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COMMENTARY

Blood–brain barrier crossing and breakthroughs in glioblastoma therapy

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Glioblastoma is a heterogeneous tumour type which is highly resistant to radiotherapy and chemotherapy. Clinical results following standard therapy as well as new approaches using targeted agents as monotherapy are still disappointing and bid for new breakthrough strategies to combat this aggressive malignancy. Rundle-Thiele *et al.* [1] explored alternative treatment options via literature review and identified clinically approved drugs which are routinely used against several disorders, which could be repurposed as anti-cancer agents. This strategy of drug selection based on previous knowledge could facilitate the identification of anti-cancer drugs which can pass the blood-brain barrier and enhance the effect of radiotherapy. In addition, novel targeted agents might be developed, based on this knowledge. This new methodology allows pre-selection of anti-cancer drugs with a low toxicity profile, which are potentially effective in the treatment of glioblastoma.

Glioblastoma therapy

Despite aggressive therapy consisting of surgery, postoperative radiotherapy with concomitant and adjuvant temozolomide, the median survival of patients with a glioblastoma (GBM) is only about 15 months following diagnosis. The majority of patients die from locally recurrent disease, which is due to the infiltrative growth behaviour and resistance to radiotherapy and chemotherapy. Eradication of radioresistant cells, which include cancer stem cells, genetically aberrant cancer cells and oxygen deprived hypoxic cancer cells via dose escalation in radiotherapy is limited by the radiation tolerance of the surrounding normal brain tissue. Delivery of most chemotherapeutic agents is abrogated by the presence of the blood–brain barrier (BBB) [2, 3]. Current studies on optimization of GBM therapy focus on the development of new treatment methods as well as on the use of tumour-tailored, therapeutic agents, which selectively attack genetic and pathological aberrant glioma cells [4]. Phase 1/2 clinical trials using targeted agents as monotherapy are ongoing, but unfortunately no breakthrough has been reported yet [5].

Anti-cancer efficacy of existing drugs

But why not look away from cancer, to other classes of drugs that are already marketed, are safely used in clinical practice and may have anti-cancer potential? With this different approach, Rundle-Thiele *et al.* [1] reviewed the literature and identified a number of drugs that could provide a new treatment paradigm. A comprehensive list of drug classes, including antidepressants, statins and anti-hypertensive drugs, which possess anti-cancer efficacy in preclinical brain tumour models and occasional patient studies, is presented. The drugs were selected for their ability to pass the BBB. This is important since the BBB forms a major problem in the therapy of brain tumours because it prevents the delivery of most chemotherapeutic and targeted agents to the tumour location. For many years, different strategies have been investigated to facilitate BBB crossing of therapeutics [2, 6]. Currents methods to enhance the delivery of drugs to brain tumours include (1) the use of non-invasive techniques, such as radiotherapy, ultrasound and biological approaches via cell penetrating peptides and viral vectors, (2) invasive techniques, e.g. convection enhanced delivery and (3) alternative routes via, for example, intranasal application, therewith bypassing the cardiovascular system [6]. A most promising drug delivery approach for glioma is the use of conjugated or surface functionalized nanocarriers which can cross the BBB. Using glutathione PEGylated liposomes, the delivery of doxorubicin to murine brain tumours was found to be improved [7]. In a phase 1/2 A study on brain metastases and recurrent high grade gliomas, this approach was found to be safe, well tolerated and active. A phase 2 clinical and pharmacological study to determine preliminary efficacy of treatment with glutathione PEGylated liposomal doxorubicin hydrochloride formulation (2B3–101) in patients with leptomeningeal

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metastases of breast cancer is currently recruiting participants (ClinicalTrials.gov: NCT 01118713). Many of these and other drugs antagonize pathological features of GBM and/or have a proven mechanistic rationale for their anti-neoplastic effect. Rundle-Thiele *et al*. [1] propose to explore further their efficacy in an adjuvant setting to the current standard radio-chemotherapy GBM regimen.

Drug selection strategies

The methodology of Rundle-Thiele *et al*. [1] can be seen as a nice example of the upcoming data integration era. Publically available resources of pharmaceutical and drug discovery data enable researchers to use qualitative or quantitative approaches for repurposing small molecule drugs against cancer. These repurposing strategies consist of re-use of drugs selected for other disease indications such as provided by Rundle-Thiele *et al*. [1] or re-use of drugs that have been clinically tested but have remained on the shelf because of lack of efficacy.

To identify these small molecule drugs with desired biopharmaceutical parameters, many public data sources have become available during the last two decades, providing bioactivity, molecular fingerprint and toxicity data. Bioactivity data could point to drugs that have desired poly-pharmacological (i.e. multi-target) features that optimally match individualized features. For instance, current epidermal growth factor receptor (EGFR) inhibitors against GBM have insufficient efficacy because of toxicity, resulting in insufficient drug concentrations in the tumour. Identification of drugs that do penetrate the brain and also demonstrate EGFR inhibitory function, which was previously considered as off target, might be of benefit. In addition, molecular fingerprints using drugs that show clinical efficacy could help to identify candidate drugs with desired efficacy against brain cancer. Regarding toxicity, information about BBB passage through cerebrospinal fluid drug concentration measurement would be helpful. These novel and integrated approaches using previous knowledge could enable identification of small molecule drugs with optimal characteristics against gliomas such as high BBB passage while avoiding neurotoxicity.

Heterogeneity of glioblastoma and resistance to therapy

Another challenging factor for effective therapies against high grade brain tumours is their high resistance to both radio- and chemotherapy, likely caused by the heterogeneous nature of this tumour type in which subpopulations of glioblastoma cells have distinct features. Intratumoural heterogeneity consists of genetic, signalling and lineage heterogeneity [8]. Current knowledge on the heterogeneity aspects of GBMs and related resistance to therapy, the limited space for radiation dose escalation because of normal brain radiation tolerance, the presence of the BBB preventing drug delivery to the tumour site and disappointing clinical results so far using targeted agents as monotherapy, bid for new breakthrough strategies to attack this aggressive malignancy. On the basis of the state of the art and currently available tools, the most effective GBM therapy would comprise surgery followed by high precision external beam radiotherapy together with personalized synergistic and radiosensitizing combination of dual or even triple targeted agents to be locally delivered to the tumour site.

Interaction between irradiation and drugs

The interaction between irradiation and drugs is still underexplored in brain tumour research. Fractionated radiotherapy, i.e. 60 Gy applied in daily 2 Gy fractions, 10 Gy per week for 6 weeks, forms the core of the current standard regimen for GBM patients. Preclinical drug research in GBM should therefore caution to identify radiosensitizing compounds which enhance the effect of irradiation, additional to their own cytotoxic effect. A crucial issue is the scheduling of the administration of radiosensitizing agents during the 6 weeks course of radiotherapy. Current intervention options are inhibiting the repair of radiation-induced DNA lesions, increasing radiosensitivity, disturbing cell cycle (re)distribution, inhibiting tumour cell repopulation and/or increasing tumour re-oxygenation, via vascular normalization, the typical basic principles of radiobiology [9–11]. Interaction with irradiation has also been demonstrated for some older drugs, like the anti-epileptic drug VPA, discussed by Rundle-Thiele *et al*. [1]. The screening of new drugs on the basis of monotherapy efficacy only may fail to identify agents that ultimately provide their strongest clinical impact by exploiting the above mentioned 5Rs of radiobiology. Consequently, contemporary clinical investigation of molecular targeted therapeutics may overlook agents that work most effectively in combination with irradiation [10].

Final remarks

Because of the still disappointing clinical results in the treatment of GBMs, there is great need to make the right choices in an enormous parameter space of treatment options. The war against this destructive tumour type needs better weapons and strategies. New techniques for selective delivery of synergistic targeted agents with radiosensitizing efficacy, optimized translational *in vitro* and *in vivo* laboratory models together with fully integrated bio-informatic personalized pathological, molecular and genetic brain tumour fingerprint efforts will give us breakthrough news. Does it however matter if existing 'older' or 'newer' drugs are used, provided that they are safe? Clinical outcome will give the answer.

Competing Interests

Both authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organization for the submitted work, no financial relationships with any organization that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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