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The Blood-Brain Barrier: Implications For Chemotherapy And Its Delivery To The Brain In Primary And Metastatic Brain Tumor, A Novel Approach

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ABSTRACT

Nearly 12.5 million new cancer cases are diagnosed worldwide each year. Although new treatments have been developed, most new anticancer drugs that are effective outside the brain have failed in clinical trials against brain tumors, in part due to poor penetration across the BBB and the blood–brain tumor barrier. Conventional treatment using radiation and intravenous chemotherapy often prove unsuccessful primarily because the anticancer drugs fail to cross the BBB in sufficient quantities. The focus is now on targeted drug therapy by not only supplementing conventional chemotherapy and radiotherapy, but also by preventing toxicity in normal tissues and drug resistance.Hence this work aims to investigate the therapeutic regimen of primary and metastatic brain tumors and drugs that fail to cross the BBB in sufficient quantities through conventional treatment and a novel approach for the delivery of these drugs. A total number of 30 patients were enrolled from 5 different hospitals of Karachi. Each prescription was scrutinized and the treatment line was noted down. The treatment strategy was the main highlight of this study as to what was planned for the patient to get the most effective result.

Key-words: blood brain barrier, drug delivery , novel approach

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INTRODUCTION

Brain tumor treatment is one of the biggest challenges in oncology. Brain tumors include wide variety of neoplasms that can be primary or metastatic. The primary brain tumours are thought to be derived from glial cells/ their progenitors and are generically can be classified as gliomas. The metastatic arise from systemic malignancies and then develop within the brain parenchyma [1,2]. Chemotherapy is not used to treat all brain tumors. It may be used for people with high-grade primary brain tumors, either as an initial treatment alongside radiotherapy, or where the tumor has come back. Chemotherapy is unlikely to be able to cure a brain tumor but it can shrink a tumor down or slow its growth, which can reduce symptoms[3]. .

There are many different chemotherapy drugs. Not all of them can be used to treat brain tumors because they can't cross the blood-brain barrier. The main chemotherapy drugs used to treat primary brain tumors include: temozolomide ,carmustine ,lomustine procarbazine and vincristine.

Advances in anticancer drug discovery and development but there has been little improvement on the prognosis of patients with brain tumor. It has been found that promising agents for primary brain cancers *in vitro* have had very little impact on disease in clinical trials [4]. These disappointing results can be the inability to deliver therapeutic agents to the CNS across the blood-brain barrier (BBB) avoiding various resistance mechanisms and to reach the desired targets [5]. Moreover, it should be also taken into account that chemotherapeutics that has low-molecular weight do not achieve and maintain effective steady state concentrations within malignant glioma cells because of short blood half-lives [6].

Novel advances in drug delivery to brain cancer.

The therapy of brain tumors has been limited by a lack of effective methods of drug delivery to the brain. Systemic administration is often associated with toxic side effects and ultimately fails to achieve therapeutic concentrations within a tumor. An attractive strategy that has gained importance in brain tumor therapy has relied on local and controlled delivery of chemotherapeutic agents by biodegradable polymers. This technique allows direct exposure of tumor cells to a therapeutic agent for a prolonged period of time and has been shown to prolong the survival of patients with malignant brain tumors. The use of polymers for local drug delivery greatly expands the spectrum of drugs available for the treatment of malignant brain tumors. This review discusses the rationale for local drug delivery, describes the development of currently available polymer-based therapeutic agents, and highlights examples of promising non-polymer based drug delivery methods for use in the treatment of malignant brain tumors.

Possible systems for drug delivery:-

(a) Colloidal drug carriers:-

Colloidal drug carrier systems such asmicellar solutions, vesicle and liquid crystal dispersions, as well as nanoparticle dispersions consisting of small particles of 10– 400 nm diameter show great promise as drug delivery systems.

(b) Micelles:-

Micelles formed by self-assembly of amphiphilic block copolymers (5-50 nm) in aqueous solutions are of great interest for drug delivery applications. The drugs can be physically entrapped in the core of block copolymer micelles and transported at concentrations that can exceed their intrinsic water- solubility.

(C) Liposomes :-

Liposomes were first produced in England in 1961 by Alec D.Bangham. One end of each molecule is water soluble, while the opposite end is water insoluble. Water-soluble medications added to the water

were trapped inside the aggregation of the hydrophobic ends; fat-soluble medications were incorporated into thephospholipid layer.

(d) Nano technology:-

One of the possibilities to deliver drugs to the brain is the employment ofnanoparticles.Nanopartiacles are polymeric particles made of natural or artificial polymers ranging in size between about 10 and 1000 nm (1 mm) .Drugs may be bound inform of a solid solution or dispersion or be adsorbed to the surface or chemically attached.

METHODOLOGY

Patients with histologically proven malignant gliomas, primitive neuroectodermal tumors, primary CNS lymphomas, and metastatic disease to the brain were enrolled from different hospitals in Karachi. A total number of 30 patients were taken from different hospitals. Each and every prescription was scrutinized and the treatment line was noted down. The treatment strategy was the main highlight of the study as to what treatment strategy was planned for the patient to get the most effective result. The objective treatment line is high-dose chemotherapy, intraarterial injections, intrathecal injections, induction of hyperosmolarity to make the BBB permeable glidel wafers, nanoparticles, immuno liposomes and peptide vectors.

RESULT AND DISCUSSIONS:

Out of 30 patients most of them were getting radiotherapy i.e. gamma knife radiotherapy which shows that the incidence of prescribing chemotherapy is relatively less as it is less effective in brain tumor. Other than that some patients were treated with Stereotactic radiosurgery. Radiosurgery uses multiple beams of radiation to give a highly focused form of radiation treatment to kill the tumor cells in a very small area. Each beam of radiation isn't particularly powerful, but the point where all the beams meet — at the brain tumor — receives a very large dose of radiation to kill the tumor cells.

The graph shows that the use of radiotherapy to treat brain tumor increases as the chemotherapy is less effective to treat brain tumor. The use of chemotherapy is less because of the decrease penetration of the chemotherapeutic drugs across BBB. This decrease penetration of chemotherapeutic is in effective to treat brain tumors.

Brain Targeting has got the attention of the many researchers due to its application in various diseases related to CNS. The drugs that can can penetrate the BBB and enters the CNS, are few in numbers so various systems are developed for drug delivery. It emerges that the use of nanotechnology and by using other routes of drug administration like intra nasal technique drug can penetrate the BBB efficiently. Further the modified colloidal particles and various modified liposomes enhance exposure of the BBB due to prolonged blood circulation and it favors interaction and penetration into brain endothelial cells. This system has clinical benefits like reduced drug dose ultimately decreased side effects, non invasive routes and more patient compliance. We still require developing a cost effective system that can be used in various CNS disorders efficiently with minimum side effect.

CONCLUSION:

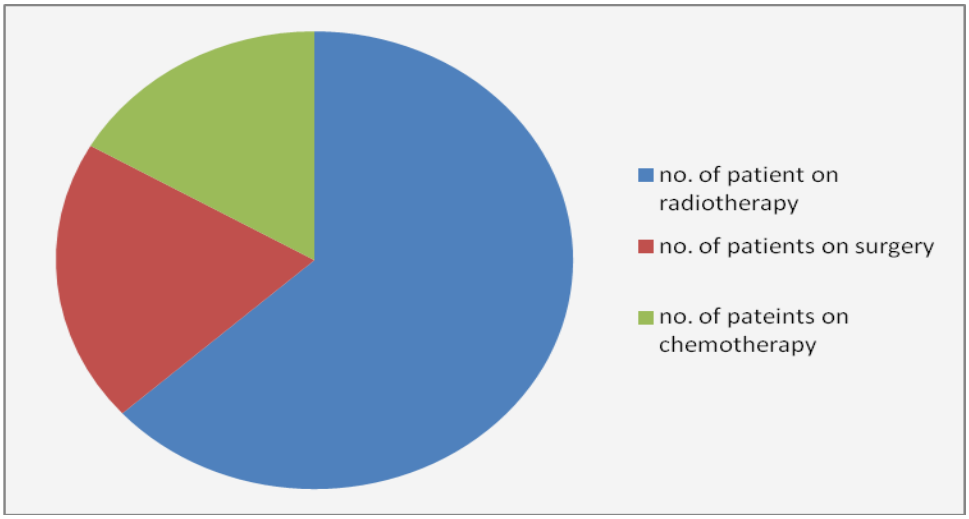
Our result concluded that the blood brain barrier is the most important reason for which the indication of chemotherapy is relatively less. In most of the hospitals the first line of treatment for treating primary and metastatic brain tumor is radiotherapy/radiosurgery. Chemotherapy is now used as the last line agent in the hospitals because of the lack of novel drug delivery in the chemo side. Glidal wafers as chemotherapy has not been used so far and the alternative treatments are considered. As for oral drugs

there is a limited use in brain tumors because the oral drugs mostly do not cross the blood brain barrier. Intrathecal and intra articular drugs are still in use. But as for the comparison their use is relatively low. Targeted delivery is the best option for treating brain tumor in the western countries but as for treating brain tumor in Pakistan we do not have many options. We have also compared the treatment line that is being used in the western world with the treatment given here. Analysis of the available data indicates that novel approaches may be useful for CNS delivery an appreciation of pharmacokinetic issues, and improved knowledge of tumor biology will be needed to significantly impact drug delivery to the target site.

Table 1 :Comparison of different therapies used in brain tumors:

Total no. of patients	Patients on radiotherapy	Patients on surgery	Patients on chemotherapy
30	19	6	5

Figure 1:



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