Editorial

Our failure to advance new treatments for glioma to market

JOHN H. SAMPSON, M.D., PH.D., M.H.SC., 1,2,5 THOMAS J. KAMINSKI, M.B.A., 3 AND KEVIN A. SCHULMAN, M.D. 3,5

1Brain Tumor Immunotherapy Program, 2Preston Robert Tisch Brain Tumor Center, Division of Neurosurgery, Department of Surgery, 3Duke Clinical Research Institute, and 4Department of Medicine, Duke University School of Medicine, and 5Health Sector Management Program, Fuqua School of Business, Duke University, Durham, North Carolina

In this issue of the Journal of Neurosurgery, Muragaki and colleagues 8 present the results from an early phase clinical trial using formalin-fixed, autologous tumor as a vaccine in patients with newly diagnosed glioblastoma. The vaccine appears safe and promising. This is a timely piece because, more and more now, we are seeing the promise of immunotherapy realized in cancer. In just the last few months alone, Sipuleucel-T (Provenge), 17 a vaccine for prostate cancer, 1 and a monoclonal antibody (ipilimumab) that blocks an inhibitory molecule on the surface of T lymphocytes, cytotoxic T-lymphocyte antigen-4 (CTLA-4), 23 showed positive results in a double-blind, placebo-controlled, and randomized Phase III trial in patients with progressive unresectable Stage III and IV melanoma for which no other therapies have shown benefit. 4 Similarly, we have been seeing promising results using immunotherapy for brain tumors for some time now. 1,3,5,7–16,19–22,24–31

So why isn’t immunotherapy a reality for patients with glioblastoma? The study by Muragaki et al. 8 provides an opportunity to highlight some of the most important barriers to drug development in neurooncology. Like this immunotherapy study (and our own work), 2,3,18 most clinical trials for patients with brain tumors are single-arm studies conducted at one center or a small number of centers and enroll a small number of patients with unique eligibility criteria. Such studies are simply unable to provide evidence of efficacy needed for drug approval. As a result, these promising advances wilt.

To better understand the current landscape and infrastructure supporting brain cancer clinical research, we examined the trials listed at clinicaltrials.gov. A list of all active clinical trials having the terms “glioblastoma,” “brain cancer,” or “brain neoplasm” as a condition was retrieved and information about target enrollment and the number of sites involved for the trial was abstracted from the trial description. Of the 801 brain cancer trials registered through clinicaltrials.gov in “recruiting” or “active, not recruiting” status, the majority (58%) involved only a single site, and only 24% of the trials had an estimated enrollment of more than 100 patients—a number insufficient to establish drug efficacy in almost all cases. While one may suggest that these statistics are a primary function of the pharmaceutical pipeline given that few trials were late-phase studies (only 9% of trials were Phase III or IV), the fact remains that relatively little multisite collaboration and data collection exist, resulting in trials that are too small to be definitive. While registries and multisite networks have been indispensable to drug development and quality initiatives for many other therapeutic areas, this has not been realized for brain cancer.

One could argue that a robust multisite network and infrastructure could push quality initiatives forward by tracking clinical practice and outcomes for existing treatments as well as help advance promising therapies like the one reported here by Muragaki et al. 8 by reducing the time required to enroll patients and lowering the cost to perform studies. While we must continue to advocate for support of the federally funded cooperative groups, there remains considerable controversy around the continued role of the cooperative groups, such as the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, Pediatric Brain Tumor Consortium, and the American Brain Tumor Consortium, in meeting the need for a core infrastructure to advance the science in this field. If cooperative groups are to remain part of the solution, the time needed to develop protocols in these groups must be dramatically reduced and the impact these groups have on advancing treatment of this disease must be enhanced by allowing for more rapid translation of newly developed drugs and innovative treatment approaches. 5

Given the relatively weak pipeline for brain cancer drugs, another factor to consider is the incentive for pharmaceutical investment. From a practical perspective, the incidence of primary brain cancers is very low compared with that of other types of cancers, so it is not surprising that companies may focus resources on other cancer indications at the expense of scientific advancements specific to brain tumors. Bevacizumab, Roche’s largest drug in terms of revenue, demonstrates this point. Bevacizumab is the second largest drug for the treatment of brain cancer in terms of revenue, yet revenue for the brain cancer indication accounts for only an estimated 3% of the overall $7 billion for the product.

A small patient population, such as patients with malignant primary brain tumors, does not necessarily mean a small market opportunity for pharmaceutical companies though. The incidence of chronic myelogenous leukemia is approximately half that of glioblastoma, yet the primary drug for treating the disease, imatinib mesylate (Gleevec), is one of the top 20 revenue-producing drugs in the industry and is the second largest revenue-producing drug for Novartis, with more than $4 billion expected for 2010. Similarly, sales of eculizumab (Soliris) for Alexion Pharmaceuticals, probably the world’s most expensive drug (costing $409,500 for a year of treatment), 2 are

See the corresponding article in this issue, pp 248–255.
expected to top $500 million this year and grow to $1 billion by 2014. Eculizumab is used to treat paroxysmal nocturnal hemoglobinuria, a rare blood disease affecting an estimated 8,000–10,000 patients in North America and Europe combined—less than half of the prevalence of glioblastoma. Even for glioblastoma, temozolomide (Temodar) produced more than $1 billion for Merck in 2009 making it Merck’s 11th-largest drug. While temozolomide revenue is expected to decline rapidly as its patent expires, it still demonstrates that drugs targeted to treat a small patient population can have a significant impact on pharmaceutical company financial performance. Given these potential rewards, it is unclear why the industry is not responding with the development of new and innovative therapies for glioblastoma. The culture of single-site clinical studies, the lack of an accessible infrastructure for multicenter clinical research, and the limited tradition of systematic evaluation of therapies in an evidence-based medicine framework may all be contributing to this result.

Conclusions

If we want to develop novel therapies for glioblastoma, like the vaccine reported by Muragaki et al. in this edition of the Journal, we have to improve incentives for drug development in glioblastoma and eliminate barriers to advancing the science of cancer treatment in this field. This will require that we streamline established clinical consortia, develop a robust, new infrastructure focused on early and innovative approaches (the AANS/CNS Section on Tumors is currently considering such a proposal); aggressively lobby pharmaceutical companies with cogent pathways for clinical development; leverage the development of drugs for more common cancers by looking for innovative ways to apply them to brain cancer; and reduce the costs of clinical development programs through coordination of clinical sites to spur the advancement of robust, multicenter clinical trials.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

References