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Clinical trials in neuro-oncology: one step forward, two steps back?

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Clinical trials in Neuro-Oncology: one step forward, two steps back?

Neuro-oncology, specifically the field of glioma, has witnessed an impressive increase in the number of prospective, clinical trials over the last decade. Over 1000 glioma trials are registered in www.clinicaltrials.gov, and over 400 are actively recruiting patients (compare with > 800 recruiting trials in colorectal cancer, or > 1600 recruiting breast cancer trials). Despite these comparatively numerous trials in a rare disease, progress has been slow and a number of randomized trials have failed. Have we embarked prematurely on ill-designed clinical trials?

Gliomas and its most aggressive type, glioblastoma, are a heterogeneous diseases with variable cells of origin and unique pathogenesis. Although histologically and clinically indistinguishable, molecular characteristics of primary (de novo) and secondary (arising from a prior lower grade glioma) glioblastoma are distinct; e.g epidermal growth factor receptor (EGFR) overexpression and lack of p53 mutations are characteristic for primary glioblastoma, and isocitrate dehydrogenase (*IDH*) mutations have recently been identified to be a typical feature of low-grade glioma and secondary glioblastoma, suggesting that this is an early event in glioma genesis {Yan, 2009 #1155}.

Grossman and colleagues recently pointed out that data from three independent phase II trials examining the addition of either the glutamate receptor antagonist talampanel, the immune stimulator poly-ICLC, or the integrin antagonist cilengitide all appeared to confer a survival benefit compared with standard temozolomide radiochemotherapy alone compared to historical controls {Grossman, 2010 #1067}. How likely is it that all three new treatment strategies are truly active? The answer is: very unlikely. This underscores the importance of randomized controlled trials.

At this year`s ASCO Meeting, the first results of the so far largest trial in glioblastoma ever performed were presented {Gilbert, 2011 #1133}. The RTOG0525/ EORTC/NCCTG Intergroup Study investigated adjuvant temozolomide dose intensification, compared to the standard EORTC-NCIC treatment schedule {Stupp, 2005 #699}. The trial design was based on (i) the moderate-to-low toxicity of temozolomide, (ii) suggestion of an increased antitumor activity with dose-dense

(alternating week or continuous administration 21/28 days) {Wick, 2004 #670} temozolomide regimen in recurrent glioma, (iii) consumption and depletion of the O6-methylguaninemethyltransferase (MGMT) repair protein in peripheral blood mononuclear cells by a protracted temozolomide administration {Tolcher, 2003 #533}. The trial was timely and the question pertinent, as almost 1200 patients were enrolled within 2 years, and 833 patients were eligible for randomization and adjuvant therapy after completing concomitant chemoradiotherapy {Gilbert, 2011 #1133}. There was no difference in overall survival (the primary endpoint), and even subgroup analysis of the most resistant *MGMT*-unmethylated tumors, or the patients whose tumors harboured a methylated (silenced *MGMT* gene) and were thus more sensitive to alkylating agent chemotherapy, show no hint for improved outcome with temozolomide dose intensification. Nevertheless, the design of this trial mandated provision of sufficient tumor tissue in order to centrally determine *MGMT* promoter methylation status and allows for exploratory analyses of many other molecular abbertions {Aldape, 2011 #1132}. It indeed confirmed the prognostic value of MGMT, it demonstrated that time-critical centralized molecular assessment and histopathological review is feasible even in a large cooperative group setting, and it will be a invaluable resource for further exploratory analyses that shall lead to the identification of critical targets, and allow to individualize treatment strategy based on molecular tumor characteristics.

We have recently completed accrual to a randomized phase III trial (CENTRIC-EORTC # 26071-22072) investigating the adjunction of the integrin inhibitor cilengitide in over 500 patients with a methylated *MGMT* promoter, based on a (too) small uncontrolled pilot phase II trial {Stupp, 2010 #1071}. Results are not yet available. Similarly, the addition of bevacizumab to standard chemoradiotherapy has been investigated in two randomized phase III trials (accrual completed). Long-term results of the initial promising reports have been rather disappointing {Lai, 2008 #944}{Lai, 2011 #1136}. Despite encouraging results of VEGF inhibition by the ligand neutralizing antibody bevacizumab {Friedman, 2009 #1036} or receptor tyrosine kinase inhibition by cediranib {Batchelor, 2007 #881}{Batchelor, 2010 #1072}, this strategy failed to prolong survival in a definitive controlled and randomized trial in recurrent disease {Batchelor, 2010 #1131}

Only with controlled trials we will be able to fully appreciate the potential benefit of each strategy. Theoretically, it would be attractive to actually combine both integrin and VEGF inhibition, however, the current regulatory and pharmaceutical framework makes the testing of 2 unregistered agents in combination quite challenging.

At present, we are facing yet another very promising strategy for the treatment of newly diagnosed glioblastoma, that is, vaccination with a peptide representing an immunogenic epitope of the epidermal growth factor receptor (EGFR) variant III mutation, a characteristic type of EGFR mutation found in approximately 25% of all glioblastoma patients. Again, uncontrolled phase II look promising {Sampson, 2010 #1141}, but there is no way around a formal, blinded, comparative study to determine whether the promising initial observations result from patient selection or true biological activity. The latter would be a highly welcome next step towards more treatment options and more individualized cancer therapy for patients with glioblastoma.

Critical questions arise: what data is needed to justify moving toward pivotal large randomized trials. We cannot and do not want to test every “promising” strategy in large phase III trials, and a minimum number of patients should be exposed to ultimately ineffective novel therapies, while true progress needs to be made available as quick as possible. Therefore solid early clinical development is needed, randomized phase II trials with one or multiple experimental arms may be a way to go forward.

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