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Critical Reviews in Oncology/Hematology 96 (2015) 257–261

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

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Limited advances in therapy of glioblastoma trigger re-consideration of research policy

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Accepted 19 May 2015

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Abstract

Glioblastoma (GB – WHO grade IV) is the most frequent and lethal primary brain tumour with median overall survival of 7–15 months after diagnosis. As in other cancer research areas, an overwhelming amount of pre-clinical research acquisitions in the GB field have not been translated to patients' benefit, potentially due to inappropriate treatment schedules and/or trial designs in the clinical setting. The recent failure of promising anti-VEGF bevacizumab to improve GB patients' overall survival recapitulates this sense of frustration. The following measures are proposed:

1. to change Phase II design. Bevacizumab and other drugs may have failed in Phase III just because of an inappropriate clinical treatment schedule adopted. Multiple-step Phase II clinical trials allowing more thorough definition of treatment protocols to be extensively studied in Phase III should be designed.
2. to monitor standards of care by documenting survival rates of GB patients in European Cancer Units, in order to homogenize GB treatment quality to the highest possible level all over EU28.
3. to introduce the therapeutic impact factor (*TIF*) and therapeutic (*t*) index bibliometric parameters, in order to orientate pre-clinical research toward more therapy-focussed activities.

Keywords: Glioma; Bevacizumab; Treatment protocol; Treatment quality; Bibliometrics

1. The glioblastoma problem

Glioblastoma (GB – World Health Organization Grade IV) is the most common malignant primary brain tumour. These heterogeneous neoplasms are driven by an intricate network of signaling pathways and despite patients' median overall

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http://dx.doi.org/10.1016/j.critrevonc.2015.05.013
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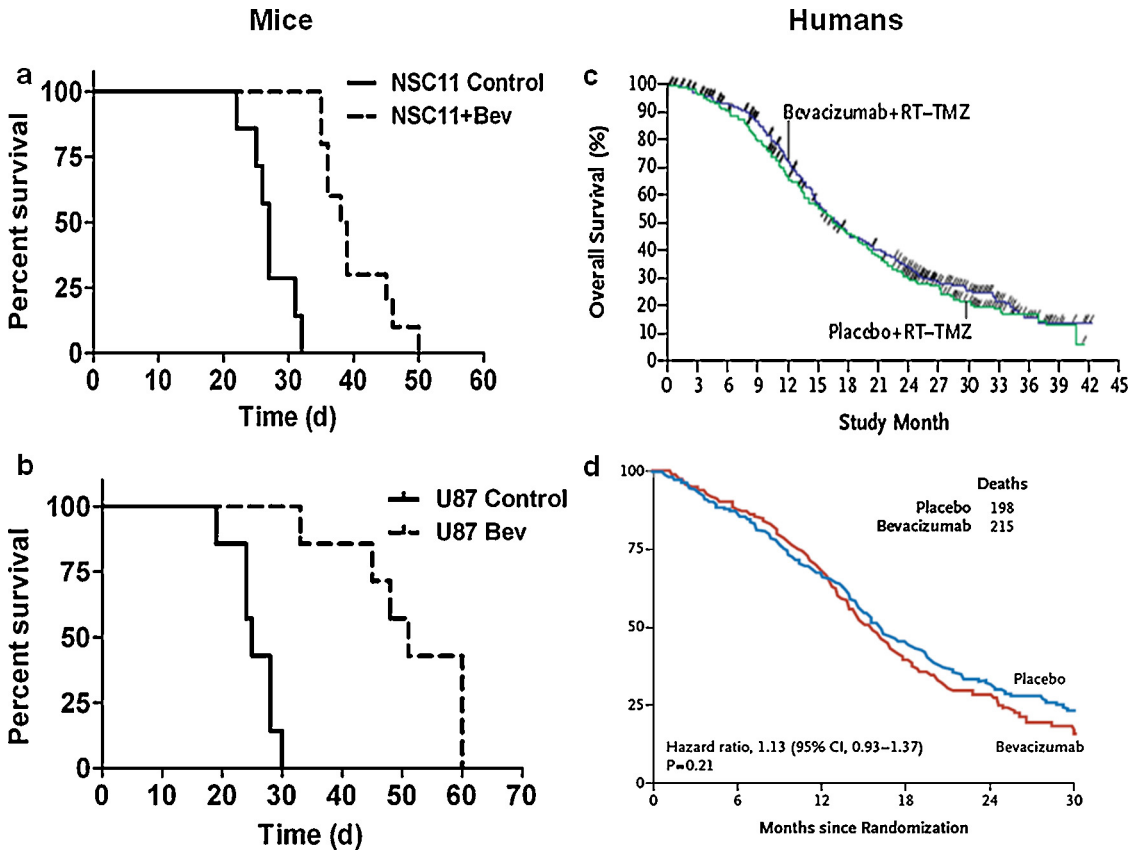

Fig. 1. Kaplan–Meier estimates of OS after bevacizumab treatment in mice and humans. Kaplan–Meier estimates of survival in mice bearing primary NSC11 (a) or established U87, (b) glioma cells-driven orthotopic tumours show prolonged survival in mice treated with bevacizumab. In contrast, Kaplan–Meier estimates of survival in GB patients show no significant difference between patients treated with bevacizumab and placebo (c and d).
Data from Refs. [8,9,22] with permission.

survival (OS) has modestly increased in recent years, still is only 7–15 months and less than 10% of patients survive 5 years after diagnosis [1]. Patients often report seizures as their first symptom and magnetic resonance imaging (MRI) may show a hyperintense signal on T2-weighted sequences. These early observed occurrences of GB develop rapidly with the tumour size in some cases multiplying by 32 in one month [1]. Standard treatment of GB in good performance patients consists of maximal safe surgical resection to achieve tumour debulking followed by focal, fractionated, external beam radiotherapy (RT) alone or in combination with concurrent and adjuvant temozolomide (TMZ) [2]. Patients are usually tapered off corticosteroids to the lowest dose necessary to treat neurologic dysfunction. In patients with neurologic dysfunction secondary to tumour edema and mass effect who are not amenable to surgery, the use of bevacizumab may be considered in order to improve neurologic function and quality of life (QoL) [3]. At recurrence, patients in good performance status are usually treated with cytotoxic chemotherapy following, if feasible, repeat surgery but there is actually no standard treatment in recurrent GB and OS ranges from 3 to 9 months [4,5]. Temozolomide (TMZ) is the preferred chemotherapeutic agent in patients without prior exposure; lomustine is often used for tumours resistant to TMZ. Given these limited treatment options at tumour recurrence, consideration for new therapies is a must. Despite an overwhelming increase in our knowledge of the molecular and genomic changes in GB, translation of these findings to effective therapies remains the exception, with an amazing lack of clinical validation [6]. Results from small studies are rarely translated to successful larger confirmatory studies, potentially related to failed identification of appropriate treatment schedule and/or lack of adequate trial design [7]. Merely to quote the most recent instance, early promising preclinical and phase II clinical studies using bevacizumab in both newly diagnosed and recurrent GB have not been confirmed in two recent phase III trials (Fig. 1). In the first one, Chinot et al. evaluated the effect of the addition of bevacizumab to the Stupp protocol for the treatment of newly diagnosed GB [8]. The addition of bevacizumab (10 mg/kg every other week) to radiotherapy-TMZ did not improve OS in patients with GB but improved PFS and temporarily stabilized baseline QoL and performance status. The rate of adverse events was higher with bevacizumab than with placebo. Similar conclusions were drawn by Gilbert and coworkers in an independent NCI-funded clinical trial [9] (Fig. 1). Hence, using the

aforementioned treatment schedule, bevacizumab seems safe and tolerable and to prolong PFS but not OS in newly diagnosed GB. As discussed below (Section 2.1), the negative results of the two phase III trials on OS improvement do not allow to conclude that bevacizumab cannot prolong OS in GB patients [10,11].

2. What to do?

The relatively low frequency of GB patients [12], while being a fortune, may yet narrow the statistical power of trials and reduce the interest of for-profit pharmaceutical companies, with limited sponsoring of GB-related research. Further, albeit a considerable amount of knowledge on GB has been generated in recent years, the development of new therapies is stagnating, in part due to lack of clinical validation. The question arises whether we have so far beaten the right trees in order to improve OS in GB and what can be done to accelerate achievement of this chimera [13]. We propose the following three measures.

2.1. Determine the right treatment schedule

Why bevacizumab increases OS in mice but not in humans (Fig. 1), likewise a number of other experimental drugs in clinical cancer research? The genotypic/phenotypic homogeneity of the mouse laboratory strains and established cell lines used for development of orthotopic tumours do play a role. This is supported by the reduced therapeutic effect observed when orthotopic tumours are developed using primary GIC rather than established cell lines (Fig. 1 and [14]). In other words, the profound polymorphic nature of humans and their tumours may damp the therapeutic effects in aggregate studies. Further confounding factors in human experimentation on GB include the surgery technique, the concept of total resection, if patients can be subjected to MRI 24/48 h after having performed surgery and if after relapse a new surgical resection is possible. Of particular importance, the efficacy of different treatment schedules cannot be adequately investigated in GB patients, for statistical reasons. For instance, the observed short-lived clinical benefit of bevacizumab in GB [8,9] may not mean that bevacizumab cannot improve OS of GB patients but rather, that the employed treatment schedule was wrong. In our preclinical studies with ATM inhibitors as GB radiosensitizers, we observed efficacy under a narrow combination of ATM inhibitor concentration and radiation dose [14] and the treatment schedule was profoundly affected by the cell's environment: the same GIC line could be radiosensitized in our preclinical studies with different treatment schedules if grown into a petri dish or orthotopically in a mouse brain, and, most probably the same will happen when tumours will have to be treated in human brains (Fig. 2). For unclear reasons, no appropriately designed phaseI/II studies evaluating optimal delivery, efficacy and time schedule of escalating doses of bevacizumab in GB patients have been performed (http://clinicaltrials.gov/ct2/show/NCT01269853?term=NCT01269853&rank=1 [11,15]). Hence, administration mode, dosing and timing that provide optimal control of GB remain unknown and the disappointing results of phase III trials should not amaze. Multiple variations of the intravenous bevacizumab 10 mg/kg-every-other-week schedule will have to be explored, before concluding that bevacizumab is useless to improve OS of GB patients [11]. The same may apply to other pre-clinically active drugs [16]. Modifications of standard trial designs may be required accordingly. GB patients are (fortunately) sparse and smaller treatment groups/arms with respect to trials for big killers such as breast, lung or colorectal cancer, will have to be planned. In other words, more treatment schedules with smaller patients' groups may allow to pilot screen an initial large number (e.g. 20) of dosing and schedule combinations. The most promising (e.g. 4–5) combinations resulting from the initial screening will have to be confirmed in appropriately randomized Phase IIB trials designed with increased statistical potency. In case of positive outcome, a further increase of statistical potency in a randomized Phase IIC study may identify the most effective procedure. Should efficacy be again confirmed, a final traditional Phase III trial will say a definite word on the reliability of the selected treatment. To summarize, increased scale progressivity and multicentric distribution may be required with GB trials in order to be able to correct mistakes along the drug development process. Those snakes and ladders are long and winding but may be more rewarding than what has been achieved so far (Fig. 2). Finally, albeit the main concern of caregivers is understandably to guarantee full treatment tolerability, limited and provisional increases in toxicity may be rewarding to the patient as suggested by some recently observed paradoxical effects [17].

2.2. Monitor standards of care

Significant variations on medical practice exist among Organisation for Economic Co-operation and Development (OECD) countries [18] and survival of GB patients is variable ranging from 7 to 15 months or more [19]. It would be desirable that this fork is reduced, among individual patients and among institutions. Concerning the latter, GB survival may be calculated as the average time elapsing from diagnosis of GB to GB-related death in a given therapeutic unit. Considering that (a) GB is not amenable to screening and/or early detection; (b) dates of GB diagnosis and the identification of therapeutic units can be easily obtained through cancer registries; (c) GB does not metastasize; (d) treatment guidelines are relatively uniform at least for first line therapy (NCCN guidelines – so-called "Stupp" protocol); (e) the disease is rapidly lethal; (f) certifications on the cause/date of death are usually reliable and available through cancer registries; calculating the average time elapsing from diagnosis of GB to GB-related death in a given therapeutic unit would be feasible

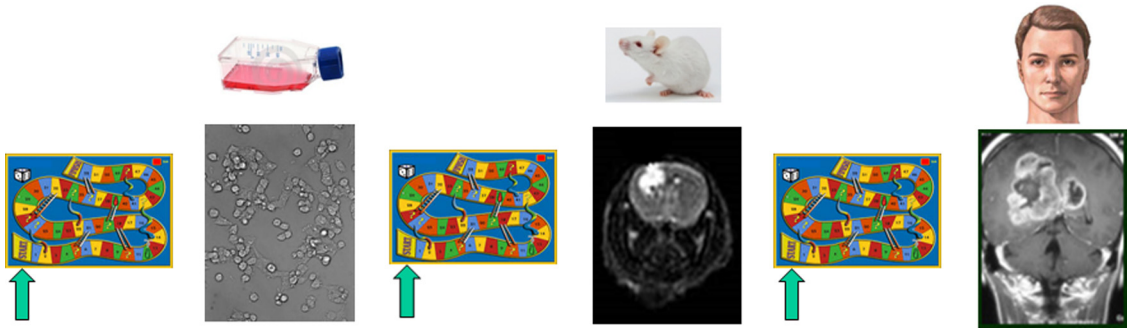

Fig. 2. Changing GIC environment. Determining effective treatment conditions may be snakes and ladders that start each time from the beginning when moving from in vitro (left) to animal (center) to clinical (right) studies.
MRI of mouse GB reproduced from Ref. [14], with permission. MRI of human GB courtesy of Radiology Teacher file server http://www.radiologyteacher.com/index.cgi?&nav=view&DatID=1125.

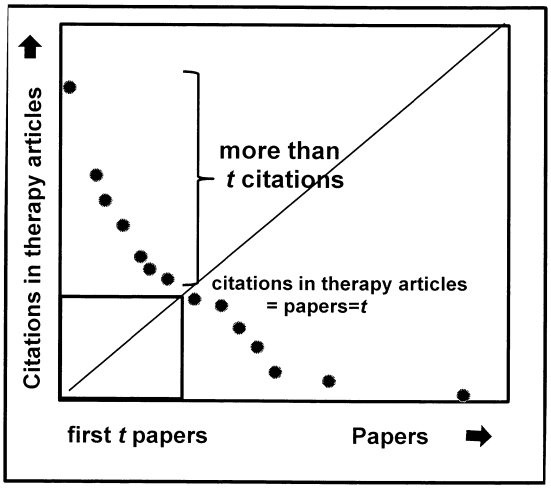

Fig. 3. The therapeutic (*t*) index. Graph of decreasing citations in Cancer Therapy articles as a function of numbered papers. The *t* index is the number of papers with a number of citations in Cancer Therapy articles $\geq t$.

thus allowing to identify critical issues in implementation of currently available therapeutic protocols and rectify them.

2.3. Boost therapy-aimed research

A bibliometric methodology for evaluating the impact of research on definition of clinical guidelines has been published [20]. We extend herein that proposal to the impact of pre-clinical research on therapies by introducing the therapeutic impact factor (*TIF*) and the therapeutic (*t*) – index bibliometric parameters (Fig. 3). The *TIF* of an academic journal would be a measure reflecting the average number of citations in the Therapy sections of oncological journals (e.g. the Cancer Therapy Sections of *Clinical Cancer Research* or *International Journal of Cancer*) to recent articles published in that academic journal. It may help to determine the relative importance of a journal to orientate therapies, that is (or should be) a major aim of cancer research. In any given year, the *TIF* of a journal would be the average number of citations in therapeutic sections received *per* article published in that journal during the two preceding years. For instance, the 2014 *TIF* of a journal would be calculated as *A*/*B* where *A* is the number of times that all articles published in that journal in 2012 and 2013 were cited by therapeutic sections during 2014 and *B* is the total number of articles published by that journal in 2012 and 2013.

The *h*-index is an index that attempts to measure the impact of the published work of a scientist or scholar. The *h*-index is based on the set of the scientist's most cited papers and the number of citations that they have received in other publications. Various proposals to modify the *h*-index in order to emphasize different features have been made [21]. We propose herein to introduce the therapeutic (*t*) – index (Fig. 3). As *TIF* would measure the importance of a journal to propose and orientate therapies, the *t*-index would measure the importance of a scholar. The *t*-index would be based on the distribution of citations received by a scholar's publications in the therapeutic sections of cancer research journals. In other words, a scholar with an index of *t* has published *t* papers each of which has been cited in cancer therapy articles at least *t* times (Fig. 3). Thus, the *t*-index reflects both the number of publications and the number of citations in cancer therapy articles. Both *TIF* and *t*-index could be determined using appropriately set automatic tools such as Scopus, Web of Science or Harzing's *Publish or Perish*. These bibliometric parameters would measure the extent to which an academic journal or a scientist' work impact on therapies. In other words, how translatable to patients' benefit is research. Possible increases in publication bias could be evaded by restrictive criteria adopted by the editorial boards with respect to the actual therapeutic implications of submitted results. To summarize, both *TIF* and *t*-index may help to re-evaluate those research programs that, while ensuring visibility to cancer centers and scientists, do not actually bring significant benefits to patients.

Conflict of interest

The author declares no conflict of interest.

Acknowledgements

I thank Dr. Domenico Franco Merlo, Dr. Valerio Gennaro (Epidemiology and Clinical Trials, IRCCS AOU San Martino-IST) and Dr. Alessandro Fortunelli (National Research Council, Pisa, Italy) for helpful discussions on analysis of GB patients' survival and related research policy. I also thank Dr. Anna Rachele Bogliolo (Scientific Secretariat and Library, IRCCS AOU San Martino-IST) for helpful discussions on the *t* index. Work partially supported by Compagnia San Paolo, Turin, Italy (Grant 2010.1944).

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Biography

Guido Frosina received his Laurea in Biological Sciences cum laude at University and Scuola Normale Superiore of Pisa in 1981 and a Ph.D. in Genetics at University of Ferrara, Italy in 1987. He has spent research stays at Institut Gustave Roussy, Villejuif, France (1985–1986) and at Imperial Cancer Research Fund, South Mimms, UK (1988–1989). He became deputy head of the Mutagenesis laboratory at IRCCS AOU San Martino-IST (formerly National Cancer Institute), Genova, Italy in 1987 where currently works. His research areas include DNA repair and Mutagenesis with focus on mechanisms of brain tumour resistance and novel radiotherapeutic approaches to overcome them. He has been or is PI of national and international research projects sponsored by several funding Agencies including the European Union, the Italian Association for Cancer Research, Telethon and the Bank Foundation Compagnia S. Paolo. He is reviewer for scientific journals including Antioxidants & Redox Signaling, Cancer Research, Clinical Cancer Research, Free Radicals Biology & Medicine, International Journal of Cancer, Nature Nanotechnology, Nucleic Acids Research, Oncogene, Trends in Biochemical Sciences and funding agencies including Association for International Cancer Research, Austrian Academy of Sciences, Samantha Dixon Brain Tumour Trust, Swiss National Science Foundation.