Drug repurposing – a novel approach for the treatment of brain tumours

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We desperately need new and effective therapies for the treatment of brain tumours. One promising approach is to assess the potential clinical benefit for brain tumours of drugs which are already in use for the treatment of other conditions. This is called drug repurposing [1]. As the drugs will have been tested for safety and are already in use in the clinic, the time period required to get them to the patient should be much shorter than that required for the development of new therapies. These drugs could potentially be used either alone or in combination with existing treatment strategies to make them more effective. In addition to identifying new therapeutic uses for existing drugs, repurposing may also involve the development of different formulations for the existing drug or the creation of new combinations of drugs previously used as separate products.

A number of initiatives have been introduced at a regulatory level which promise to speed up the approval of new drugs. The European Medicines Agency has piloted the adaptive licensing programme which allows drugs to be used in the clinic for a specific sub-population of patients while the later stage clinical trials for a wider group of patients are still taking place [2]. The PRIority MEdicines programme (PRIME) will ensure that the timeline from the submission of a marketing application to potential approval is streamlined. This programme is focused upon drugs which will treat diseases which are considered as being of "unmet need" – where there are few or no effective treatments currently available. New treatments for brain tumours fall into this category and a number of drugs are currently being considered within this programme. While these are promising advances, they focus largely on the development of new drugs, and their development may be some time away. Furthermore, there has been a significant attrition rate as many of the new drugs fail to reach their primary endpoint and the trials are abandoned.

A clear understanding of the changes that occur in brain tumour cells is key for the development of new therapeutic strategies, including drug repurposing. For example, an increase in mitochondrial function is essential for tumour cell division and may therefore serve as a viable drug target. Under normal circumstances, tumour cells consume increased levels of glucose to feed the process of aerobic glycolysis. One approach to restrict glucose levels is the use of the low-carbohydrate ketogenic diet (KD). This was initially developed for the treatment of intractable paediatric epilepsy due to its capacity to dampen down neuronal activity. Because of the reduced levels of carbohydrate associated with this diet, the liver converts fat into fatty acids and ketone bodies. The ketone bodies then replace glucose as the primary energy source. This provides sufficient levels of cellular energy for the majority of cell types. However, it was suggested that its ability to restrict cellular energy levels in tumour cells, thus making it a potential treatment for brain tumours. The anti-neoplastic potential of the KD has previously been explored in a number of pre-clinical brain tumour models [3]. In addition to a reduction in tumour cell division, migration and invasion, it has also been reported to enhance the effectiveness of radiotherapy and chemotherapy. There have also been preliminary reports which suggest that other agents which increase ketone levels and therefore reducing glucose utilisation, such as ß-hydroxybutyrate, may also demonstrate a clinical benefit [3]. Clinical studies are now underway to assess the potential therapeutic benefit of the KD for specific types of brain tumour, although the rigorous nature of the diet may be challenging for some patients.

Tumour cells can also utilise the amino acid arginine as a source of energy, so a decrease in its availability may also demonstrate a beneficial anti-tumour effect [4]. Initial studies have suggested that plasma arginine deprivation using pegylated arginine deaminase (ADI-PEG 20) may be beneficial in the treatment of acute myeloid leukaemia [5]. Trials are being planned which will assess the potential benefits for patients with glioblastoma. Another drug which mediates its effects through dietary intervention is the food additive triacetin which acts to decrease the levels of acetate in the brain and also decrease energy levels. Pre-clinical studies have suggested that this can halt cell growth and may potentiate the effect of existing therapies including temozolomide [6].

Consultations with people affected by brain tumours were carried out in the UK by the James Lind Alliance Priority Setting Partnership in neuro-oncology. This identified lifestyle uncertainties (including whether or not diet-related approaches could influence brain tumour growth) as one of the top unanswered research questions for people affected by brain tumours. Therefore, dietary studies based on a solid scientific rationale are of particular importance for the development of new therapies.

The identification of drugs which are not currently in use for the treatment of cancer but which may be effective in the treatment of brain

tumours can be achieved using a number of complementary approaches. Clinical observations associated with large-scale population studies may reveal an unintended additional benefit of a drug. Studies have suggested that chronic treatment with tricyclic anti-depressant drugs may be associated with a reduced incidence of glioma [7]. The findings from this study supported the results of previous in vitro research which reported an anti-neoplastic effect of the drug, potentially due to its actions on mitochondrial functioning [8]. A more recent study which used a systematic bioinformatics approach also identified tricyclic anti-depressant drugs as potential anti-tumour agents [9].

A further challenge to the development of a drug repurposing programme for the treatment of brain tumours is the blood-brain barrier (BBB). While this exists to protect the brain from harmful substances, it also prevents the entry of many drugs into the brain. This is one of the key reasons underlying the failure of a number of existing anti-neoplastic agents to effectively treat brain tumours. Therefore, the repurposing drugs which are known to cross the BBB, such as tricyclic antidepressants, provides an attractive possibility for the identification of new drugs which may have anti-tumour properties.

Autophagy is a fundamental catabolic process by which materials are degraded within the cell by lysosomes for energy production or stress elimination. In cancer cells, autophagy can serve as a cell survival pathway in order to maintain homeostasis in cases of starvation and stress. However, it can also produce tumour-suppressive effect by inducing autophagic cell death, either in collaboration with apoptosis or as a back-up mechanism in the case of this being defective. Brain tumours with a BRAF genetic mutation have been reported to be autophagy-dependant and therefore treatment with an autophagy inhibitor may provide an appropriate therapeutic approach. Initial clinical studies have reported that the co-administration of the anti-malarial drug chloroquine potentiates the action of the existing anti-cancer drugs through the inhibition of autophagy in a number of patients with brain tumours. Further research using other autophagy inhibitors is required in order to verify this therapeutic approach [10]. However, other studies have suggested that another anti-malarial drug dihydroartemisinin may exhibit an anti-tumour effect through the promotion of autophagy [11]. This underlines the differential effects of drugs on a single cellular target and highlights the importance of our understanding of tumour heterogeneity.

One of the key challenges facing the process of repurposing is the lack of investment. Most of the drugs that are likely to be tested for repurposing are off-patent i.e. the companies which initially developed them no longer have market exclusivity for their use and they are generally available in a generic form. Therefore, there is a lack of incentive for any pharmaceutical companies to invest in new clinical trials. Furthermore, drug repurposing is often led by academic units and medical research charities with minimal industrial involvement.

A number of political initiatives have been taken within the UK in recent years to try to address this problem, with a number of bills being debated in Parliament. In addition to drug repurposing, there is a growing body of evidence that some existing cancer therapies may be effective "off-licence" i.e. for uses other than those for which they have obtained regulatory approval. This approach has been used for the use if immunotherapeutic agents which have not been approved for the treatment of brain tumours. The clinician must take personal responsibility for any adverse effects that may occur. This has led to an inconsistent availability of these drugs. Although the Bills were unsuccessful, they have led to the establishment of a Department of Health Working Group which is examining ways in which repurposing may be possible within the existing legislative guidelines. This is an area that has been highlighted as being key by the charity Brain Tumour Research in its research manifesto and was also identified in the Governmental Task and Finish Group which was established in response to the UK Petitions' Committee report about the poor level of funding into brain tumours. Because of its potential to develop new treatment strategies for the treatment of brain tumours in the shorter term, research to develop drug repurposing programmes needs to remain a key research priority as we move forwards.

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