RESULTS OF ANTINEOPLASTIC CHEMOTHERAPEUTIC AGENTS IN MALIGNANT BRAIN TUMORS

Thesis

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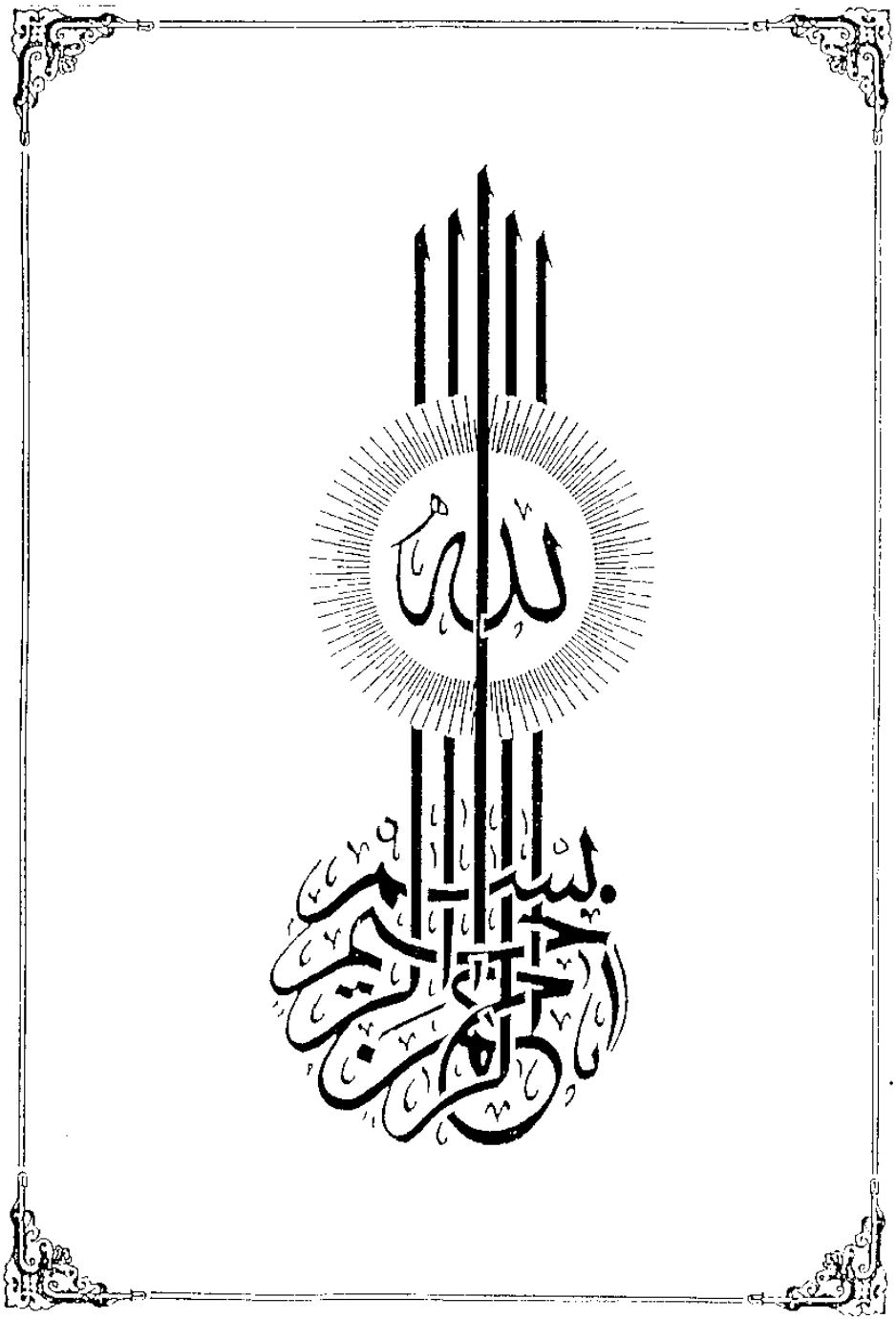

ABBREVIATIONS

AZQ	:	2, 5 - Diaziridinyl - 3, 6-bis Carboethoxy Amino - 1- 4- Benzoquinone
BCNU	:	1, 3, bis (2 chloroethyl) 1 Nitrosourea
BTSG	:	Brain Tumor Study Group
CCS	:	Cell Cycle Specific
CCNS	:	Cell Cycle Nonspecific
CCNU	:	1-(2-Chloroethyl)-3-Cyclohexyl 1-Nitrosourea
CDP	:	Cisplatinum
CSG	:	Children's Cancer Study Group
DAG	:	1, 2: 2, 6 Dianhydrogalactitol
DBD	:	Dibromodulcitol
DDP	:	Cis - Diammine Dichloro Platinum
DFS	:	Disease Free Survival
GF	:	Growth Fraction
HDMTX	:	High Dose Methotrexate
HU	:	Hydroxyurea
MeCCNU	:	Methyl CCNU
MSKCC	:	Memorial Sloan Kettering Center.
MST	:	Median Survival time
MTP	:	Median Time to Progression
MTX	:	Methotrexate
MOPP	:	Mustard, Vincristine (Oncovin), Prednisone, Procarbazine
PCB	:	Procarbizine
PCNU	:	1 - (2-Chloroethyl) - 2 - (2, 6 Dioxo -3- Piperidyl) -1- Nitrosourea
PCV	:	Procarbazine, CCNU, Vincristine
POG	:	Pediatric Oncology Group
SIOP	:	International Society of Pediatric Oncology
Tc	:	Cell Cycle Time
VCR	:	Vincristine
VM-26	:	4-Demethyl - Epipodophylline
5-FU	:	5-Flurouracil

CONTENTS

INTRODUCTION AND AIM OF THE WORK

INTRODUCTION

Malignant tumors of the brain, spinal cord, cranial nerves, and dural coverings are a diverse lot. Of the fifteen or so cell types that give rise to these tumors, those of glial and especially astrocytic origin are by for the most common. Although it is probable that each tumor has a unique features control growth and modulate the expression of the malignant phenotype, none of the available antineoplastic drugs selectively kills tumor cells in perferance to normal cells. Unfortunately, current antineoplastic drugs are predominantly cytotoxic agents directed at DNA synthesis or expression. The effectiveness of these agents is dependent on factors such as (1) pharmacologic biodistribution, (2) normal tissue tolerance and toxicity, and (3) cellular mechanisms to reverse the drug-induced damage to DNA and other reproductive functions of tumor cells. Therefore, unless tumor cells carry within their genome characterstics that confer sensitivity to these cytotoxins, the therapeutic benefit of current agents will be limited and the therapeutic index will be very narrow; the response to the antineoplastic cytotoxin is transient.

When dealing with tumors located in the parenchyma of the central nervous system (CNS) additional factors must be

considered. A primary consideration is that of restricted drug delivery, Levin et al., 1980. The blood-brain barrier (BBB) normally protects the brain from certain biomolecules that can upset the milieu and functioning of the brain. In addition, the BBB protects the nervous system from a whole spectrum of man-made and natural toxins, including auticancer agents such as vincristine (VCR), adriamycin, bleomycin, cisplatin, Laws et al., 1984.

There is still a paucity of effective agents with which to treat primary malignant brain tumors. Although clever drug combinations have been tried, for the most part therapy still revolves around the nitrosoureas (BCNU and CCNU) and procarbazine (PCB) and, to a lesser extent, minor agents such as cisplatin, aziridinylbenzoquinone (AZQ), and nitorgen mustard. As a modality, chemotherapy is palliative. Although little solace to the patient, from our clinical and laboratory experience we now have more insight and understanding of the chemotherapy of infiltrative brain tumors.

In this thesis, chemotherapy of malignant glioma has been discussed in relation to recent advances in experimental and clinical studies. It is now obvious that chemotherapy is of increasing importance in the multidisciplinary treatment of malignant gliomas. Survival time of patients was prolonged

by intensive and prolonged chemotherapy and by second treatment upon tumor recurrence. Further progress of chemotherapy will be gained by the progressive accumulation of all expriences, however small, in all the varied routes of approach.

CHEMOTHERAPEUTIC AGENTS IN USE

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The Progress in the past few years in oncology has not been in the discovery of many new drugs but rather in a better understanding of such chemotherapeutic concepts as mechanisms of drug action, drug synergisim and antagonism, adjuvant chemotherapy and drug toxicity, Calabrese et al., 1980. These concepts are crucial to the treatment of almost all cancer since the only tumors that can predictably be cured by single-agent chemotherapy are choriocarcinoma in women with methotrexate, and Burkitt's lymyhoma with cyclophosphamide, Keiser, 1977. The great advances made in the treatment of acute lymphocytic leukemia in children, Hodgkin's disease, non-Hodgkin's lymphoma, testicular cancer and many childhood solid tumors have been due to combination chemotherapy.

Most of the studies cited in this section on chemotherapeutic agents have evaluated the efficacy of single drugs against malignant brain tumors. While the results have not been overly impressive, it must be remembered that many of these agents showed only minimal activity when used alone against many of the tumors cited above. When they were used in combination with Schedules recognizing cell Kinetics, cell cycle phase specificity,

therapeutic synergism, cellular heterogenity and toxicity, there were remarkable improvement in survival.

Phamacology of Specific Chemotherapeutic Agents:

Antineoplastic agents may be classified according to their presumed mechanism of action. Traditionally, cytotoxic agents fall into one of two major groups, drugs that act during specific phases of the cell cycle (cell cycle specific, CCS), including the folate antagonists, pyrimidine analogs, purine analogs, and vinca alkaloids, and those whose activity does not depend on the cell cycle phase (cell cycle nonspecific, CCNS), inculding the alkylating agents, many antitumor antibiotics, and a variety of miscellaneous compounds. CCS drugs arrest proliferating cells by interefering with crucial functions such as DNA replication, protein synthesis, or mitotic spindle formation. CCNS agents are equally toxic to both resting and proliferating cells. Theoretically, cell cycle specific agents are ideally suited to the treatment of CNS neoplasms since tumor cells represent the only actively proliferating cells in the target tissue, Schold et al., 1985. However, single-agent chemotherapy using CCS drugs has been disappointing. The most effective drugs to date have been the CCNS drugs, including the nitrosoureas (especially

BCNU), procarbazine, cisplatin, and diaziquone, Schold et al., 1985. The failure of CCS chemotherapeutic agents has been attributed to the low proportion of tumor cells that are actively dividing (i.e. low growth fraction) in many CNS neoplasms. Nevertheless, selected CCS drugs (eq., hydroxyurea, VM-26, Vincristive) may prove useful when adminstered in combination with the alkylating agents, Table 1 lists the common chemotherapeutic agents and their chemical name.

Table 1: Common and Chemical Names of Chemotherapeutic Agents Used in thesis

Common name	Chemical name
Carmustine (BCNU)	1,3-Bis (2-chloroethyl)-1-nitrosourea
lomustine (CCNU)	1- (2-chloroethyl) -3- cyclohexyl. 1- nitrosourea
Semustine (methyl-CCNU)	1- (2- chloroethyl) -3- (4- methyl cyclo hexyl) -1- nitrosourea
PCNU	1- (2- chloroethyl) -2- (2,6 dioxo -3- piperidyl) -1- nitrosourea
Procarbazine	-N-isopropyl - - (2-methyl hydrozino) -p-tolnamide hydrochloride
Cisplatinum (DDP)	Cis- diammine dichloro platinum II.
Dianhydrogalactitol (DAG)	1,2: 5,6. Dianhydrogalactitol
VM-26	4- Demethyl-epipodophylline 9- (4, 6 -0- thenylidine -B-D gluco pyranoside).
Vincristine	Vincristine sulfate
5-FU	5- Flurocuracil
HU	hydroxyurea
Methotrexate (MTX)	4- amino -4- deoxy -10 methyl petroylglutamic acid
AZQ	2,5-Diaziridinyl -3,6-bis carboethoxy amino -1,4- benzoquinone

Alkylating agents:

An alkylating agent, nitrogen mustard, was the first modern chemotherapeutic agent used in the treatment of malignant glioma. French, et al., 1952. Carmustine (BCNU), also an alkylating agent, is currently recognized as the most effective single chemotherapeutic agent against this tumor, Walker, 1980. Other drugs which have shown promise, such as dianhydrogalactitol, Cisplatin, and spirohydantoin are also believed to act Via alkylation of genetic material.

While alkylating agents are generally divided into two Subgroups, classical alkylating agents and nitrosoureas, they share a number of characteristics first, they are electrophilic or spontaneously decompose into electrophilic species in vitro and in vivo, for example nitrogen mustard rapidly undergoes cyclyation in aqueous solution to form carbonium ions which are highly reactive and electrophilic. Although there are many nucleophilic sites with which the carbonium may react, several lines of evidence indicate that DNA is the primary target, Connors, 1980. Nitrosoureas undergo a similar series of reactions. Alkylation of DNA is persumed to be the mechanism whereby these agents are teratogenic, carcinogenic and cytotoxic.

The classical alkylating agents, including nitrogen mustard and chlorambucil, most frequently form covalent

bonds with the 7 position of guanine, Calabrese, 1980.

These drugs are bifunctional, i.e they contain two alkylating moieties, and can link two guanine bases in the form of intrastrand or interstrand cross-linkages. When guanine is alkylated in the 7 position, miscoding with thymidin occurs. When two strands of DNA are cross linked, DNA can not replicate. Other consequences of alkylation include inhibition of glycolysis, respiration, and protein synthesis, but it is the cross-linking of DNA which appears most toxic, Connors, 1979.

Most alkylating agents are cell cycle nonspecific. The classical alkylating agents have been found to be quite hydrophilic, Connors, 1980. This spurred the development of more lipophilic agents which might be more effective in solid tumors and more readily cross into the central nervous system (CNS). Spirohydantoin mustard is an example of a more lypophilic alkylating agent that might be effective against malignant gliomas. The clinical experience with the classical alkylating agents against malignant gliomas has been reviewed recently, Edwards et al., 1980.

The nitrosoureas constitutes the second group of alkylating agents. The include BCNU, CCNU, methyl-CCNU, PCNU, streptozotocin and chlorozotocin. Their mode of action appears to be the same as that for the classical alkylating