The Prognostic Impact of Addition of Adjuvant Temozolomide after Radiotherapy for Patients with Anaplastic Astrocytoma

Protocol for thesis submitted for fulfillment of master degree in clinical oncology and Nuclear Medicine oncology

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List of contents

Title	Page
List of abbreviation	1
Aim of the Work	5
Review of Literature	7
Patients and methods	97
Results	103
Discussion	131
Summary and Conclusion	148
List of figures	151
List of tables	152
References	154
Arabic Summary	173

Aim of the Work

- **The aim of this study** is to assess the efficacy and safety of the use of temozolomide with radiotherapy as adjuvant treatment following radiotherapy in anaplastic astrocytoma patients.

- Temozolomide was used following radiotherapy ,maximum 6 cycles adjuvant temozolamide.

- **Primary end point:**

1. Progression free survival
2. Toxicity

- **Secondary end point:**
  overall survival.

- **Place of work:**
  Ain Shams University Hospitals

Review ofliterature

Introduction:

Gliomas account for half of all intrinsic brain tumours. WHO grade IV glioblastomas are the most malignant variant of glioma and make up around half of such tumours. At a population level, median survival for patients with glioblastoma remains less than 6 months**. (CBTRUS)**

Anaplastic gliomas are classified by the WHO as grade 3 malignant tumors and include the anaplastic astrocytoma, anaplastic oligodendroglioma, and anaplastic oligoastrocytoma or mixed glioma. These highly aggressive tumors often occur in young adults and typically recur or progress to a grade 4 glioblastoma within several years of diagnosis, despite treatment with surgery, radiotherapy, and chemotherapy. There is some evidence that anaplastic glioma is a molecular precursor to glioblastoma. **(KleihuesP.,et al.,2007)**

Anaplastic astrocytoma (WHO grade III), a less common malignant glioma with an overall better prognosis than grade IV glioblastoma, shares molecular features and poor outcome with glioblastomas**. (Barnholtz-Sloan J.,et al.,2008)**

The treatment of AA as for all high-grade gliomas (HGG) is unsatisfying. Current therapies are only modestly effective, and there is a limited consensus on therapy for either initial treatment or recurrent disease. Treatment for newly diagnosed patients includes surgery, chemotherapy**. (Chang S.,et al.,2004)**

Treatment of the anaplastic astrocytoma has been less variable. This tumor is more resistant to therapy and patients have a shorter median survival of only 2 to 3 years, compared with 5 years for anaplastic oligodendroglioma. Most physicians in the United States treat patients with maximal safe resection and involved field radiotherapy with concurrent and adjuvant temozolomide, identical to the regimen now considered the standard of care for glioblastoma. However, the potential benefit of adding chemotherapy in these patients has never been established, although temozolomide was initially granted accelerated approval by the US Food and Drug Administration based on its efficacy in patients with recurrent anaplastic astrocytoma**. (StuppR.,et al.,2005)**

Survival data for AA is available from population-based cancer registries of 18 European countries in the EUROCARE study. The survival analysis covered 1064 adults with a diagnosis of AA during the period 1990–1994 and followed up until 1999. Prognosis for AA is poor. Relative survival for adults diagnosed withAAduring 1990–1994was 44% at 1 year, 22% at 3 years and 16% at 5 years, showing no difference between men and women. Five-year relative survival decreased markedly with age from 33% in the youngest (15–45 years) age group, to 2% in the oldest age group of patients (65 years and over). There have been significant improvements in survival since the early 1980s. In Europe, during the period 1983–1994, 1-year survival rose from 26% to 43%, and the 5-year survival improved from 9% to 16%. **(RoazziP.,et al.,2003)**

Epidemiology :

Incidence and Prevalence:

There are two major data sources can be considered, including the Surveillance, Epidemiology, and End Results

(SEER) Program of the National Cancer Institute, and the Central Brain Tumor Registry of the United States. **(CBTRUS)**

The SEER registry reports that the incidence of primary CNS tumors is between 2.2 and 8.3 per 100,000 people per year, based on race and gender (for all races, the incidence is 7.7/100,000 men and 5.4/100,000 women, with the extreme deviations being 8.3/100,000white men and 2.2/100,000 American Indian/Alaska Native women). This translates to anestimated case load in 2007 of 20,500 (11,170 men and 9,330 women), with an anticipated 12,740 deaths, and an age-adjusted death rate of 4.4/100, 000. In the SEER system, the incidence rate of primary malignant brain and CNS tumors (excluding lymphomas, leukemia, tumors of pituitary and pineal glands, and olfactory tumors of the nasal cavity) for the years 2005-2009 is 6.5 cases per 100,000. This rate is higher in males (7.7 per 100,000) than females (5.4 per 100,000). **(HowladerN.,et al., 2012)**

The CBTRUS database quotes the incidence of new CNS tumors in the United States at twice the figure quoted in the SEER database, at 43,800 cases, primarily because they include both benign and malignant histology in their

assessment In the CBTRUS system, the incidence rate of all primary malignant and non-malignant brain and CNS tumors is 20.6 cases per 100,000 (7.3 per 100,000 for malignant tumors and 13.3per 100,000 for non–malignant tumors). The rate is higher in females (22.3 per100, 000) than males (18.8 per 100,000). **(DolecekT.,et al., 2012)**

The National Cancer Registry Program of Egypt (NCRPE).Damietta profileover 2009, 67 Brain and Nervous System cancer cases were registered . Glioblastoma was the most predominant histological type, (35.7%) followed by astrocytoma (21.4%). **(Ibrahim A.,et al., 2010)**

The National Cancer Registry Program of Egypt (NCRPE). El-Miniaprofile Over 2009, 343 Brain and Nervous System cancer cases were registered in Minia. Out of 69 cases with registered pathological diagnosis,glioblastoma was the most predominant histological type(21.7%), followed by astrocytoma (17.4%). (**The National Cancer Registry Program of Egypt (NCRPE). El-Minia 2009)**

In the Clinical Oncology department of Ain Shams University Hospitals, all newly diagnosed cases with CNS

tumors have been registered from 30 May 2012 to 1st June 2013 using the NCRPE registry form. CNS tumors accounted for 53 newly diagnosed cases(5.6%)and was ranked as the fourth common cancer in both sexes. 54.7% of CNS tumors occurred in males . The mean age was 43.1 years +/- 19.5 SD. 62.3% of the cases were from Cairo, 20.8% were from Upper Egypt and 8% were from Lower Egypt. 54% of the lesions were overlapping and 13% of the cases were presented with frontal lobe lesions at time of diagnosis. Glioblastoma Multiforme was the most common pathology occurring in about 43.3% of the presented cases. **(Anwar W.,et al.,2014)**

Etiological Factors:

i. Environmental Factors:

The key epidemiologic determinants of glioma risk include advancing age, male sex, and Caucasian race. Ionizing radiation is one of the few factors shown to have a strong association with the development of brain tumors. Exposure to ionizing radiation represents the most important exogenous risk factor for childhood brain tumors. Prenatal diagnostic x-ray exposure increases the risk of childhood brain tumors. A large amount of data has been accumulated on the incidence of brain tumors in patients who received cranial irradiation for the treatment of acute lymphoblastic leukemia (ALL). The estimated cumulative risk of secondary malignant brain tumors after childhood ALL therapy is 0.5% at 10 years after completion of therapy. **(Jimmy T.,2011)**

Interest has emerged in a possible association between use of cellular telephones and the risk of brain tumors. Case-control studies were unable to show a correlation between the duration of cell phone use and the development of gliomas, meningiomas, and acoustic neuromas. **(WrenschM.,et al.,**

2005). Other large case-control studies also have failed to find any association between cell phone use and the risk of developing brain tumors. Nevertheless, some still claim that there is a link between cell phone use and brain tumors. **(Hepworth S.,et al., 2006)**

ii. Viral Associations:

Although certain canine and feline CNS tumors may have a viral association, the human evidence remains weak. Specifically, no increase in the risk of developing a brain tumor has been associated with previous polio vaccination, which discredits claims that simian virus 40 contaminating older polio vaccine preparations cause brain tumors. **(Brenner A.,et al.,2003)**

iii. Hereditary Syndromes:

Most gliomas are sporadic, but genetic susceptibility is suspected based on the occurrence of multiple brain tumors in families with germline mutation of the TP53 suppressor gene and patients with neurofibromatosis type I, Li-Fraumeni syndrome as well as the rare patients who have been diagnosed with Turcot's syndrome. A heritable syndrome contributes to less than 5% of GBMs. **(Farrell J.andPlotkin R., 2007)**