Editorial

Tumor treating fields—effective, but at what cost?

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Comment on: Bernard-Arnoux F, Lamure M, Ducray F, *et al*. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. Neuro Oncol 2016;18:1129-36.

Submitted Nov 15, 2016. Accepted for publication Nov 21, 2016.

doi: 10.21037/tcr.2016.12.45

View this article at: http://dx.doi.org/10.21037/tcr.2016.12.45

Each year in the United States, 21,500 adults are diagnosed with a neuroepithelial brain tumor. Most are an aggressive malignant neoplasm called glioblastoma multiforme (GBM) (1). Despite extensive resection, combined chemoradiation therapy, salvage chemotherapy with alkylating agents and monoclonal antibodies targeting vascular endothelial derived growth factor (VEGF), the median survival after a diagnosis of GBM is 14.6 months. Only 4.3% of patients live five years or more (1).

Following improvements in neurosurgical techniques, maximal safe surgical resection became the standard of care. Postoperative radiotherapy became routine when phase III trials showed a near tripling of survival to approximately 1 year with postoperative irradiation (2-4). A meta-analysis was required to show a survival benefit with nitrosourea chemotherapy (5). The standard of care changed after 2005, when Stupp *et al*. published data showing combined temozolomide with radiation therapy produced modest improvements in survival from 12.1 to 14.6 months, with remarkable increases in 2 year survivals from 10% to 26% (6). A companion article published simultaneously showed an even greater increase in 2 year survival from 22.7% to 46.0% in a subset of patients with a methylated gene repair protein called O6-methylguanine–DNA methyltransferase (MGMT) (7).

Increased survivals for an incurable disease have traditionally and predictably been accompanied by increased costs. Costs themselves can be challenging to quantify, especially for neurologic diseases. There are the direct costs of treatments, including the costs for surgeries, radiation, drugs, together with administration and supervision fees. However, there are also savings, with oral chemotherapies or less toxic interventions carrying fewer costs: in addition, many studies fail to consider costs to the patient. Increased travel times, time away from the workplace, disability costs, and end of life care. In neurologic diseases, disability measures may be more meaningful than overall survival scores. A patient who survives in a severely dependent state for a longer period of time may incur more costs than one who lives a shorter time in a highly functional state. Therefore, treatments that reduce debility may be more valuable than those that prolong life.

In an effort to quantify the cost:benefit ratio of new treatments, a single academic institution in Lyon, France found a mean cost of €71,148/patient for GBM treatment of in patients treated in 2008, an increase from €54,388/patient in 2004 (8). The increase in costs was attributed mostly to the increased use of temozolomide in newly diagnosed disease and bevacizumab at recurrence. The authors found survival increased by 3.7 months for an incremental cost-effectiveness ratio (ICER) to be €54,355 per life year gained (LYG).

When evaluating the cost-effectiveness of the addition of temozolomide for newly diagnosed disease, a range of ICERs have been reported, based on the cost of drugs and variations in measured direct and indirect costs. An ICER of €37,361 per LYG and €42,912 per quality-adjusted life-year (QALY) have been reported in Europe, which are considered acceptable for many countries (9-11). However, a separate Chinese study calculated an ICER of $87,941 compared to radiation alone and argued that temozolomide is not cost-effective in a resource-limited setting (12). To evaluate the costs of using Temodar brand temozolomide versus generic temozolomide, Messali *et al*. found that the ICER per QALY decreased dramatically from $103,364 to

$8,875, which meets the willingness-to-pay threshold of many more countries (13).

The cost of temozolomide can be better understood when evaluating it in the context of other novel approaches in the care of glioblastoma patients. Two approaches that augment a standard resection are carmustine wafers and 5-ALA fluorescence-guided resection. The placement of carmustine wafers in the operative bed was a novel therapeutic approach to address operative bed failures despite surgery, radiotherapy, and systemic chemotherapy that became possible with the development of appropriate biodegradable polymers. It was adopted at many centers after it was shown to increase survival by 2.3 months in a placebo-controlled phase III trial, despite an increase in post-operative complications (14). This median survival gain came at a cost of an additional $112,795 per QALY (11).

Glioblastoma resection guided by 5-ALA fluorescence increased the rate of complete resection and improved survival in a phase III trial for patients with Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA) classes IV and V, but not in RTOG RPA class III patients (15-17). The use of 5-ALA costs €1,000–2,000 per patient and a separate study calculated an ICER of €6700/LYG, which is well within the tolerated range for most developed countries (18). 5-ALA fluorescence guided surgery is not routinely available outside clinical trials in the United States.

It is evident that increasing costs of disease management have followed the use of novel technologies such as implantable carmustine wafers, 5-ALA fluorescence guided surgery, and intensity modulated radiation therapy. Unsurprisingly, doing more simply costs more.

The emergence of tumor treating fields (TTF)

The use of alternating electric fields, called 'TTF', to disrupt mitosis represents a novel approach to GBM management. The technique was as effective as salvage chemotherapy in recurrent GBM patients, with less adverse effects. A randomized, prospective phase III clinical trial evaluated TTF in newly diagnosed GBM patients, entitled EF-14, and demonstrated a significant improvement in median survival from 15.6 to 20.5 months (19). The treatment had limited adverse events, mainly restricted to skin irritation from wearing the device. These results were exciting for both physicians and patients alike. A survival benefit of this magnitude in this population had not been seen in a decade. However, almost immediately after the results of this study were presented, questions about the cost of treatment –$21,000 per month—were raised. Moreover, the non-economic costs of using the device for the recommended 18 hours per day have been a barrier to widespread adoption.

In an attempt to address the question of the cost-effectiveness of this new therapy, Bernard-Arnoux *et al*. created a decision-analysis (Markov) model using patients with the same characteristics as the EF-14 trial to predict the ICER for using TTF in the upfront setting (20). In this model, patients could be in one of three health states (stable disease, progression, or death), and patients in the TTF group could be maintained on TTF for up to 24 months in the stable state, or up to 2 months past progression (as patients in the EF-14 protocol were allowed to continue treatment until their 2nd relapse). Direct costs were calculated and the effectiveness outcome was measured in LYG, as opposed to QALYs, because of the lack of available data. An arbitrary willingness-to-pay threshold of €100,000/LYG was chosen, which is arguably within the range of acceptability in the United States.

Using the data from EF-14 to inform their health state models and probability of progression, the use of TTF was associated with 0.34 LYG (4.08 months) at an added cost of €185,476, leading to an ICER of €549,909/LYG. ICERs this high have rarely been seen in field of oncology, even with the introduction of targeted therapies and immunotherapies for other malignancies. This figure is even more alarming when one considers that only direct costs were calculated, and did not account for additional significant costs that may be encountered as patients live longer and additional services may be required. Surveillance imaging is frequently performed, and salvage surgery, multiply cited as the highest cost part of treatment for gliomas, may be used on one or more additional occasions (8,17). Moreover, since TTF have minimal toxicity and no overlapping toxicities, it does not need to be used instead of standard chemotherapy. It does not need to replace an older, less effective therapy, but may be given in combination with any other therapy. Therefore, this cannot reduce costs by replacing other therapies, it can only increase them.

How do we make the use of TTF acceptable?

The cost and cost-effectiveness of this therapy are striking, but should not immediately cause us to reject this new therapy; instead, we should ask, how do we either (I) target patients who will benefit the most or (II) make the treatment more affordable?

It has been documented that patients with methylation of the MGMT promoter region garner more significant gains from temozolomide; however, any the predictive value of this mutation is not known for TTF. As a part of the EF-14 trial, MGMT methylation was recorded but any effect of methylation on treatment response has not yet been reported. If a difference in survival is seen based on this, or other molecular markers, then TTF therapy could be tailored to a population where a greater, and most cost-effective, benefit is seen.

The second option to make widespread adoption of TTF more palatable is to lower the cost of treatment. This was also discussed in the study by Bernard-Arnoux *et al.*, where a threshold sensitivity analysis was performed using theoretical costs between €2,000 and €21,000 per month. To meet the predetermined acceptable threshold of €100,000, the direct monthly costs of TTF would need to be limited to €3,000, and would create an ICER of €98,862. Although the costs of equipment and maintenance of the product are not publically available, a price reduction of such magnitude seems far from feasible. Similar to other new drugs and devices, both the patent and period in which only one product controls the market are limited. The development of a competing or superior product that reaches the clinical market may be expected to drive the cost down to a level that is closer to a more generally acceptable ICER.

Novocure—still not a cure

With increasing health care costs around the globe, but especially in the United States, the costs and cost-effectiveness, or value of treatments have come under strict scrutiny. One difficulty in defining cost-effective treatments is the lack of a uniform definition of what costs are acceptable for every LYG or QALY gained. In 2001, the World Health Organization suggested that interventions that cost less than three times the per capita gross domestic product (GDP) of a country would represent a worthwhile cost (21). Using this approximation, the acceptable threshold in the US would roughly be $159,000 (GDP of $53,000), versus $127,500 in France (GDP of $42,500), and $125,400 in the United Kingdom (GDP of $41,800). While this is one recommendation, Messali *et al.* suggested that the acceptable costs can also be gauged by the threshold values used in publications of cost-effectiveness in each respective country (22). Along these lines, an upper limit of $150,000 per QALY was used in their study evaluating temozolomide and carmustine, and found these interventions to be cost-effective (13). Using regional norms in the UK, Garside *et al.* set the upper limit was set at £30,000, a figure which is far below the cost of both temozolomide and carmustine wafers (11).

TTF is not yet available to all patients who might benefit from its use for a number of reasons. Individual national regulatory bodies like the FDA may or may not include cost-effectiveness as a component of evaluating whether or not a drug or device may be marketed. For example, the FDA includes considerations of safety and effectiveness, but not of cost-effectiveness. Great Britain's National Institute for Health and Care Excellence (NICE) provides evidence-based recommendations to the National Health Service (NHS) across a broad range of topics in health and social care that include an evaluation of cost-effectiveness. TTF is available in the United States, but not in Great Britain and a number of other developed countries. Even in countries where TTF is marketed, third party payers may decline to cover its use.

We are constantly reminded that health care is not an unlimited resource, and at times, our ability to pay for marginal improvements cannot keep up with the interventions that offer such improvements. As standards of care evolve and each new drug and technological advancement is judged against a relatively arbitrary societal norm, the total cost of care tends to be forgotten. We have seen the relative widespread acceptance of radiation and temozolomide for patients who are candidates for this therapy; however, the total cost of surgery and this adjuvant therapy has been quoted at $82,018 (23). While this number is acceptable to many, given the poor survival of patients with GBM, it translates into a cost of $202,089 per each QALY (23). Although 3–4 months of additional survival would be desirable for any patient with a dismal diagnosis, a long term cure is still not obtained, and at an ICER of over $800,000 (€549,909 for TTF plus $202,089 for surgery and adjuvant radiation with temozolomide) when calculating the costs of disease treatment only is far from feasible in even the wealthiest countries.

As healthcare providers, our desire is to provide the best care possible, regardless of expense or thought of allocation of societal resources; however, this attitude is becoming more unrealistic as the affordability of health care becomes a global concern. Every patient with a newly diagnosed glioblastoma should have access to this device, but the current cost precludes all developing and many developed nations from routinely offering TTF. Price elasticity models can be developed that demonstrate revenue maximization by

keeping the costs of treatment high and serving only limited markets. Alternative models may show that strategically lowering the costs for TTF will increase worldwide sales and revenue by serving ever greater numbers of glioblastoma patients.

If TTF were shown to be a cure for glioblastoma, high costs associated with its use would be much more palatable. This is not the case, however, and in light of the current costs of TTF, gatekeepers in many health systems bar or severely limit access to this therapy. A careful re-alignment of costs with documented benefits will help improve access, which is still probably a good thing, even if it isn't a cure.

Acknowledgments

We would like to acknowledge Dr. Alexis Demopoulous for his perspective and assistance in preparation of this manuscript.
Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xian-Xin Qiu (Department of Neurosurgery, the Children's Hospital of Medical College, Zhejiang University, Hangzhou, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.12.45). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Zhang I, Knisely JP. Tumor treating fields—effective, but at what cost? Transl Cancer Res 2016;5(Suppl 7):S1349-S1353. doi: 10.21037/tcr.2016.12.45

