Cancer and brain tumor: Management and Treatment

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ABSTRACT

Cancer is the most common disease and major cause of death now days. Cancer word is derived from a Greek word “Karkinos” which means carcinoma. Around 8 lakh cases are found in India every year with death of around 5.5 lakh people. There are different cancers causing factors like UV radiations, Tobacco etc. Brain tumor is also a type of cancer and it is malignant in nature. There are various therapies available for cancer and brain tumor treatment but the permanent treatment is still not available. The main hurdle in the treatment of brain tumor is Blood brain barrier which prevent the delivery of drugs to brain. Some strategies have been developed to overcome these barriers and promote targeting of drug to brain tumor. This review summarizes statistics, factors and therapies available for treatment of cancer and different methods used for enhancing the drug delivery to brain along with some nanoformulations.

Keywords: cancer, types of cancer, brain tumor, treatment of cancer, approaches of brain targeting

INTRODUCTION

Cancer is defined as the process of abnormal growth of cell which has the property to invade and spread to other part of the body. It is the most common disease in India and also the 2nd most common cause of death. This word is derived from a Greek word "karkinos" and it means carcinoma[1, 2]. There are different types of cancer like prostate, breast, mouth, cervical, skin, lung cancer and leukemia etc[3]. The death from cancer is increasing at a very rapid rate and the numbers of patients up to 2015 are 520865, 470674 and 991539 for female, male and total number of patients respectively[4]. Various types of theories have been published about cancer like humoral, lymph, Blastema, chronic irritation, trauma, parasite theory[5, 6]. There are various factors which cause cancer like tobacco, alcohol, diet, UV radiation, virus, pesticides, dioxane, and vinyl chloride etc[7]. There are various therapies given for the treatment of cancer like radiation therapy, chemotherapy, hormone, targeted therapy, surgery etc[8]. The most common cancer in male and female is oral and breast cancer respectively but brain tumor also occur in most of the population and it is very difficult to treat the brain tumor because the brain is surrounded by a barrier which is called as blood brain barrier and most of the drugs are restricted by blood brain barrier. There are very less chances of survival in case of brain tumor[9].

Brain is the central organ of the nervous system. It consists of cerebrum, cerebellum and other parts like brain stem. Brain is the organ which sends instructions on the basis of information it receives from organs. The cerebrum is the largest part of the brain and divided into 2 cerebral hemispheres. Each hemisphere is divided into 4 lobes which are Frontal lobe, Temporal lobe, Parietal lobe and Occipital lobe[10]. There are various diseases of the brain which can be fatal or non-fatal like meningitis, encephalitis, brain abscess, brain tumor, glioblastoma, hydrocephalus, hemorrhagic stroke etc[11].

Brain tumor occurs when abnormal growth of cells takes place in brain. There are 2 types of tumors which are malignant tumor (cancerous tumor) and benign tumors. Malignant tumor is further divided into 2 types which are primary tumor which start in the brain itself and secondary tumor which spread from other part of body is known as metastasis tumor. Brain and CNS tumor are categorized on the basis of supposed tissue of origin which are neuro-epithelial originated, paraspinal and cranial nerves originated and tumor of sellar region. Malignant tumors are destructive disease which attracts massive attention due to its property of poor prediction and high repetition[12].

According to WHO, neuro-epithelial originated glioma divided into 4 grades which are based on their malignancies.

Grade I Benign = non-cancerous (do not spread)

Grade II Relatively slow growing, but come back as a higher-grade tumor several times.

Grade III Malignant = cancerous (spread into other part of brain and come back as tumor of higher grade)

Grade IV Most dangerous and malignant. Grow and spread very fast to other part of the brain which is nearby. To maintain growth, it forms new blood vessels[13, 14].

History of Cancer

The most universal cause of deaths in the world is cardiovascular diseases and after this the 2nd number is of cancer. It is not a new disease, many people suffered from this earlier also. This word is derived from a Greek word "karkinos" and it means carcinoma and this meaning was given by physician Hippocrates (460-370 B.C.). It has been identified before the Hippocrates in Egypt in 1600B.C. where Egyptian mummies are having bone cancer. The earliest incident was found in Egypt in 1500B.C. and it was the incident of breast cancer. There are various types of old theories about cancer like **Humoral theory** (blood, phlegm, yellow bile and black bile), **Lymph theory** (cancer was due to the fluid called lymph), **Blastema theory** (cancer made up of cells and not with fluid in 1938 muller demonstrated), **Chronic irritation theory** (cancer is caused by chronic irritation, said by Virchow), **Trauma theory** (trauma was the cause of cancer, thought from late 1800-1920), **Parasite theory** (cancer was contagious and spread by parasite, it was believed till 1800)[5,6] (Figure 1).

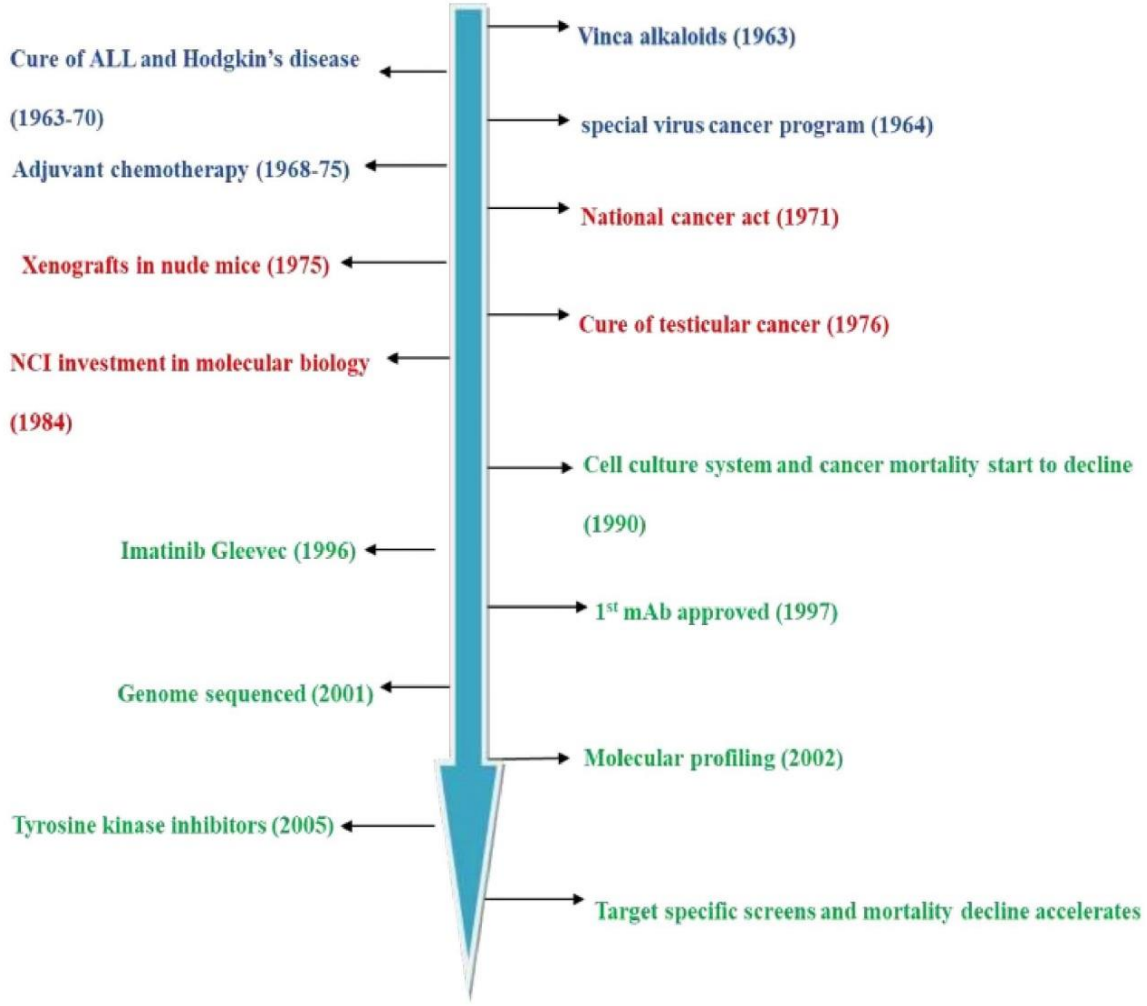

Figure 1: History of cancer according to National Cancer Registry Programmer (ICMR), Bangalore[6]

The gene responsible for the cancer in the oncogenes and these are formed from proto-oncogenes (gene responsible for normal growth) by mutation. The oncogenes were discovered during 1970s. One more gene that was discovered during 1970s was tumor suppressor gene which control cell division and tell cell when to die and when TSG (tumor suppressor gene) does not function properly, the cell grow abnormally which is called as cancer. The signs and symptoms may include lump formation, weight loss and changes in bowel movement. There are some of the characteristics which are required to form malignant tumor which are cell growth and division without proper signal, growth and division continuously after giving contrary signal, avoid apoptosis, unlimited cell division, construction of blood vessel promotion, invasion of tissue and metastasis formation.

The formation of cancer cell from a normal cell involves various steps which are known as malignant progression[1, 2].

Statistics of Cancer

In our country, many advanced researches are there and some are going on and then also, cancer is the very big problem in our country. This is the 2nd most common disease in world. The number of patients of cancer increases every year with a rapid rate. About 7% and 23% deaths in India and USA is due to the cancer. The occurrence of cancer in India is about 2.5 million with 8 lakh new cases and 5.5lakh deaths per year. According to census data of India (1991), about 609000 cases of cancer are there and this has been drastically increased to 806,000 by the end of the last century. Up to 2010, approx. 70% cases of cancer have been diagnosed and treated in which few patients survived[15].

A data was formed of cancer patients from 2005-2020 in India and shown in (Figure 2) and on the basis of increasing trends of cancer every year, the cancer patients have been predicted in 2020 in India. The data show that the number of females, male and total number of patients of cancer in 2005 is 432643, 400356 and 832999 respectively. The number of patients increases at a rapid rate up to 2015 with 550486, 500654 and 1051140 cases for female, male and total number of patients respectively[4]. Before the age of 75 years, the percent of risk of cancer was Men: 9.81% and women: 9.42%.

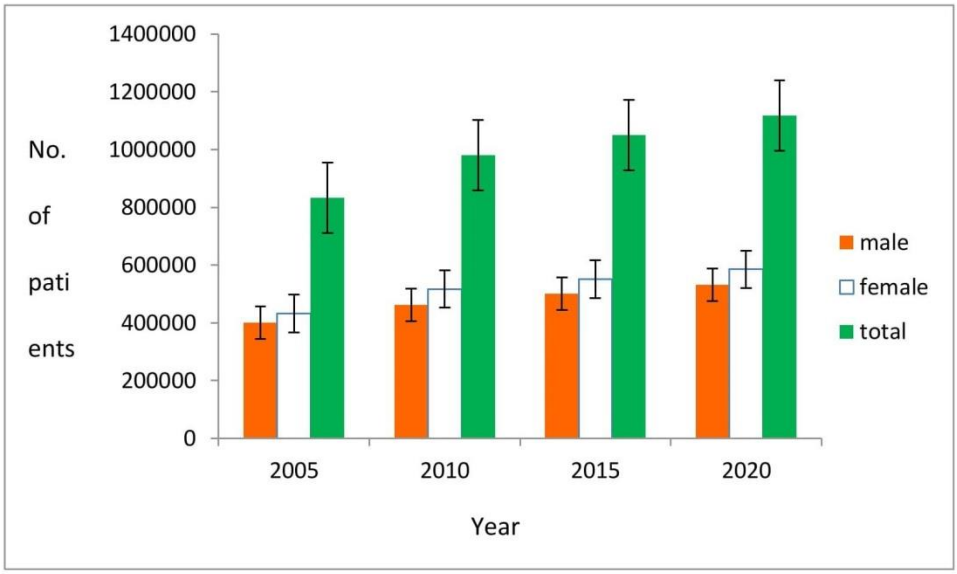

Figure 2: Number of cancer patients from 2005-2020[16, 17]

Factors causing Cancer

There are various factors which causes cancer like

Tobacco

Most common cause of the cancer. Around 22% of the cancer deaths are due to the tobacco eating.

Diet/weight/physical inactivity/alcohol

Around 10% of the cancer deaths are due to these reasons.

UV radiation

These are the rays which causes mutation or changes in the cell which lead to development of cancer.

Viruses and bacteria

Around 15% of the cancer are due to various viruses and bacteria like H. pylori (cause gastritis), hepatitis B, hepatitis C (cause hepatitis), human papillomavirus infection cause changes like cervical cells) and HIV.

Ionizing radiation

These include X-rays, Y-rays. These cause mutation in the cell which leads to generation of many diseases like cancer.

Pesticides

These include urea like substances which causes many diseases when it comes in contact of our body like dermatitis, cancer. High ingestion of urea is toxic because ammonia is toxic.

Metals

Heavy metals like lead, mercury can be dangerous to our body because it affects many cycles which are going on in our body which lead to development of adverse effects.

Dioxane

It is the substance which is used in cosmetics and now days it is banned to use it in cosmetics because it causes cancer.

Vinyl chloride and Benzedrine

Benzedrine is the drug that contains amphetamine and D-amphetamine cause disruption of signal across ontogeny in zebrafish. Vinyl chloride is human carcinogen and it also causes liver toxicity and neurological symptoms[7].

Types of cancer

There are different types of cancer which are as follows

Breast cancer

It is a type of cancer which forms in the cells of breast.

Prostate cancer

It is a type of cancer which occurs in a small walnut size gland known as prostate which secret seminal fluid.

Colon cancer

It is a type of cancer in lower end of digestive tract (colon and rectum).

Skin cancer

It is the most dangerous cancer because it is the cancer of skin.

Lung cancer

It is a type of cancer which occurs in the lungs and mostly in smokers.

Leukemia

It is a type of blood cancer which weakens the immunity of body. It does not show the growth of the tumor like other types of cancer[3].

Treatment of Cancer

The cancer can be treated by the following ways: -

Radiation therapy

It is a type of treatment which uses high radiations to kill the cancer-causing cells. It is a localized therapy and high energy radiations are targeted to a cancer cell directly. The cancer which can be treated by this therapy involves lip, breast, skin, prostate, cervical, neck etc and the cancer which cannot be treated by this therapy are Wilms tumor, colorectal, embryonal carcinoma of testis etc. There are 3 types of radiation therapy i.e. External therapy (use high energy rays delivered by machine into tumor), Internal therapy (use radioactive pellet which was placed near the tumor) and Systemic therapy (use radioactive chemicals).

The advantages are large number of cancer cells died, other microscopic diseases also cured, safe for the patient, painless and organs are preserved means they are not removed. The disadvantages of radiation therapy are unable to kill all the cancer cells, contraindications, very less killing of cancer

cells in oxygen deficient area, cause damage to the nearby tissues and inconvenient to the patient as it can be given daily[18, 19].

The radio immunotherapy was first explained by Pressman and Korngold in 1953. In this therapy, cancer cells are targeted which are associated with antigen using monoclonal antibodies which are labeled with a radionuclide. (Table 1 and 2).

Table 1: Monoclonal antibodies for advanced radio immunotherapy of cancer

S. No.	Drug	Antibody form	Radio nuclide	Antigen	Disease	Clinical trial status	Ref.
1	^{131}I-L19 (Radretumab®)	L19	^{131}I	Fibronectin	Non-small Cell Lung cancer, brain cancer	Discontinued in Italy and United Kingdon in 2018	42
2	^{90}Y-clivatuzumab Tetraxetan (PAM4)	muIgG1	^{90}Y	MUC1	Pancreatic Adeno carcinoma	Phase-II terminated	43
3	Labetuzumab (CEA-Cide)	huIgG1	^{90}Y or ^{131}I	CEA	Colorectal Carcinoma	Suspended	44
4	Pemtumomab (Theragyn®)	muIgG1	^{90}Y	PEM	Ovarian cancer, gastric carcinoma	Phase-III discontinued for gastric in UK and for Ovarian in Australia and Austria	45
5	^{131}I-metuximab (Licartin®)	Hab18 F(ab')2	^{131}I	Hab18G/ CD147	Hepato cellular carcinoma	Phase-II	46
6	Ibritumomab Tiuxetan (Zevalin®)	muIgG1	^{90}Y	CD20	Non-Hodking's lymphoma	Approved by FDA	47
7	Epratuzumab	huIgG1	^{90}Y	CD22	Chronic	Discontinued	48

	(lymphocide®)	(LL2)			Lymphocyte Leukemia, immune diseases	in Canada and Australia in 2020	
8	Tositumomab (Bexxar®)	muIgG2a	^{131}I	CD20	Non-Hodking's lymphoma	Approved by FDA in 2003	49
9	^{131}I-Lym-1 (oncolym®)	huIgG1	^{131}I	HLA-DR10	Non-Hodking's lymphoma,	Discontinued	50
10	131I-chTNT-1/B (Cotara®)	chIgG1	^{131}I	DNA	Glioblastoma multiforme, Anaplastic astrocytoma	Phase- III	51

CEA – Carcinoembryonic Antigen; CLL – Chronic Lymphocytic Leukemia; HCC – Hepatocellular Carcinoma; HLA – Human Leukocyte Antigen; HuIg – Human Immunoglobulin; muIg – Murin Immunoglobulin; NHL – Non-Hodking's Lymphoma; PEM – Polymorphic Epithelial Mucin.

Table 2: Commonly used Radiopharmaceuticals for tumor[52]

S.No.	Radiopharmaceutical	Targeting mechanism	Indication
1	^{131}I-iodide	Thyroid hormone synthesis	Grave's disease, Hyperfunctioning nodules, Differentiated thyroid cancer,
2	^{131}I-MIBG	Active transport into neuroendocrine cells and intracellular storage	Neuroblastoma, Carcinoid, Medullary thyroid carcinoma, pheochromacytoma, paraganglioma
3	^{90}Y-microspheres	Intravascular trapping	Liver metastasis, Hepatocellular carcinoma
4	^{90}Y-octreotide	Somatostatin receptor binding	Neuroendocrine tumors

Hormone therapy

It is very useful therapy when the cancer is related to the hormone imbalance like in case of prostate and breast cancer. The disadvantage of hormone therapy is that the tumor becomes resistant and due to this it works temporarily[8].

Surgery

A surgery helps in the prevention of spreading of cancerous cells by removing lymph nodes. The disadvantages of surgery are that it can act on local cancer and when tumor is nicked, the cancer cells escape into the body[8].

Chemotherapy

It is a type of therapy which aims the rapidly dividing cells and kills them but it can have serious side effects like baldness. Chemotherapy involves the use of drugs. It is preferable than radiation and surgery therapy because it can spread in the whole body whereas radiation and surgery are used to treat the local cancer or one area.

The advantages of chemotherapy are slow down the growth and shrink the cancer, reduce the chance of cancer to come back after surgery and convenient for the patient.

The disadvantages of chemotherapy are not suitable for everyone means do not show effect on some patients, patient has to go to the hospital for checkup and treatment and development of resistance for the drugs[20].

Immunotherapy

This therapy is used to boost the immune system and to fight with the cancer-causing cells (Figure 3)[21].

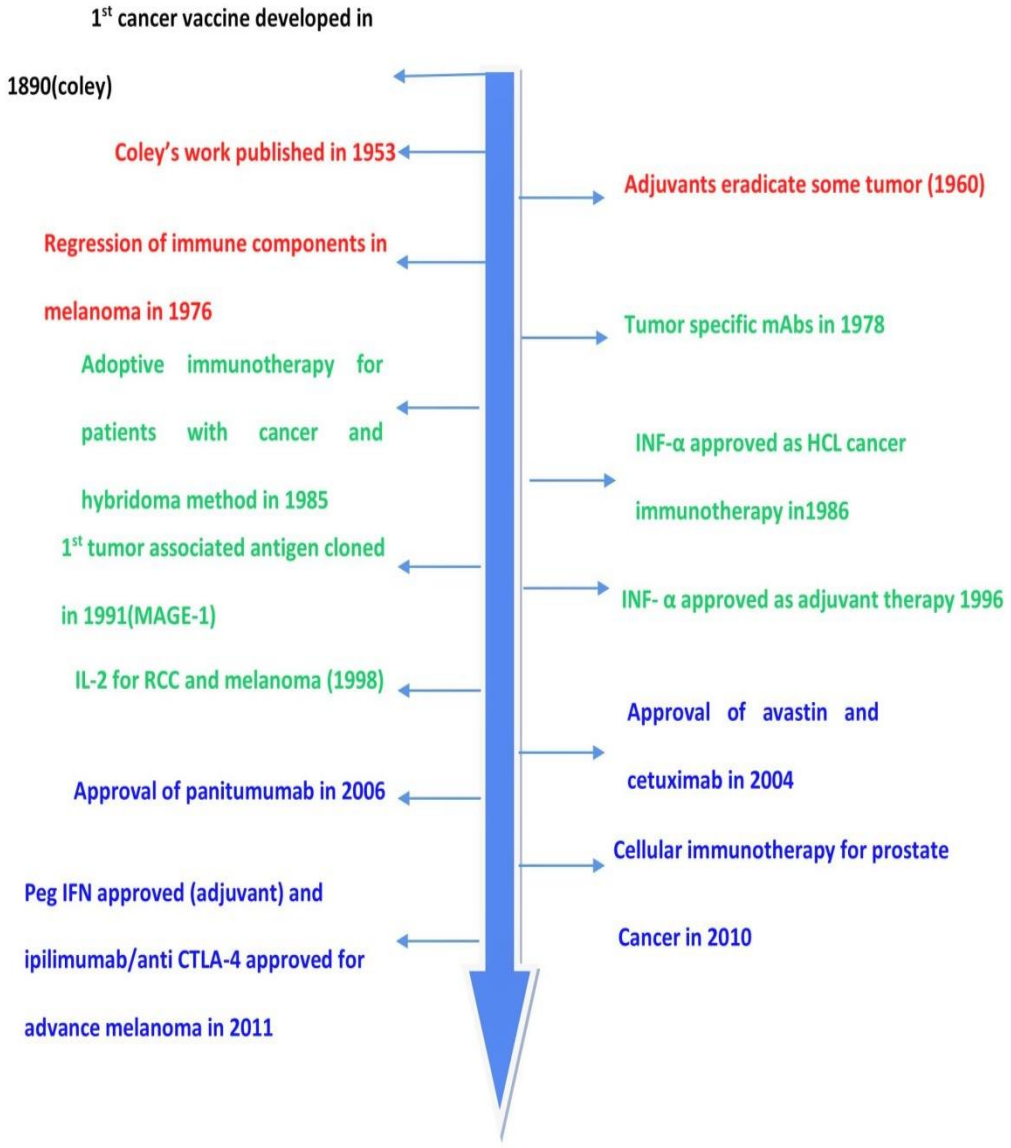

Figure 3: History of immunotherapy[21, 22]

The examples of this type of therapy are checkpoint inhibitor and adoptive cell transfer[22].

The immune check point therapy is only useful for patients with specific type of tumor. The clinical trials on combinational immune check point therapy are going on using anti-CTLA-4 and anti PD-1 on 94 patients with 5 different types of cancer. After treatment with anti PD-1, CD73 macrophages were found in glioblastoma. For successful combinational immune therapy, CD73 was targeted in mice and results showed that survival increase in glioblastoma after treatment with combinational immunotherapy of anti-CTLA-4 and anti PD-1 in absence of CD73[23].

Targeted therapy

This therapy is used to target the cancer cell. It works within the cancer cell and stop the growth of it. Examples are monoclonal antibodies and small molecule drugs[8].

Stem cell transplant

It is very special type of therapy for the people suffering from blood cancer like lymphoma and leukemia. In this, the cells (RBC OR WBC) are removed from the body which has been destroyed by the chemotherapy and then those cells were strengthened and put back inside the body[8].

Brain Tumor

Brain tumor occurs when abnormal growth of cells takes place in brain. There are 2 types of tumors which are malignant tumor (cancerous tumor) and benign tumors. Malignant tumor is further divided into 2 types which are primary tumor which start in the brain itself and secondary tumor which spread from other part of body is known as metastasis tumor.

Barriers in brain tumor targeting

The brain is separated from peripheral part of the body or peripheral circulation by 3 barriers which are Blood brain barrier, Blood cerebrospinal fluid barrier, Ependymal barrier.

From these barriers, the most specific and useful barrier is blood brain barrier which is formed by endothelial cells which restrict the entry of substances into the brain.

The ependymal barrier consists of epithelial cells and it regulates the diffusion of substances from cerebrospinal fluid to brain.

The blood brain barrier is the main target site for the delivery of drug to brain because it is the main interruption between blood and brain parenchyma. Blood brain barrier have tight junctions through which very less amount of substances passes through and these are formed by reversible insertion of transmembrane protein (occludin and claudin) and cytoplasmic proteins. These tight junctions are known as zonulae occludance. Only the compound with diameter less than 4A° can penetrate through tight junction[24, 25].

Strategies for enhancing brain drug delivery

By passing the blood brain barrier

The BBB can be bypassed by local delivery that is wafer which is encapsulated by the drug can be implanted in tumor cavity by surgery. A gliadel wafer, polifeprosan20 polymer matrix containing carmustine is the 1st implant approved by FDA for treating gliomas[26].

Disrupting the blood brain barrier

This can be done with the help of biochemical reagents such as surfactants, hyperosmotic agents (mannitol, alkyl glycerol) or physical method (focused ultrasound sonication, magnetic nanoparticle induced hyperthermia).

FUS is the method in which ultrasounds with frequency of less than 1 MHz are used for reversible disruption of BBB with the help of micro bubbles. It can be used for delivery of theranostic agents and is already under clinical trial. The ultrasmall nanoparticles of Cu-Se which were labeled with near-infrared dyes were used for FUS induced reversible opening of BBB in pre-clinical trial. Above nanoparticles were loaded with doxorubicin were used on tumor models along with FUS & photodynamic therapy and showed high efficacy[27].

Penetrating the blood brain barrier

This can be done by using the transporter and receptors which are endogenous which can lead to improvement of neutral penetration of drugs in a non-invasive manner and efficiency should be high. There are several strategies for penetrating the blood brain barrier which are like nanoparticle synthesis, focused ultrasound sonication, ligand mediated delivery, hyperthermia etc.

The delivery of the drug through nasal route and in that route olfactory and trigeminal nerve plays an important role. This method is non-invasive and patient friendly method for targeting the brain. This delivery system has the capacity to pass peripheral clearance, decrease the toxicity of system and reduce the dose required. Example is the delivery of 3H-5-fluorouracil by intranasal route has higher drug conc. in cerebrospinal fluid as compared to when given intravenously[24, 28].

Approaches of brain targeting

To overcome the barriers which restricting the drug from entering into the brain, several approaches have been developed which are as follows (Figure 4)

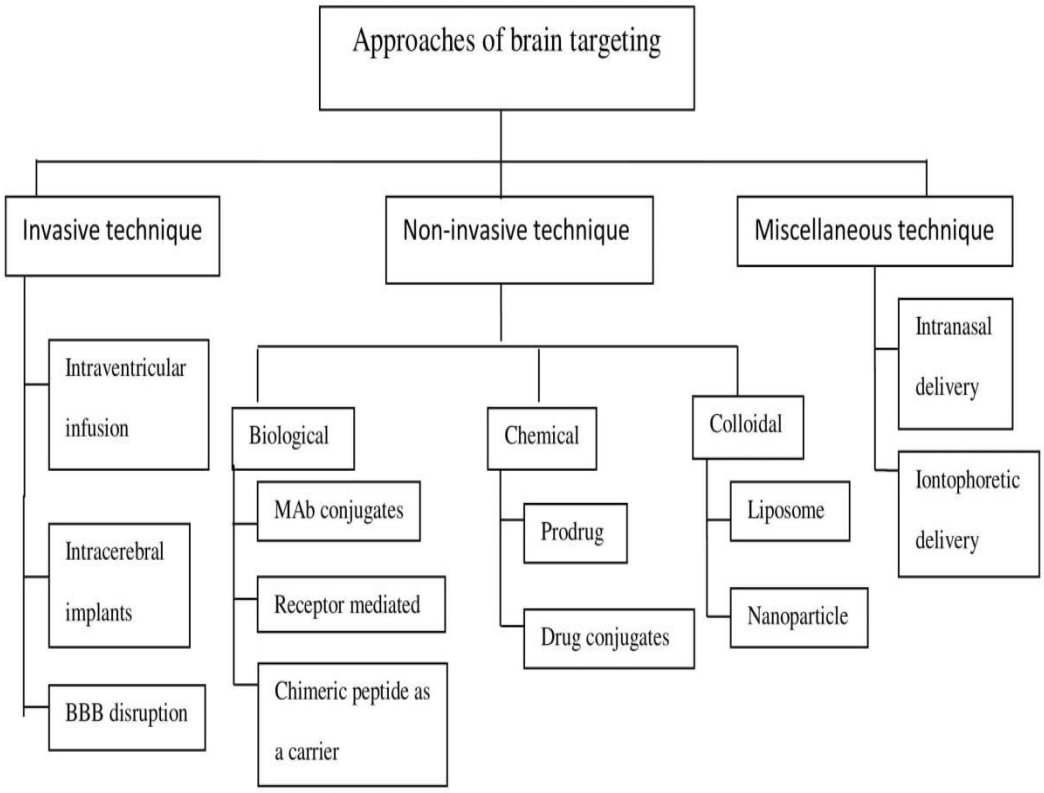

Figure 4: Various approaches for brain targeting: Invasive, non-invasive and miscellaneous[30]

Invasive method

In this mechanism, low molecular weight, lipid soluble drugs and few peptides can cross the blood brain barrier either with passive diffusion or by any transport mechanism. In this method, the drug directly targets to the brain tissue. It includes

Intraventricular infusion

This technique is widely used in clinical trials. In this, an ommaya reservoir (plastic reservoir) was implanted subcutaneously in scalp and then connected to ventricles which are in the brain via outlet catheter. It is having a disadvantage that this is suitable for the parts that are close to the ventricles.

Intracerebral implants

In this method, the drug is directly delivered to the parenchymal space of brain. The transport mechanism is passive diffusion and it is used to treat various diseases of brain like Parkinsonism and brain tumor etc. The drug can be administered by various ways like Control release matrix, direct injection with the help of intrathecal catheter and Microencapsulated chemical.

Blood brain barrier disruption

In this method, the BBB is disrupted which lead to opening of the tight junction. The disruption can be done by various techniques like Disruption by osmotic pressure [hypertonic solution (25% mannitol) is used to deliver the macromolecule like vaccine], Focused ultrasound guided by MRI (by this technique, the distribution of drug in brain increases by 50%), Using vasoactive compound (this is not used much due to its less efficiency in phase II and phase III) and there is one endotoxin which disrupts the tight junction known as zonulae occludans.

Non-invasive method

This method used the blood vessel network of brain for increasing the distribution of drug in brain. This method is divided into 3 technique which are chemical (prodrug and drug conjugate), biological (mAb conjugate, receptor mediated and chimeric peptide as a carrier) and colloidal (liposome and nanoparticle).

Biological method

This method includes monoclonal antibodies conjugates, receptor/vector mediated and chimeric/aprotinin peptide as a carrier.

MAb conjugates

The mAb are prepared with the help of hybridoma technology. In this technology, the tumor cell was combined with the antitumor antibodies against a specific antigen found on the surface of malignant cells. The monoclonal antibodies are used for brain targeting after modifying them to genetically engineered mAbs.

Receptor/vector mediated

In this method, the drug is delivered to the brain by using various receptors or vectors.

Cationic proteins

This method works on the basis of the isoelectric point of the brain. In this method, the protein was charged into cationic form and these proteins can be easily transported through blood brain barrier by interacting with the anionic functional group which is present on the surface of the brain. Several cationic proteins which can be transported are histone, avidin and protamine.

Chimeric peptide

In this method, the drug is combined with the transport entity. So that, the drug can be easily transported into the brain. The entity can be mAb (monoclonal antibody), endogenous peptide etc. Example is Insulin and transferring undergo transcytosis by receptors present at blood brain barrier.

Chemical method

This method includes use of prodrug and drug conjugates.

Prodrug

It means the inactive form of the drug. This method is used for the delivery of various acidic drugs like levodopa. Example

Phenylethylamine + nicotinic acid ⟶ N-methyl nicotinic acid ester and amide

Drug conjugates

In this, the hydrophilic drug is conjugated with the lipophilic drug and this conjugation passes the blood brain barrier and reaches to the brain tissue. Example is N-methylpuridinium-2-carbaldoxime chloride

Colloidal method

This method includes the novel drug delivery system like liposome and nanoparticle.

Liposomes

It consists of two words i.e. lipo means lipid and soma means body and made up of phospholipid. It is a structure consists of lipid bilayer in which both hydrophilic and lipophilic drugs can be entrapped and carried to the target site. Hydrophilic drugs are entrapped in the hydrophilic region means inside the liposome and lipophilic drugs are entrapped in lipophilic portion of the liposome. The basic mechanism of transport of targeting is receptor mediated transcytosis and absorptive mediated transcytosis.

Nanoparticle

There are various types of nano systems which are used to deliver the drug to the brain like nanosuspension, nanotubes, polymeric nanoparticle, nano emulsion etc. These nanoparticles enter the brain by crossing blood brain barrier with the help of endocytosis. Example is

Apo E- albumin nanoparticles enter into brain with the help of transcytosis and release the drug in parenchymal part of brain.

Miscellaneous method

This method includes intranasal delivery and Iontophoretic delivery.

Intranasal delivery

In this method, the drug is given by intranasal route and first reaches to respiratory epithelium and then it reaches to the olfactory lobe and from there it crosses the blood brain barrier and reaches to the target site in the brain or cerebrospinal fluid. There is one disadvantage of this method that loss of drug can take place because drug reaches to the systemic circulation with the help of diffusion process.

Iontophoretic delivery

In this method, the drug is charged and converts it into ionic form and then this drug is transported to the brain with the help of electric current. There is some disadvantage of this method which are other ions can act as competitor for the drug and other is drug should be in aqueous and charged form[29,30,31,32,33].

Mechanism of drug targeting to brain

There are various mechanisms of targeting the drug into the brain as there are various types of nanoformulations present in the market (table 3), so on the basis of those drugs, the mechanisms are classified like

Craniotomy based drug delivery system

In this, a hole is drilled into the head and then, the drug is administered. This process is called as craniotomy. By using this technique, any type of drug (small or large) can be administered inside the brain either by using Intracerebral (IC) or intracerebroventricular (ICV) injection. This DDS is inefficient because the volume of drug administered into brain was less than 1% and there are very few or no disease that can be treated by this concentration[34]. So, a more efficient route of drug delivery to brain is vascular route which include intravenous and systemic injections.

Blood brain barrier drug targeting mechanism

It includes various types of targeting which are as follows

Lipid mediated transport

There are 2 ways to make the drug lipid soluble. First is by masking the polar group of hydrophilic drugs by lipid soluble carrier and second is by conjugating the hydrophilic drug with lipophilic drug. There are 2 problems which are adverse pharmacokinetic and increased molecular weight.

Carrier mediated transport

It includes the use of carriers for the delivery of drugs to the brain like LAT1 is used to deliver L-DOPA inside the brain by crossing BBB and then converted into dopamine for the treatment of Parkinsonism. Other transporters are CAT1 (for cationic amino acid), GLUT1 (for glucose).

Active efflux transporter

These are the transporters which help in delivering the metabolites from brain to the blood like P-gp, BCRP, OATP, BSAT etc.

Receptor mediated transport

These types of transport required for the delivery of large nucleopeptides like transferrin, insulin. These can be transported across BBB with the help of receptors like insulin receptor, transferring receptor[35].

Table 3: Available marketed nanoformulations for brain tumor[27]

S.No.	Drug	Nanocarriers used	In vivo model used for experiment	Carrier / Receptor	Results of in vivo experiment	Ref.
1	Doxorubicin	Liposome	U87 mouse xenografts	Transferrin, Octarginin	Enhanced survival of glioma patients	53
2	Prodrug of Methotrexate	Solid lipid nanoparticles	Healthy rats	Transferrin, Insulin	More accumulation of Methotrexate in brain	54
3	Temozolomide	Polymeric nanoparticles	C6/ICR mouse glioma models	Angiopep-2	Increases biodistribution and efficacy	55
4	Interferon-ϒ-inducible protein	PLGA nanoparticles	U87-EGFRvIII cells xenografts	Angiopep-2, EGFRvIII scFv	Increase survival of glioma models and Decrease tumor growth	56
5	Saporin	Polymersomes	U87 mouse xenografts	Apo E	Provide increased efficacy for brain tumors	57
6	Aurora kinase B siRNA	Olive oil nanoparticles	GL26I/C57BL/6 mouse model	Lf	Increased survival of glioma models when treated with TMZ and nanoparticles.	58
7	Vincristine & TMZ	NLC	U87 Xenografts	Lf, RGD	Increased biodistribution and efficacy	59
8	TMZ	Olive oil nanoparticles	GL26I/C57BL/6 mouse model	Lf	Increased biodistribution and efficacy	60
9	PTX	PEG-PLA micelles	U87 Xenografts	EGFR/EGFRvIII targeting peptide	Reduce tumor growth and specific delivery of micelles in brain	61

10	Porphyrin	Lipid nanoparticles	U87 Xenografts	Apo E3	Accumulation of drug selectively in brain as compared to healthy parenchyma	62
11	Prodrug of MTX	SLN	F98/Fischer rat glioma model	Apo E chiera peptide	Increased efficacy and accumulation of drug in brain	63
12	ATF5 siRNA	Calcium phosphate nanoparticles	C6 mouse xenografts	Apo E	Increased survival of Xenografts and tumor targeting	64
13	Doxorubicin	PCL nanoparticles	C6/ wistar rat glioma models	Angiopep-2	Increased survival of glioma model and uptake of drug	65
14	DOX	BSA nanoparticles	C6/ wistar rat glioma models	Lf	Increase uptake of DOX in brain	66
15	DOX	PEGylated liposomes	U87 mouse xenografts	GSH	Inhibit growth of brain tumor and increase retention of drug in brain	67
16	Vincristine and DOX	Liposomes	C6/ICR mouse glioma model	T7 & ^{D}A7R	Increase efficacy and distribution in brain of liposomes	68
17	-	Liposomes	U87 mouse xenografts	Cetuximab	Enhanced liposomes accumulation in brain	69
18	PTX	PEG-PLA nanoparticles	C6 mouse xenografts	F3 peptide & tLyp-I peptide	Increased survival and penetration at tumor location	70
19	PTX	PEG-PLA nanoparticles	C6 mouse xenografts	Lf and tLyp-I peptide	Increased survival and accumulation of drug at tumor site	71
20	^{99m}Tc-BMEDA	Liposomes	Mice	Lf	Increase	72

					accumulation of drug in brain	

Lf: Lactoferrin; ^{99m}Tc-BMEDA: ^{99m}Tc labeled N,N-bis(2-mercaptoethyl)-N',N'-diethylethylenediamine; PTX: Paclitaxel; PEG: polyethylenglycol; PLA: Poly-lactide; MTX: Methotrexate; DOX: Doxorubicin; GSH: Glutathione; NLC: Nanostructured lipid carrier; siRNA: small interfering ribonucleic acid; PCL: poly-e-caprolactone

Some other information related to brain tumors

Glioblastoma is a type of tumor which spread very rapidly. A study was done to determine the distribution of dose in brain mainly in cognitive area using volumetric modulated arc therapy and helical tomotherapy. In this, 37 patients were treated with these therapies using dose of 60Gy. The results showed that volumetric modulated arc therapy showed better results as compared to helical tomotherapy and provided improvement in glioblastoma with healthy tissue[36]. EEF1A2 (Eukaryotic elongation factor 1 alpha 2) was considered as oncogene for different types of cancer according to previous studies but in a recent study the role of this protein in progression of brain tumor was determined which showed lower amount of EEF1A2 in tumor as compared to normal tissue[37]. In malignant brain tumor, in-vivo patient screening was done and Otx2 and c-MYC were identified as inducers of malignant brain tumor. It was found out that SMARCA4 decrease the tumor causing activity of Otx2 and c-MYC while SMARCA4 inhibit the proteogenic activity and tazemetostat decrease the tumorigenic activity both ex-vivo and in human cerebrum organ culture[38]. In newly diagnosed tumor patients, the combination therapy of lomustine and temozolomide was found to be better than mono therapy of temozolomide. The study was carried out in 16 patients and safety was evaluated. The results increased safety with more chances of survival[39]. Death of children due to brain tumor is increasing today. The use of molecular targeted therapy can be beneficial but the development of these therapeutic agents is a challenging task due to genetic differences and clinical trials in pediatric patients but the development of TRK inhibitors for tumor treatment in pediatric patients has increased development of these targeted agents for tumor in children. Larotrectinib, a tyrosine receptor kinase inhibitor showed anti-tumor activity in most pediatric as well as adult patients which led to FDA approval of drug[40]. There are some of the anticancer medicines which was approved by FDA in 2021(Table 4)

Table 4: Some anticancer drugs which was approved in 2020 by FDA[73]

Trade name	Generic name	Date of approval	Route of administration	Strength	Indications
Keytruda	Pembrolizumab	8th jan, 2020	Oral	200mg every 3 week	non-muscle invasive bladder cancer
Ayvakit	Avapritinib	9th jan, 2020	Oral	300mg	metastatic gastrointestinal stromal tumor
Tazverik	Tazemetostat	23rd Jan, 2020	Oral	800mg	epithelioid sarcoma
Nerlynx	Neratinib+ capecitabine	25th feb, 2020	Oral	240mg(once) +750mg/m^2 (twice)	breast cancer
Sarclisa	Isatuximab+ pomalidomide+ dexamethasone	2nd march, 2020	Intravenous infusion	10mg/kg	multiple myeloma
Imfinzi	Durvalimab+etoposide	30th march, 2020	Oral	1500mg every 3 week	extensive-stage small cell lung cancer
Braftovi	Encorafenib+cetuximab	8th april, 2020	Oral	300 mg	colorectal cancer
Jelmyto	Mitomycin	15th april, 2020	Infusion using ureteral cathetar	4mg/ml, 60mg mitomycin	low-grade upper tract urothelial cancer
Zejula	Niraparib	29th april, 2020	Oral	200mg or 300mg	primary peritoneal cancer
Tabrecta	Capmatinib	6th may, 2020	Oral	400mg twice daily	non-small cell lung cancer
Qinlock	Ipretinib	15th may, 2020	Oral	150mg once	gastrointestinal stromal tumor
Cyramza	Ramucirumab+ erlotinib	29th may, 2020	Intravenous infusion	10mg/kg every 2 week	non-small cell lung cancer
Opdivo	Nivolumab	10th june, 2020	Intravenous infusion	240mg every 2 week and 480mg every	esophageal squamous cell carcinoma

				4 week	
Xpovio	Selinexor	22nd june, 2020	Oral	60mg on day 1 and 3	diffuse large B-cell lymphoma
Bavencio	Avelumab	30th june, 2020	Intravenous infusion	800mg	metastatic urothelial carcinoma
Inqovi	Decitabine+ cedazuridine	7th july, 2020	Oral	35mg+ 100mg	myelodysplastic syndromes
Tecartus	Brexucabtagene	24th july, 2020	Intravenous infusion	2 x 106 CAR-positive viable T cells/kg	mantle cell lymphoma
Tecentriq	Atezolizumab+ cobimetinib+ vemurafenib	30th july, 2020	Oral	840mg+ 60mg once+ 720mg twice	BRAF V600 mutation-positive unresectable or metastatic melanoma
Blenrep	Belantamab mafodotin-blmf	5th august, 2020	Intravenous infusion	2.5mg/kg	refractory multiple myeloma
Kyprolis+ darzalex	Carfilzomib+daratumumab+ dexamethasone	20th august, 2020	Intravenous	16mg/kg	refractory multiple myeloma

Patent

There is a list of patents given in the table below (Table 5)

Table 5: List of patents for brain tumor

S. No.	Patent No.	Patent title	Year	Ref.
1	CN110522720	Preparation and application of targeted lauric acid-phycocyanin-cordycepin reverse micelle for brain tumor treatment	2019	74
2	CN110627876	A7R glycopeptide and application thereof in preparation of tumor diagnosis and treatment drug	2019	75
3	CN1110179753	Nanometer drug delivery system targeted for brain tumors and tumor stem cells thereof and preparation and application of nanometer drug	2019	76

		delivery system		
4	CN110585207	Application of liensinine in preparation of drug for preventing and treating brain glioma	2019	77
5	US20190328677	Decreased adhesivity receptor-targeted nanoparticles for fn14-positive tumors	2019	78
6	KR1020190042939	Pharmaceutical composition for preventing or treating cancer containing mnpii as active ingredients	2019	79
7	CN110862428	Novel anti-tumor epirubicin compound	2020	80
8	KR1020190042940	Pharmaceutical composition for preventing or treating cancer containing bietpc as active ingredients	2019	81
9	US20190223938	Device and methods for delivery of high frequency electrical pulses for non-thermal ablation	2019	82
10	US20190255144	Specific oligopeptides as anti-angiogenic drugs	2019	83
11	CN110468210	CDC45 as marker of glioblastoma multiforme and application of CDC45 as therapeutic target	2019	84
12	CN106667986	Rhein/chitosan hydrogel as well as preparation method and application thereof	2017	85
13	WO2019206069	Diaryl macrocyclic compound and pharmaceutical composition, and use thereof	2019	86
14	CN106619613	Application of bilobalide serving as brain-targeting synergist to preparation of drug For preventing brain tumor	2017	87
15	CN107028882	Physically encapsulated tumor targeted nano drug delivery system and preparing method and application	2017	88

CONCLUSION

Scientists are doing many researches on complete cure of cancer by damaging the cancer cells without harming normal cells since 1953. Till now, many therapies have been developed to cross blood brain barrier but each of them are associated with some drawbacks. We can see from statistical data that number of cancer patients and death rate is increasing. Different drugs have been approved by FDA.

But the complete and permanent cure for cancer is still not available. Scientists are still working in this field for developing safe and effective medicine for permanent treatment of cancer. Now days, Scientists are working on a new therapy which is called as photodynamic therapy. In this therapy, the drug become active in presence of light and act on the cancerous cell and to improve these drugs, carbon dots are used by the scientists. This therapy is cost-effective and very useful. An Australian company named as "Imugene" has engineered a new virus which is based on cowpox that is able to kill approx. every known type of cancer and human trial will begin soon on breast and other types of cancer and it is engineered by Prof. Yuman Fong The treatment is known as CF33 and this leads to shrinking of tumor in mice[41].

STATEMENT OF ETHICS

Author stated that their guardians have given informed consent for publication including images.

CONFLICT OF INTEREST

The authors have no conflict of interest.

AUTHOR'S CONTRIBUTION

All authors have equal contribution.

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