

Name of Disorder: Brain Tumour/Cancer - Medulloblastoma

Essay title: Medulloblastoma enters the era of personalised medicine

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Content:

Medulloblastoma is a brain cancer arising in the cerebellum which is the part of the brain required for motor control. It is characterised by the unchecked proliferation of undifferentiated neural stem cells which are the cells that lay down new neural connections in the developing brain. Medulloblastoma typically affects infants (less than 4 years old represent 21% of patients) and children (age of 4-16 represent 67% of patients) many of whom present with metastasis at original diagnosis [1].

Current treatments are effective and have achieved overall survival rates of up to 80% using protocols including surgical resection, chemotherapy and radiation therapy [2]. However, as one may expect, removal of part of the brain and ongoing chemotherapy and radiotherapy on developing brains have lasting side-effects. The majority of long term medulloblastoma survivors suffer from lifelong neurological deficits. Despite these sombre facts there is good reason for optimism. The lack of treatment options which cure disease whilst retaining quality of life has led clinicians and researchers to undertake massive studies in order to define the underlying genetic and biochemical causes of this disease which is providing breakthroughs already changing patient management.

The generosity of patients and their families have enabled large collaborative research teams to collect hundreds of medulloblastoma samples accompanied with records of diagnosis, treatment and patient outcomes. Analysis of the underlying genetic mutations and gene expression data was performed on these patient samples to better understand medulloblastoma and ultimately generate effective targeted therapeutic regimens. What was immediately apparent from these analysis was that medulloblastoma is not a single disease, but rather a disease with at least 4 distinct subgroups distinguished by genetic and gene expression data, the cell of origin and histology [3]. Importantly these subgroups show very different patient outcomes. One subgroup (WNT) was found to have good prognosis and low incidence of metastasis. New less aggressive treatment protocols are being trialled for these patients which is showing promise both in terms of patient survival, but importantly also in quality of life following treatment. Another subgroup is driven by genetic mutations which activate a single biochemical pathway (SHH). Pharmaceutical companies have developed chemical compounds which specifically block this pathway and clinical trials using these compounds to treat this (SHH) subtype of medulloblastoma are proving effective [4].

In contrast to the success in improving patient outcomes in the WNT and SHH subgroup of medulloblastoma there has been little or no improvement for those with the more aggressive group 3 and group 4 medulloblastoma. Patients from these groups show increased genetic heterogeneity in tumour tissue which makes it difficult to define a causative mutation amongst the multitude of "passenger" genetic mutations. However, some recent advances have been made. Group 3 medulloblastoma patients commonly have mutations in the cMyc gene. Researchers have now been

able to use this information to generate a mouse model which closely resembles the human disease. This breakthrough enables research teams to accurately define the importance of particular genetic mutations and biochemical pathways in this subgroup of medulloblastoma. Moreover, it enables the pre-clinical testing of chemical inhibitors which is a critical first step towards new therapies for patients.

Medulloblastoma, once thought of as a single disease, has benefitted greatly from the genomic era of medical science and is a prime candidate for tailoring patient treatment to their specific genetic profile to give optimal outcomes - a process called personalised medicine. Whilst researchers and clinicians have made major inroads towards the treatment of 2 of the 4 medulloblastoma subgroups more work is required to define the causes of the two most aggressive subgroups. The continued improvement of treatment protocols for medulloblastoma patients requires the ongoing support of patients, funding sources and large scale collaborations between clinical and research teams.

References:

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3. Northcott, P.A., et al., *Medulloblastomics: the end of the beginning*. Nat Rev Cancer, 2012. 12(12): p. 818-34.
4. Rudin, C.M., et al., *Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449*. N Engl J Med, 2009. 361(12): p. 1173-8.