

- 1) Name of Disorder – Brain Tumours
- 2) Essay Title - Glioblastoma (GBM): The most aggressive and lethal primary brain tumour
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Introduction

In NSW, the incidence of brain cancer is 1 in 96 and 1 in 163 by the age of 85 in males and females respectively (Cancer Institute, NSW). Although brain tumours are rare, the incidence of newly diagnosed malignant cases in Australia has increased over the last two decades (1). This is likely due to more sophisticated diagnostic techniques and lower threshold for investigation. Unfortunately, therapeutic options for this highly malignant and aggressive tumour have not kept pace with the increased incidence. As the name suggests, these tumors consists of various forms of cells (Multi-forme) and can present to a pathologist with multiple forms (multi-forme) of histology. This results in resistance to current treatments and difficulty in diagnosis by a pathologist.

Incidence

This high grade (Grade IV) astrocytoma accounts for more than 80% of all malignant brain tumours. Indeed, in terms of years of life lost, the population burden from Glioblastoma Multiforme (GBM) is the highest of all malignant cancers (2). GBM, the most lethal primary brain tumour, has a median survival of 14.6 months (3).

Impact

Social: Approximately 1600 brain cancers are diagnosed annually in Australia; that is roughly one person diagnosed with brain cancer every six hours and one passes away every 8 hours (4). Relative survival rates (five-year relative survival) for brain cancer have increased less than 2% between the periods of 1982-1987 and 2006-2010. Only one in five people diagnosed with brain cancer will survive for at least five years (5).

Economic: In 2012, brain cancer was estimated to account for 21,500 disability adjusted life years (DALYs) in Australia; of these 20,200 were years lost due to premature death and 1,300 were years of healthy life lost due to disease, disability or injury (6). Brain cancer costs more per patient than any other cancer because it is highly debilitating, affects people in their prime and often means family members cannot work if they become carers (7). For those aged 35 to 44, brain cancer accounted for the highest proportion of cancer expenditure, totalling \$32 million (8).

Causes

Genetics and Environment – Harmful radiation including Ultra-violet, X-rays, Gamma rays and radiation have been well known to cause DNA-damage which stimulates the repair mechanisms in our bodies. Like everything our repair mechanisms are also not 100% efficient. Therefore, this result in defects, which if occur in places crucial for the function of a crucial gene or protein is called an active Mutation. These Mutations can activate cancer promoting genes or even silence tumour suppressing genes, causing uncontrolled growth of defective cells, which is nothing but cancer. Notably, a recent study identified the molecular mechanism by which constitutive DNA-damage in cancer cells promotes the process of carcinogenesis (9). Several key genes like C/EBP and STAT3 have been recently implicated in the process of promoting cancer in the brain and may be relevant therapeutic targets (10). Additionally, several fusion genes like FGFR-TACC have recently been implicated in GBM (11). Evidence for the role of non-coding RNAs called micro-RNAs (miRNAs) (12) and cancer stem cells (CSCs) (13, 14) in promoting GBM growth is also rapidly emerging.

Symptoms

Symptoms that occur are mainly dictated by the location of the tumour in the brain. If one has a tumour in the frontal lobe, he or she may experience changes in mood, personality or even unilateral paralysis. If the tumour is in the temporal lobe, he or she may have problems with speech and memory. Other common signs like headaches, vision loss, and decrease in motor control function usually occur in the advanced stages of glioblastoma, and maybe compounded by other factors like stress, immunity and environment.

Diagnosis

A neurological assessment of the person's senses, reflexes, motor skills and memory is the first thing a physician normally does. Oncologists are then usually consulted for future management. Usually, physical examination is followed up by a CT scan or MRI scan of the brain using an intravenous contrast dye. The contrast dye is absorbed by the tumour and brightens it up (known as enhancement) which makes it easier to pinpoint and see the location and size of the tumour. In most cases this followed by a biopsy with the consent of the patient. A biopsy can help in differentiating between a malignant or benign tumour by a pathologist. Pseudopalisading necrosis, atypical nuclei with mitotic activity and neovascularization are the histological features used to identify GBM. The biopsy involves making a small hole in the cranium (craniotomy) and excision of a small piece of tissue from the tumour for microscopic analysis.

Treatment

Currently, surgical resection (debulking) followed by radiotherapy with concomitant and adjuvant chemotherapy (Temozolomide) constitutes the mainstay for current

treatment of GBMs (15, 16). However, tumour recurrence and associated patient mortality is almost inevitable. This is mainly due to the highly invasive nature of GBMs and their resistance to both chemo- and radiotherapy. Ironically, Radiation is both a risk and a treatment modality for GBMs. Severe side effects are commonly observed in patients treated with chemo and radiotherapies.

Prognosis

Prognosis of GBM patients is usually poor. Recurrence is very commonly seen. Lack of progress in GBM treatment can be attributed to a combination of factors foremost amongst which are a general lack of understanding of its aetiology, delayed diagnosis, tumour invasiveness and inoperability and resistance to currently available treatment modalities.

Future Research

New biomarkers to better predict the patients that may respond to a particular type of targeted therapy should be being extensively searched for. This personalized approach would be important due to patient heterogeneity, difference in immunity, exposure to environment and the difference in the genetic makeup of each patient are some of the most common and difficult challenges to be overcome and to have an effective therapy against aggressive tumours like GBM. Presence of blood brain barrier is also a factor to be considered, especially when screening and designing new therapeutics and delivery systems, as its presence hinders new therapies to reach the target (tumour).

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