, and 2-year survival rate</td>
</tr>
<tr>
<td>RTOG 0525 (70)</td>
<td>Newly diagnosed GBM</td>
<td>Dose dense vs. standard temozolomide</td>
<td>III</td>
<td>No improvement in OS or PFS with dose dense</td>
</tr>
<tr>
<td>RTOG 0825 (38)</td>
<td>Newly diagnosed GBM</td>
<td>Standard chemotherapy + bevacizumab vs. standard chemotherapy</td>
<td>III</td>
<td>PFS longer but not significant; patient outcomes worse with bevacizumab</td>
</tr>
<tr>
<td>AvaGLIO (46)</td>
<td>Newly diagnosed GBM</td>
<td>Standard chemotherapy + bevacizumab vs. standard chemotherapy</td>
<td>III</td>
<td>PFS significantly prolonged; QOL maintained longer with bevacizumab</td>
</tr>
<tr>
<td>CENTRIC (71)</td>
<td>Newly diagnosed GBM</td>
<td>Standard treatment + cilengitide vs. standard treatment</td>
<td>III</td>
<td>No improvement in OS or PFS</td>
</tr>
<tr>
<td>Enzastaurin (67)</td>
<td>Recurrent GBM</td>
<td>Enzastaurin vs. lomustine</td>
<td>III</td>
<td>No improvement in OS or PFS with enzastaurin</td>
</tr>
<tr>
<td>REGAL (59)</td>
<td>Recurrent GBM</td>
<td>Cedirinib + lomustine vs. single-agent cedirinib vs. single-agent lomustine</td>
<td>III</td>
<td>No improvement in OS or PFS with cedirinib alone or in combination with lomustine</td>
</tr>
<tr>
<td>BELOB (26)</td>
<td>Recurrent GBM</td>
<td>Bevacizumab + lomustine vs. single-agent bevacizumab vs. single-agent lomustine</td>
<td>II</td>
<td>Primary endpoint 9-month OS; only bevacizumab + lomustine reached efficacy threshold</td>
</tr>
<tr>
<td>RTOG 9402 (23)</td>
<td>Newly diagnosed AO (grade 3)</td>
<td>Intensive PCV, then radiation vs. radiation alone</td>
<td>III</td>
<td>Improved OS with PCV only for tumors with 1p 19q LOH</td>
</tr>
<tr>
<td>EORTC 26951 (22)</td>
<td>Newly diagnosed AO (grade 3)</td>
<td>Radiation, then standard PCV vs. radiation alone</td>
<td>III</td>
<td>Improved OS with PCV only for tumors with 1p 19q LOH</td>
</tr>
<tr>
<td>RTOG 9802 (21)</td>
<td>Newly diagnosed low-grade (2) glioma</td>
<td>Radiation, then standard PCV vs. radiation alone</td>
<td>III</td>
<td>Improved OS with PCV; note: molecular subtyping not yet reported</td>
</tr>
</tbody>
</table>

Abbreviations: AO, anaplastic oligodendroglioma; GBM, glioblastoma; PCV, procarbazine, CCNU (lomustine), vincristine; QOL, quality of life.

Objective response rate (ORR) has been the traditional measure in cancer studies as a screening tool for treatment activity. For most solid tumors, cross-sectional area has been replaced by single dimension (RECIST) measure, whereas in brain tumor studies, complex tumor shapes may require two-dimensional or even volume assessment (24). As with assessment of progression, some treatments may alter imaging, hampering the ability to accurately determine response.

Finally, set time point rates report the percentage of patients reaching a preset milestone time. For example, in many studies in recurrent glioblastoma, a 6-month PFS rate has been used as a metric based on strong historical data that have provided this measure for ineffective treatments (expected probability: 0) in the statistical design (25). Some examples of brain tumor clinical trials that reported
the 6-month PFS rate are listed in Table 1. Survival rate can also be used as an endpoint. In the BELOB trial the 9-month OS rate was the primary measure of efficacy (26). These measures have been primarily used for screening for efficacy, and the rate determinations are subject to the same limitations as described for PFS (imaging) and OS (cross-over or salvage treatment) metrics reported above.

Imaging Assessment of Treatment Response

Until recently, most clinical trials for malignant primary brain tumors used measures of cross-sectional area of enhancing tissue as an indication of tumor burden (27). However, it has been increasingly recognized that certain treatments may alter the degree of contrast enhancement without necessarily affecting tumor size. This is particularly germane for antiangiogenic therapies in which normalization of blood–brain barrier permeability may reduce overall tumor enhancement. This concern led to the formation of a consensus group, Response Assessment in Neuro-oncology (RANO), which has published guidelines for image analysis that include assessment of corticosteroid use, neurologic function, and nonenhancing (T2 or T2FLAIR) abnormalities in addition to the enhancing lesion (28). A summary of these guidelines is provided in Table 3. Further work is ongoing to modify the RANO guidelines to accommodate imaging changes that are anticipated with the increasing use of immunotherapies and the potential for inflammatory changes that could be misinterpreted as tumor progression rather than a desired immune response.

Hindered by the difficulties associated with interpreting most conventional brain imaging (typically MRI), there is great interest in developing advanced imaging techniques to help determine whether imaging improvements represent true response to treatment or “pseudoresponse,” or conversely, whether worsening is due to growth or “pseudoprogression” (29). Advanced MRI techniques include magnetic resonance spectroscopy (MRS), which can quantify specific molecular compounds in an area of interest (reviewed in ref. 30). Most conventional scanners can provide measures of choline, creatine, lactate, N-acetyl aspartate (NAA), and other compounds. Characteristic signatures of active tumor (high choline to creatine) or necrosis (high lactate, low NAA) are used in clinical practice, although the ability to definitively determine tumor or necrosis may be limited. In addition, tumor metabolites such as 2-hydroxyglutarate in tumors with isocitrate dehydrogenase mutations can be quantified using MRS and may prove to be a noninvasive biomarker. Other advanced imaging techniques, including dynamic contrast–enhanced MRI and dynamic susceptibility contrast MRI, may provide additional information particularly regarding integrity of tumor vasculature and blood volume (30), and can be helpful in differentiating recurrent disease from “pseudoprogression.”

PET using 18-fluorodeoxyglucose has been performed for decades in patients with brain tumors (29). Initially thought to be highly specific for tumor, false-positive testing particularly with inflammatory changes, as well as high background activity within the cortex and other metabolically active structures, has limited the clinical utility of this test. However, other PET tracers are under active investigation, including 18F-fluorodopa-, fluorohydroxytyrosine-, methionine-, and thymidine-based tracers. PET technology may be particularly helpful in determining the ability of an agent to penetrate the blood–brain barrier and be delivered to the tumor.

Table 3. Summary of RANO criteria

<table>
<thead>
<tr>
<th>Criterion</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 gadolinium–enhancing disease</td>
<td>None</td>
<td>≥50%</td>
<td>&lt;50% but &lt; 25%</td>
<td>≥25%</td>
</tr>
<tr>
<td>T2/FLAIR</td>
<td>Stable or</td>
<td>Stable or</td>
<td>Stable or</td>
<td>Present</td>
</tr>
<tr>
<td>New lesion</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>NA</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>None</td>
<td>Stable or</td>
<td>Stable or</td>
<td>NA</td>
</tr>
<tr>
<td>Clinical status</td>
<td>Stable or</td>
<td>Stable or</td>
<td>Stable or</td>
<td>Any</td>
</tr>
<tr>
<td>Requirement for response</td>
<td>All</td>
<td>All</td>
<td>All</td>
<td>Any</td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; NA, not applicable; PD, progressive disease; PR, partial response; SD, stable disease.

*Progression occurs when this criterion is present.

**Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.

include patient-reported outcomes, observed outcomes, or outcomes that are clinically assessed. Patient-reported outcomes were incorporated into one of the pivotal studies of ruxolitinib in myelofibrosis. In this trial, incorporation of a symptom scale specific to myelofibrosis provided compelling evidence of clinical improvement in the setting of disease response measured by spleen size (32). This sets the stage for the use of patient-reported outcomes in glioblastoma in which, depending on location, relatively small changes in tumor size can have a major impact on symptom burden and functional status.

**Patient-reported outcomes**

A variety of COAs have been used in brain tumor clinical trials (33). Measures of health-related quality of life have been incorporated into many of the randomized studies mainly using either the EORTC QLQ30 with the additional brain-specific BN-20 or the FACT-BR, which is also brain specific. These instruments are easy to administer and may provide important insights regarding impact of therapies and have prognostic implications, but a systematic review raises concerns that the value may be limited unless specific hypotheses are developed and an analysis plan is constructed before the implementation of the clinical trial (34, 35).

Several instruments that measure symptom burden in patients with cancer have been developed and are being increasingly used in the assessment of treatment efficacy (i.e., for ruxolitinib, discussed previously). However, currently the only symptom instrument designed specifically for the brain tumor patient population is the MD Anderson Symptom Inventory-Brain Tumor (MDASI-BT; ref. 36). This instrument contains 23 items, and patients rate the severity of their symptoms and the impact of the symptoms on activities of daily life (interference). Recent clinical trials have demonstrated that the MDASI-BT is sensitive to tumor progression, may predict OS and PFS, and is sensitive to differences in treatment arms (37, 38).

**Neurocognitive testing**

Formal neurocognitive testing provides quantitative, objective measures of patient outcomes that may be particularly germane in patients with brain tumors in which there is often pretreatment loss of function and in which longitudinal assessments may provide insights into the impact of treatment on function. Loss of neurocognitive function has also been reported to precede imaging evidence of tumor progression (39). The results from recent clinical trials in brain tumors demonstrate that baseline neurocognitive function may predict OS and PFS and, with the longitudinal assessment, can detect differences in treatment arms (37, 38, 40).

The Current State of Brain Tumor Treatments and Experimental Therapies

**Signal transduction modulators**

The current standard of care for patients with malignant gliomas remains some permutation of surgery for diagnosis and cytoreduction followed by radiation and cytotoxic chemotherapy. For glioblastoma, concurrent temozolomide with radiation followed by 6 to 12 months of maintenance temozolomide remains the international standard. For anaplastic gliomas (grade 3), a molecular test looking for allelic loss of chromosome arm 1p and 19q determines whether a combination of radiotherapy and chemotherapy is needed (1p 19q codeleted) or if the addition of chemotherapy provides no survival benefit (1p19q not codeleted). Recent results also suggest that poor-risk low-grade gliomas (age >40 or incomplete resection) also benefit from radiotherapy and chemotherapy (21). More specific recommendations based on molecular profiling will be forthcoming.

Despite the extensive knowledge about the molecular profiles of malignant glioma, no successful treatments have been developed for primary brain tumors using existing signal transduction modulators. This lack has been ascribed to the large number of pathway abnormalities and the inter-networking of signaling pathways. For most malignant gliomas, by the time a diagnosis is made there is such intratumoral heterogeneity that identifying a driver mutation is very difficult (41). The recent discovery of a chromosomal translocation of coding domains of fibroblast growth factor receptor (FGFR) to transforming acidic coiled-coil (TACC) coding domains resulting in a specific fusion protein, FGFR–TACC, that is likely a tumor driver is encouraging (42). Although this fusion occurs in only 3% of glioblastoma, if the ongoing clinical trials specifically targeting this unique protein are successful, it will provide proof of principle of this approach and encourage continued investigations.

Combination treatment regimens that incorporate agents to either target multiple signaling pathways or use multiple agents to inhibit one pathway may have more efficacy than the single-agent regimens. These studies are logistically difficult as they require the integration of molecular analysis of contemporary tumor samples coupled with an efficient selection design and often require cooperation between pharmaceutical companies (43). These studies either need to treat only tumors with specific profiles or have several treatment arms to accommodate a variety of tumor subtypes. In addition, despite a typically modest toxicity profile when a drug is used as a single agent, combination regimens have demonstrated more severe toxicity than expected. Therefore, safety testing (phase 1) has been required for these combination regimens.

**Antiangiogenic therapy**

Vascular proliferation, or angiogenesis, is one of the hallmarks of glioblastoma and accounts for the contrast enhancement on imaging studies. The VEGF pathway is the most prominent mechanism for angiogenesis in glioblastoma and VEGF-A most commonly expressed in response to tumor hypoxia (44). Angiogenesis was therefore a logical therapeutic target and after initial concerns regarding the risk of intracranial hemorrhage were allevied by early clinical
trials, a variety of antiangiogenic agents were tested in high-grade glioma. The article in this CCR Focus by Batchelor and colleagues (45) provides an overview of the putative mechanisms of angiogenesis and a review of the clinical trials that have been undertaken. Importantly, the authors also provide insights into the potential mechanisms of resistance and treatment failure. This is particularly important in light of the recent phase III trials testing bevacizumab in patients with newly diagnosed glioblastoma that showed no survival benefit (38, 46), raising questions about whether, despite its prominent role in glioblastoma biology, angiogenesis should remain a prime therapeutic target.

Immunotherapy

Immunotherapy for malignant primary brain tumors has been tried for decades. Early studies using brain tumor extracts as vaccines were not successful. Other studies involved cytokines, including interferons, which showed only minimal efficacy, or interleukins, which led to major toxicity, particularly increases in intracranial pressure. With the recent substantial increase in the understanding of tumor immunology and successes in other cancers, particularly metastatic melanoma, there has been a marked surge of interest in investigating immunotherapies for primary brain tumors. The article by Fecci and colleagues (47) in this CCR Focus reviews the increasing evidence that the brain is not “immunoprivileged” and that pursuing immunotherapy may be a very important therapeutic strategy. These authors provide a summary of the approaches that have been used as immunotherapies for brain tumors in the context of the increasing understanding of tumor-related immunosuppression. They also present an overview of the ongoing and planned clinical trials providing the additional perspective of immunotherapy research in other cancers.

Advances and Challenges in Pediatric Brain Tumors

Pediatric brain tumors, although uncommon, represent the second most common cancer of childhood and a leading cause of cancer-related death. The development of new treatments faces accrual challenges given the relative rarity of the disease, issues with response assessments, and often limited access to new agents because of safety concerns (48). In addition to the typical issues of treatment-related toxicity with cancer treatment, impact on the developing nervous system must be considered. For example, treatment of CNS cancers in young patients typically avoids or delays radiotherapy because of the profound effect on brain development.

Despite these limitations and challenges, recent seminal discoveries in childhood brain tumors highlight the importance of basic research and the potential to translate these laboratory findings into the clinical treatment decision making process. The article by Gajjar and colleagues (49) in this CCR Focus section highlights the culmination of collaborative efforts in two major pediatric brain tumors, medulloblastoma and ependymoma. These authors review the seminal findings for each disease and discuss the potential clinical implications for prognosis, treatment decisions, and ultimately for devising disease subtype–specific therapies.

Conclusions

Despite decades of research, most primary brain tumors remain incurable. However, there has been a marked increase in our knowledge and understanding of the underlying tumor biology along with the complexity and heterogeneity of these cancers. Parallel efforts are ongoing to develop multifaceted and efficient clinical–translation al studies that use tumor molecular profiles for hypothesis-based clinical trials and incorporate advanced imaging and patient outcomes measures to fully realize the potential from each trial. These goals are realistic because the recent surge of collaborations within the field indicate that a global effort is needed to actuate a real improvement in outcomes for these patients. The articles in this CCR Focus provide a snapshot of some of the exciting work that is under way.


[Note: The text contains references to various studies and clinical trials, indicating a focus on glioblastoma treatment and research.]
Facing the Future of Brain Tumor Clinical Research


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