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Kinase Inhibitors in Neurooncology

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Monografia orientada pela Professora Doutora Maria Alexandra Brito, Categoria Professora Associada com Agregação.

Mestrado Integrado em Ciências Farmacêuticas

2021

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

A neurooncologia é uma disciplina relativamente recente, e tem sofrido grande evolução nos últimos anos. Os tumores cerebrais dividem-se em primários e secundários consoante a origem primordial das células tumorais, e os mais comuns de se observarem são os gliomas, tumores embrionários, tumores pituitários e meningiomas, nos adultos, e nas crianças são o astrocitoma pilocítico, tumores embrionários e gliomas malignos. A classificação dos tumores cerebrais ainda não é consensual, no entanto esta tem vindo a integrar não só critérios baseados na histologia, como acontecia até 2016, mas agora integra critérios com base nas características moleculares do tumor.

Tratar doenças neurooncológicas é um desafio pois o sistema nervoso central não só é um ambiente privilegiado do ponto de vista imunológico, como também possui diversos elementos que funcionam como barreira à passagem dos fármacos. As neoplasias cerebrais não possuem as mesmas características em adultos e crianças. Isto dificulta encontrar uma terapêutica direcionada para a população pediátrica, cujos tumores cerebrais possuem uma elevada incidência e está mais sujeita ao aparecimento de efeitos secundários a curto e a longo prazo. Torna-se assim urgente encontrar novas técnicas e terapias que permitam um tratamento eficaz e uma adequada entrega no local de ação.

Os inibidores das cinases são fármacos cujo interesse terapêutico tem crescido nos últimos anos. Os inibidores das tirosina-cinases fazem parte deste grupo de fármacos e são os mais utilizados. Estes têm se mostrado eficazes na maioria das neoplasias. Em ensaios clínicos e estudos recentes tem-se vindo a demonstrar a sua utilidade em neurooncologia não só em monoterapia, mas também em combinação com outras técnicas. Mais estudos são necessários para demonstrar o benefício terapêutico acrescentado que possuem.

Palavras-chave: Neurooncologia, Metástases cerebrais, Inibidores das cinases, Inibidores das tirosinas-cinases

Abstract

Neurooncology is a relatively recent discipline and has undergone great evolution in recent years. Brain tumours are divided into primary and secondary according to the primordial origin of the tumour cells and the most common in adults are gliomas, embryonic tumours, pituitary tumours and meningiomas and in children are pilocytic astrocytoma, embryonic tumours and malignant gliomas. The classification of brain tumours is not yet consensual, however, this has been integrating not only criteria based on histology, as it happened until 2016, but now integrates criteria based on the molecular characteristics of the tumour.

Treating neurooncological diseases is a challenge because the central nervous system is not only a privileged environment from an immunological point of view, but also has several elements that act as a barrier to the passage of drugs. Brain neoplasms do not have the same characteristics in adults and children. This makes it difficult to find a therapy aimed at the paediatric population, whose brain tumours have a high incidence, and is more subject to the appearance of short- and long-term side effects. It is therefore urgent to find new techniques and therapies that allow an effective treatment and an adequate delivery to the place of action.

Kinase inhibitors are medicines whose therapeutic interest has grown in recent years. Tyrosine-kinase inhibitors are part of this group of medicines and are the most used. These have been shown to be effective in most neoplasms. Recent clinical trials and studies have shown its usefulness in neurooncology not only in monotherapy, but also in combination with other techniques. Further studies are needed to demonstrate the added therapeutic benefit they have.

Keywords: Neurooncology, Brain metastases, Kinase inhibitors, Tyrosine kinase inhibitors

Acknowledgments

In the first place, I would like to thank my guidance teacher Maria Alexandra Brito for giving me great advice and for always being available to answer my questions and correct my mistakes. As an experienced investigator, your tips were crucial for the delivery of this work.

Secondly, I would like to thank the team of the pharmacy of Hospital São Francisco Xavier for teaching me so much in such little time, for providing valuable information for my monograph, and for bringing me one step closer to decide what career path I want to follow.

To my best friends Carolina, Natacha, Beatriz, and Mafalda thank you for always supporting me in everything I do and for being there for me in the good and in the bad times of the writing of this monograph. Without you this would not have been possible.

To my friends at Pastoral Juvenil de Linda-a-Velha who have been my second family for all these years, thank you for helping me reach my full potential as a professional and as a human being.

To my amazing grandparents, thank you for always cheering me up me even when we could not see each other for long periods of time.

To my little brothers Vasco and Miguel, may this monograph be a reminder of the things you can achieve if you put your mind to it, and that hard work will always pay off in the end. I hope I can make you proud.

I would also like to thank my parents for always believing in me, for not letting me doubt my own capabilities, and for giving me the confidence to finish this chapter in my life knowing that you will always have my back.

Finally, I want to thank my boyfriend, Bruno. There are no words to describe how your love and support were important for the making of this monograph. I hope one day I get to repay everything you have done for me all these years, and to be there for you when you need me most.

Abbreviations

WHO - World Health Organization

CNS - Central Nervous System

IDH - Isocitrate Dehydrogenase

WBRT - Whole-Brain Radiotherapy

EGFR - Epidermal Growth Factor Receptor

BBB - Blood-Brain-Barrier

ATP- Adenosine Triphosphate

RTKs - Receptor Type Kinases

TKI - Tyrosine Kinase Inhibitor

FDA - Food and Drug Administration

EMA- European Medicines Agency

CML - Chronic Myeloid Leukaemia

NCDs - Noncommunicable Diseases

GB - Glioblastoma

MB - Medulloblastoma

NB - Neuroblastoma

BM - Brain Metastasis

CSF - Cerebral Spinal Fluid

SHH - Sonic Hedgehog Medulloblastomas

WNT – Wingless Medulloblastomas

ATXR - Alpha Thalassemia/mental Retardation syndrome X-linked

L1CAM - L1 Cell Adhesion Molecule

SEGA - Subependymal Giant Cell Astrocytoma

mTOR - Mammalian/Mechanistic Target of Rapamycin

pHGG - Paediatric High-Grade Glioma

HGG - High Grade Glioma

PET/MRI - Positron Emission Tomography/ Magnetic Resonance Imaging

EC - Endothelial cells

ABC - ATP-binding cassette

SLC - Solute Carrier

P-gp - P-glycoprotein

Bcrp - Breast cancer resistance proteins

Mrps - Multi Drug Resistance Proteins

PTKs - Protein Tyrosine Kinases

SCF - Stem Cell Factor

JAK - Janus Kinase

BTK - Bruton Tyrosine Kinase

NSCLC - Non-Small Cell Lung Cancer

NTRK - Neurotrophic Tyrosine Receptor Kinase

RET - Rearranged during Transfection protooncogene

ALCLs - Anaplastic Large Cell Lymphomas

ALK - Anaplastic lymphoma kinase

SCLC - Small Cell Lung Cancer

VEGFR - Vascular Endothelial Growth Factor Receptor.

PDGFR - Vascular Endothelial Growth Factor Receptor

BRAF - proto-onco B-Raf

GERD - Gastroesophageal Reflux Disease

RCC- Renal Cell Carcinoma

MKI - Multikinase Inhibitor

HGF - Hepatocyte Growth Factor

EMT- Epithelial-Mesenchymal Transition

FGFR1 - Fibroblast Growth Factor Receptor 1

HER2 - Human epidermal growth factor 2

IGF-1R - Insulin-like Growth Factor-1 Receptor

BCR-ABL - Breaking point Cluster Receptor – ABL

IDL - Intestinal Lung Disease

BCBM - Breast Cancer Brain Metastasis

MBM - Melanoma Brain Metastases

MTX - Methotrexate

STAT - Signal Transducers and Activators of Transcription

IFN-γ - Interferon Gamma

IFN-α - Interferon Alpha

TRK - Tropomyosin Receptor Kinase

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1 Introduction

Brain tumours are malignancies with very diverse features. Primary brain tumours arise from the intricate cells of the brain and intracranial cavity, while metastatic tumours initially arise from another malignancy which originated in a different body part before progressing to the brain parenchyma (1).

The patient´s treatment of these neoplasms has been rapidly evolving over the last few years. Up until recently, the search of molecular biomarkers was used only to predict a patient´s prognostic having no influence on the choice of treatment (2). In 2007, The World Health Organization (WHO) classification of central nervous system (CNS) tumours was only based on the histological characteristics of a tumour microscopically, which led to a lot of confusion and doubt among pathologists regarding cell origin and the level of differentiation (3). In 2016, the classification was updated, integrating the genotypic and phenotypic characteristics of the tumours in order to facilitate diagnostic, predict the effectiveness of targeted treatments and improve accuracy in clinical, experimental, and epidemiological studies (4). Since then, new entities have been recognized and the classification of others has been restructured. The new classification allowed to reach a more precise diagnostic, therefore improving patient management and prognosis, but it also depends on the availability of molecular testing which can be a downside (5–7). The advance of machine learning and artificial intelligence are factors to consider in this development (8).

Artificial intelligence has proven to be useful in the identification of molecular markers (like isocitrate dehydrogenase (IDH) mutations and 1p/19 codeletion status), that are currently used in the classification of tumours. It also aids in clinical decision support, detecting even the smallest and non-recognizable lesions, reporting them, and recognizing malignant lesions even before the biopsy, although this may lead to the providing of information that is not easily discerned by clinicians. Finally, they aid in risk assessment and treatment response. There are many challenges these technologies need to overcome. In a near future there should be an investment making specific algorithms for different populations across the globe, find a way to store a considerable amount of data so these systems can work with maximum efficacy, and regulating performance of algorithms, perfecting them, and reduce external validation by clinicians (9).

Treating neurooncological pathologies is a challenge. Therapeutic options for brain tumours generally consist in surgery, stereotactic radio-surgery/stereotactic fractionated radiotherapy,

whole-brain radiotherapy (WBRT), chemotherapy and targeted therapy (10,11). A small number of medicines targeting common alterations, such as the mutation in the epidermal growth factor receptor (EGFR), have been successful for a large number of cancers, but only few have shown efficacy in treating brain tumours (12). A greater insight is needed into the mechanisms that prevent the crossing of therapeutic agents through the blood-brain-barrier (BBB) in conjunction with the immunologic properties and singularities of the brain´s microenvironment (13). The recent development of chemotherapeutics, the morbidity and mortality rate of many cancers has decreased over the years, but compared to oncology in general, this field has not developed that quickly (14). Efforts are being made in order to understand progression of tumours in an aggressive manner to improve patients prognostic and outcomes, considering tumour heterogeneity in space and time (15,16).

The kinases are enzymes with the ability of catalysing an adenosine triphosphate (ATP) phosphate group´s transfer onto a substrate, which results in a conformational change, altering its function. This alteration precedes a signal transduction, thus helping to regulate various cellular processes. Multiple evidences have shown kinases are a promising target in multiple diseases like inflammatory bowel disease, cancer, CNS disorders and complicated diabetes (17). The importance and relevance of kinases as biological targets was recognized after the detection of the coding of cancer-causing tyrosine kinases by the SRC gene (18).

Tyrosine kinases are a group inside the kinase family (18). A receptor tyrosine kinase (RTK) monomer consists of a N-terminal extracellular domain, which attaches to the transmembrane domain, acting as a ligand, and a C-terminal intracellular domain with activity for tyrosine kinases that includes a binding site for ATP with a phosphate-binding region and a hinge region enabling them to move from one another (19,20). RTK hyperactivation oncogenic-driven through amplification and overexpression, leads to constitutive activation and ligand over-expression proceeding multiple oncogenic processes (21).

Small-molecule tyrosine kinase inhibitors (TKIs) selectively inhibit tumour growth by competing with the ATP for the dimerization sites or acting allosterically (18,22). The first TKI available and approved was imatinib (Glivec®) in 2001 by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in order to treat chronic myeloid leukaemia (CML) (18,23). Every TKI seems to have a different clinical performance on different neoplasms. Generally TKIs show significant efficacy, especially when it comes to the improvement of progression-free survival, when used as first-line or not (18). Starting March 2019, the FDA approved a total of 48 protein kinase inhibitors, the majority (25 of them) being

RTK inhibitors and 10 non-RTK inhibitors (24). This monograph will mainly be based on tyrosine kinase inhibitors, but other types of kinase inhibitors will also be mentioned.

Having all of this into account, the objectives of this monograph are:

- Give enlightenment about the most common clinically relevant primary and secondary brain tumours.
- Alert to the urgence of finding new treatment strategies for these pathologies and improving the accuracy of the diagnosis.
- Highlight what are tyrosine kinase inhibitors, especially TKIs, namely how they are currently being used and how they act in the tumour mechanism.
- Show the importance TKIs have in the treatment brain tumours now and in a near future.

2 Neurooncology: Brief context and explanation

2.1 Incidence, mortality, and most affected groups

Brain cancers are an heterogenous and rare group of cancers, which are diagnosed not only by their histological features and symptomatology but also integrating molecular parameters (7,25). A study performed in 2018 referring to the incidence and mortality of several cancers worldwide reported noncommunicable diseases (NCDs) are the number one cause of death worldwide being cancer one of them. Brain tumours specifically have a higher incidence on men than on women and represent 2,5% of cancer related mortality (26). The prognosis variates according to the histological type and the patient´s age, a higher incidence is registered among elderly patients (25). A study based on the population of Cali, Colombia, performed in 2019 showed an escalating burden of primary CNS tumours for the last 60 years, with a steady rate from the early 2010s and the median 5-year survival rate was increased. Mortality was higher in males than in females (27).

The most conventional adult brain tumours are pituitary tumours, gliomas and meningiomas (28). The current literature acknowledged meningiomas comprise 36.6% of all primary tumours of the CNS, and 53.2% of non-malignant primary CNS tumours in the United States of America being an age dependent disease, although it is still unknown if this increased incidence exists due to the upgrade of diagnostic and detection techniques over the years. It was also reported to be more prominent in African-Americans than in Caucasian individuals, with women being the most affected, probably as a consequence of the hormonal imbalance in the childbearing years (29). Pituitary tumours are also most common in women and are the third most common brain tumour in adults, accounting for 15% of all CNS adult tumours. They are invariably benign (28,30). Diffuse gliomas comprise less than 2% of all newly diagnosed cancers. Glioblastoma (GB), is the most lethal one, accounting for 70–75% of all diffuse glioma diagnoses and has a median overall survival of 1–1.5 years (31). There are vast differences between European and Asian populations in glioma incidence, which may be related with these individual´s gene code. The lowest rates were found in Asian countries (25,31).

CNS tumours remain one of the most prevalent types of paediatric cancers and are the leading cause of cancer related death in children (32). The most common CNS tumours in children are pilocytic astrocytoma, embryonal tumours, and malignant gliomas (28,33). Approximately 50% of brain tumours in infants and children are gliomas, most of them being pilocytic astrocytoma or other low-grade gliomas. They are usually indolent, having a slow progress even after

surgery. Patient survival at 10 years old is almost 85-90%. Medulloblastoma (MB) and neuroblastoma (NB) are embryonal tumours. They have poor prognosis especially at younger ages (34,35). MB accounts for almost 10% of all brain tumours in children and has a peak incidence at 7 years old. They occur exclusively in the posterior fossa and can potentially have leptomeningeal spread (35,36). It is estimated 10.5 cases per million children under 15 years of age in North America and Europe had NB, with minimal ethnic or geographic variability. MB is mostly found in little children since most of them are diagnosed before 5 years of age, with a median age of diagnosis of 19 months. It is also diagnosed more often in boys than in girls, but the difference is small. African-Americans and native-Americans are most likely to have a more aggressive disease with lower survival rates, but the aetiology of these differences remain unclear (37).

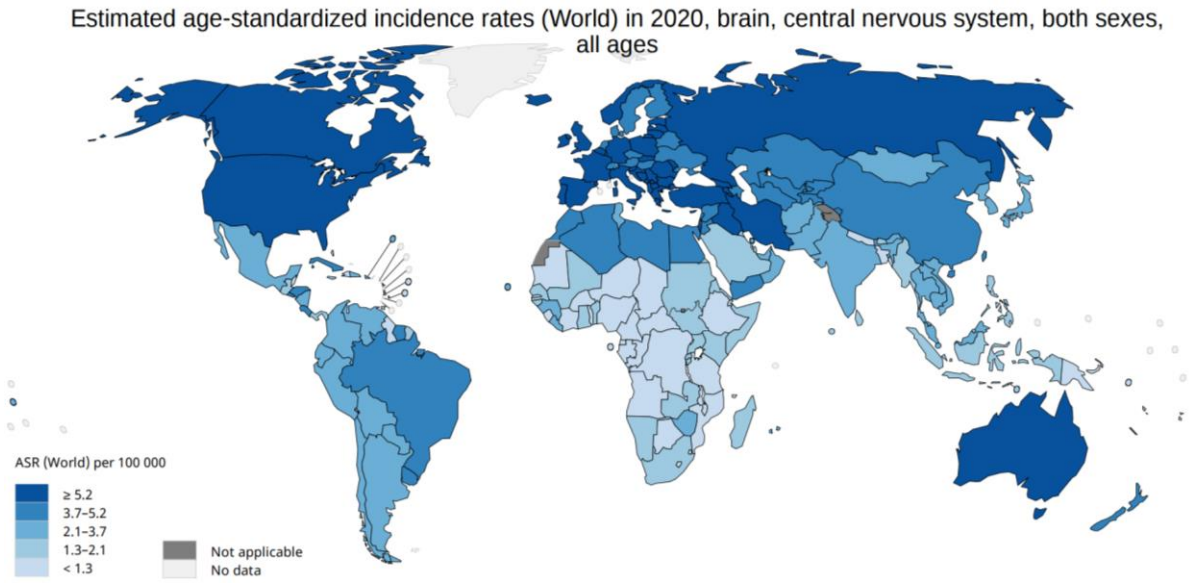

Figure 1 Worldwide incidence rates of malignant brain tumours. Ref: Taken from GLOBOCAN 2020 – Cancer today, Age-standardized incidence rates of CNS and brain cancers worldwide in both sexes and all ages, accessed September 25.

Brain metastases (BM) are linked to poor prognosis and an elevated morbidity (38). Studies estimate BMs are 10 times more frequent than primary malignant brain tumours. The frequency, incidence and mortality of these neoplasms varies significantly, but previous studies acknowledged that they occur approximately in 9% to 10% of all cancer diagnoses. Up to 10% of patients with melanoma and lung adenocarcinoma present metastasis in the brain at the time of diagnosis, and it is estimated that many more will develop intracranial disease during it. Up to 35% of patients with HER2 - positive breast cancer will develop BMs (39).

Several potential risk factors have been under investigation in the last few years, but they lack robust evidence. Ionizing radiation is a well-known risk factor for brain tumours (GB,

meningioma and nerve sheath tumours) especially in patients that had to do high-dose radiotherapy as children for some reason (40). As for genetic factors the only one that is proven to be a potential risk factor is the existence of a mutation on PTEN also known as Cowden´s syndrome (41,42), but identifying genetic risk factors is complicated because of their rarity (42). Studies made about toxic compounds like chemical agents, N-nitroso based compounds and other generic factors like alcohol, cellular and telephone use, and air pollution, have yet failed to bring conclusive evidence (40,42).

2.2 Primary tumours: Classification

2.2.1 Grading

One of the few changes observed in the 2016 WHO classification was on the grading of tumours. A new category was added ("grading unknown") generally associated to diffuse leptomeningeal glioneuronal tumour. Tumours are classified in four grades taking into account the existence of necrosis, cytological environment, mitotic activity and microvascular infiltration and proliferation (3). Grade I applies to resettable tumours with low growing and invasive potential and they are curable with surgery alone. Grade II lesions have the capability to infiltrate and are often recurrent despite their low level of proliferation abilities. They usually progress to more aggressive forms. Grade III includes tumours with histological evidence of malignancy, like enhanced mitotic activity and ultrastructure modification. Grade IV is for tumours who are cytologically malignant, with active mitosis and necrosis and are associated with quick and fatal evolution alongside poor clinical outcomes. Vascular proliferation of the surrounding tissue and widespread is also observed (43).

2.2.2 Major categories

Brain tumours are subdivided in a lot of categories, some of them might not even be malignant (44). In this monograph we will focus on gliomas, embryonic tumours, pituitary tumours and meningiomas and their respective subtypes.

Gliomas are the most common type of tumours, and they are classified according to the glial cells that originate them. The 2007 WHO classification, divides them in astrocytomas, originated in the astrocytes (45,46), oligodendrogliomas, which are originated in oligodendrocytes and account for less than 10% of all diffuse gliomas (47) and ependymomas, rare tumours, more frequent in children, which begin in the ependymal cells and spinal cord that cover the area where the cerebral spinal fluid (CSF) flows and nourishes the brain (48,49). With the 2016 WHO classification the term "diffuse astrocytoma" was introduced taking into

account the molecular features of oligodendrogliomas and astrocytomas (6), and GB (a grade IV astrocytoma according to the prior classification) was subdivided also according to its molecular features (50).

Embryonal tumours are malignant lesions originated in the embryonic cells of the brain and are most prevalent in young patients but can occur at any age. The most common type is MB but we will also discuss other relevant but rare tumour called NB (51,52). The MB classification is based on a complex diagnostic involving histological and molecular parameters. The joined result of this parameters will lead to a definitive diagnostic. According to the histological parameters MB can be classic (rare), large cell/anaplasic (very rare), desmoplastic/nodular (very rare) and extensively nodular (rare). According to the molecular parameters they can belong to the sonic-hedgehog (SHH) group (TP53 mutant or wildtypes), the WNT (wingless) group, non-WNT/non-SHH group 3 and group 4 (53,54). NB presents a wide range of clinical behaviours and has unique features (55) it develops from immature cells scattered around the body, but mainly arises in and around the adrenal glands. Some forms of NB even disappear on their own while others require treatment (56).

Pituitary adenomas are characterized for being a malignant proliferation of the cells of the anterior pituitary. Most of them are benign, but the rare forms (pituitary carcinomas) are malignant causing craniospinal metastases (57). The anterior pituitary cell types produce a number of hormones that are fundamental to the endocrine metabolism, deregulation causes a hormonal imbalance and hypersecretion of thyroid related, growth related and reproduction related hormones (30).

Meningioma is the most prevalent brain tumour. They are commonly found solo and 90% of the times are benign. They usually arise from arachnoid cells observed in the meninges in the intraspinal, intracranial and/ or orbital parts, but primary intraosseous and intraparenchymal meningiomas may occur. They are subdivided according to the grade based on histological criteria, that does not consider the molecular and genetic features of the meningioma. The most common subtypes are the Grade I meningiomas which comprise the histological subtypes meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretor, lymphoplasmacytic-rich, metaplastic and chordoid (58).

A simplified scheme of the location where the brain tumours previously discussed arise can be found on Figure 2.

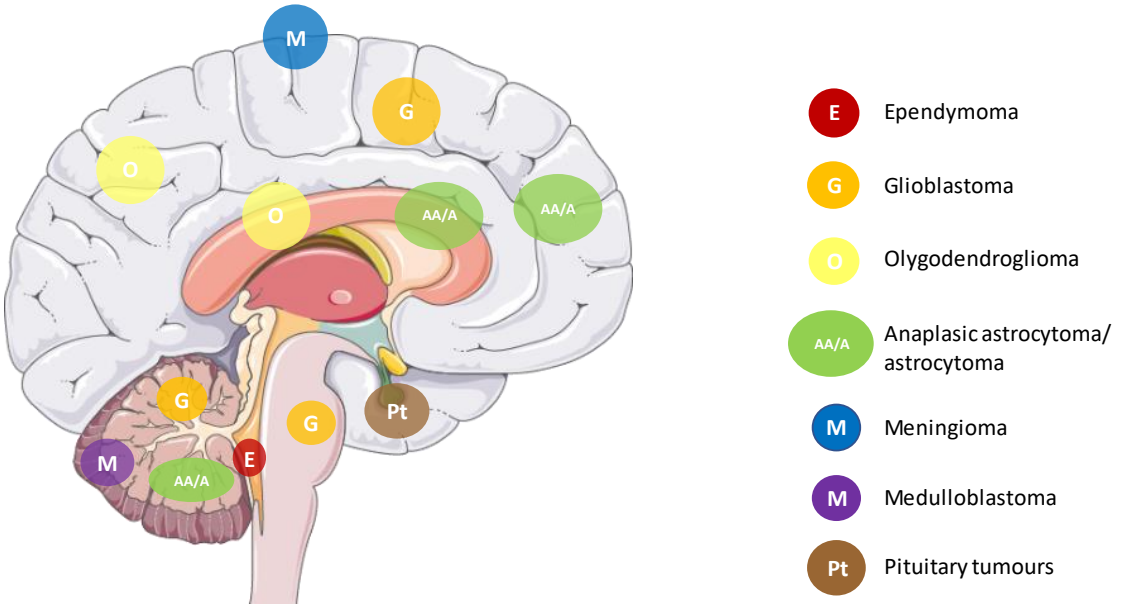

Figure 2 Locations of primary brain tumours. This figure was made using elements from https://smart.servier.com/.

2.2.3 Categories according to molecular testing

As mentioned before, the 2016 WHO classification update introduced important changes to the classification of gliomas, introducing the term diffuse glioma.

Diffusely infiltrating gliomas (astrocytomas, oligodendrogliomas and oligodendroastrocytomas) are now classified in accordance with two highly recurrent molecular alterations: the mutation on IDH and the 1p/19q codeletion. Other histological parameters are also taken into account (5). The alpha thalassemia/mental retardation syndrome X-linked (ATXR) gene loss and the TP53 mutation are other parameters that can be taken into account, but they are not mandatory to verify in order to reach a definitive diagnostic (7).

GB, according to the current classification, is a separate entity because the prior classification was not enough to describe all the malignant features of GB and/or the patients response to treatment (50). They are now separated in IDH-mutant and IDH-wild type because it is a mutation present in 90% of glioblastomas and it is associated with better prognosis. Other less common mutations are PTEN loss, EGFR amplification and MGMT methylation (7,50).

The "NOS" term was also introduced in this new classification system. It stands for "not otherwise specified" and it is a histological diagnosis in the absence of molecular testing or if it was inconclusive (59).

A scheme of the molecular classification of gliomas and glioblastomas is presented in Figure 3.

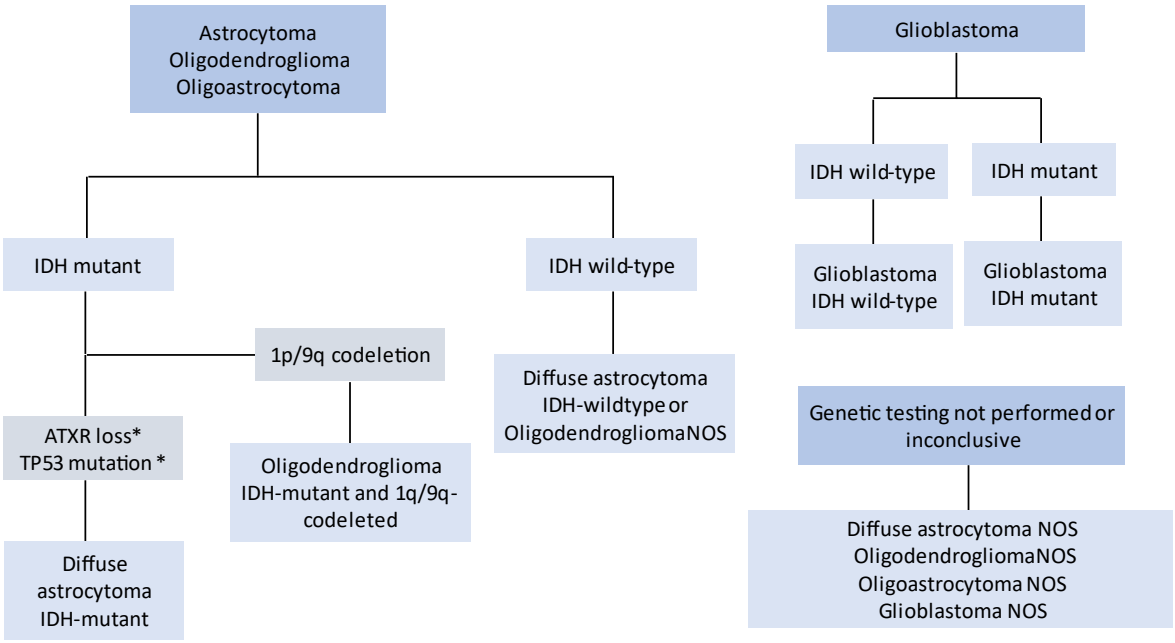

Figure 3 Classification scheme of gliomas and glioblastoma. Ref: Adapted from Dewitt, John C. Mock, Andreas Louis et *al, Current Opinion in Neurology*, 2017

When it comes to MB, the prior classification did not consider the complexity and heterogeneity of this disease. To correct this problem, the 2016 WHO classification system defined two criteria for the diagnosis of this disease: genetic classification and histological classification. The histological classification is based on the microscopic well-defined features of the tumour including classic, desmoplastic/nodular, large cell/anaplastic, and extensive nodularity. The four genetically defined classifications for MBs are the WNT- activated, where patients exhibit a survival rate of 90-95% and it can also be traced by IHC β-catenin analysis with detection of monosomy 6 or CTNNB1 mutation, the SHH-activated, that accounts for 30% of all MB and it is characterized by gene expression and methylation profiling, SHH-activated TP53 wild-type and SHH-activated TP53 mutant, the latter having a higher probability to have poor clinical outcomes with metastatic progression and refractory disease, non-WNT/non-SHH which is a poorly defined category and more studies are needed to distinguish them from the others, Group 3 which represents poor clinical outcomes specially in children where MYC amplification and isochromosome 17q are alterations usually found, and finally Group 4, which accounts for the majority of MBs and the prognosis is variable and overall intermediate, plus 17q isochromosome is a usual genetic change (60).

Another new entity that was also introduced was the ependymoma RELA-fusion positive. Ependymomas are clinically relevant when it comes to paediatric tumours and harbour a fusion between the genes RELA and C11orf 95, which are originally from a local chromothripsis event on chromosome arm 11q, and are distinct of other ependymomas by the expression of L1 cell adhesion molecule (L1CAM) (61).

The classification of meningiomas from 2007 to 2016 is still imperfect because it fails to predict almost 20% of meningioma types (7) but a recent multicentred study suggested DNA methylation-based meningioma classification can be of assistance to clinically find homogenous groups and has a better ability to predict recurrence and prognosis than the current classification (62).

2.3 Secondary brain tumours

Extrinsic and intrinsic cells factors will affect cancer metabolism and promote cancer spread in the form of metastases. Interactions with the extracellular matrix, the surrounding environment composed by cells and available nutrients, affect cell metabolism on an extrinsic level. On an intrinsic level, the brain's elevated glucose demand and supply provides the ideal conditions to fuel cancer cell growth. The rapid tumour growth causes cancer cells to have high energetic and biosynthetic demands. This causes tumours often undergoing metabolic reprogramming to keep up with this demand, switching from oxidative phosphorylation to anaerobic glycolysis even in aerobic conditions. That sudden shift is caused by mutations that give cancers cells the ability to survive (63). This reprograming of cancer cells is called the Warburg effect and it is considered one of the hallmarks of cancer (64).

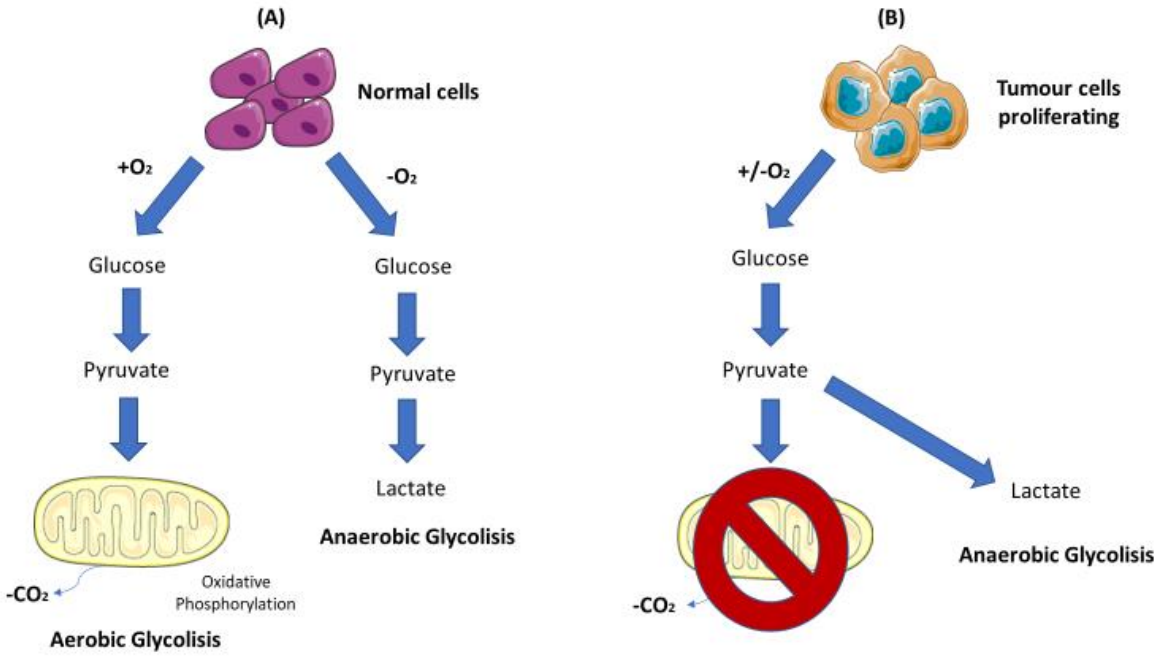

Figure 4 The Warburg effect. (A) Normal cells proliferating (B) Tumour cells doing anaerobic glycolisis in aerobic conditions. Ref: Adapted from Vander Heiden, . Matthew, Cantley C. Lewis, Thompson, Craig B. et *al, Understanding the Warburg effect: the metabolic requirements of cell proliferation*, 2009. This figure was made using elements from https://smart.servier.com/.

BMs can´t be classified in specific categories like primary tumours but the treatment should always take into account the type of primary tumour, the presence of single, multiple, solitary or extracranial metastasis, location and resectability, prior treatments applied to the patient, prognostic and patient-specific factors like age and general state (65). The cancers that most spread to the brain are lung cancer, breast cancer and melanoma. (66,67). Surgical resection or stereotactic radiosurgery alone are the current first-line treatment for patients with small lesions, limited intracranial disease, general satisfactory state, and treatable or lack of extracranial disease. Targeted therapies and immunotherapy have shown intracranial efficacy and may allow enough volume reduction to postpone surgery, stereotactic radiosurgery and whole brain radiotherapy (39).

Brain tumours do not always have an oncological aetiology. Subependymal giant cell astrocytoma (SEGA) is a rare occurrence characterized by the formation of a tumour in the wall of the lateral ventricle, foramen of Monro and occasionally in the third ventricle (68). It is a lesion derived from an also rare disease called tuberous sclerosis, a multisystemic genetic condition distinguished by the occurrence of benign tumours (hamartomas) affecting the brain, heart, lungs and kidneys (68,69). The current medicine approved to treat this disease is the mammalian/mechanistic target of rapamycin (mTOR) inhibitor everolímus (Votubia®) (70). This monograph will only be based on tumours that have an oncological origin.

2.4 Challenges of the paediatric field

Brain tumours arise differently in the paediatric population due to the biological and clinical differences between them and adult population (71,72). This is due to different mutagenic frequencies, and genetic predisposition which is a particularly important factor to take into account in this population (73). Paediatric high-grade glioma (pHGG) is histologically like high-grade glioma in adults (HGG) but its unique in a molecular level because less than 5% pHGGs present IDH1/2 mutations and 1p/19pq codelation which are very common in adults. In MB, the WNT genetic variation is more common in children while the SHH group affects individuals from childhood to adulthood (74).

The recruitment of patients to clinical trials is difficult when it comes to children because of the lower burden of the disease in them, and the reluctance of parents and doctors to subject them to uncertain treatment side effects (75). Even if patients are grouped in large cohorts, eliminating the need of many patients in each trial, the heterogeneity of these groups does not allow to have a clear understanding of the data (71).

The paediatric population is more susceptible to develop long-term adverse effects and therapeutic resistance, consequently inducing cognitive decline, vasculopathy, endocrine dysfunction and appearance of second malignancies (74,76). Despite the rapid growth of this field in the last few decades, the outcomes of neurosurgery, radiation and the introduction of targeted therapy have been the same for a long time except for MB (77). Aggressive treatments demonstrated effectiveness in some cases like in the treatment of neuroblastoma (34)

Adding to all of this, rehabilitation still possesses a key role in long-term survival of these patients because of the existence of late side effects (78) namely motor, cognitive, speech, and visual deficits. These services are not fully specified on how they should be provided and often fail to meet the needs of patients and their families (11,78).

The integration of targeted therapies and diagnostics is vital to treat these types of tumours, because they are focused on minimizing chronic and acute morbidity (79).

2.5 Main difficulties when treating neurooncological pathologies

Neurooncology is a recent and still developing discipline and there are difficulties that remain unsolved (80). One of the main challenges lies on finding new non-invasive diagnostic techniques. Positron emission tomography/ magnetic resonance imaging (PET/MRI) for example is one of them, and a much needed tool to perform diagnostic but it does not predict

the grade, malignancy or the progression potential of a lesion (81,82). To make this prediction, a multidisciplinary team and access to expensive and modern technologies of neuroimaging neurosurgery, neuropathology/molecular diagnostics, chemotherapy, radiotherapy, and rehabilitation services are needed. These services all imply qualified and specialized professionals that may not exist/be available all the time. This might explain the low incidence but high mortality in underdeveloped countries as the heterogeneity in clinical outcomes, caused by non-standardized patient care. (83).

Developing new treatment strategies to treat brain related diseases is one of the most difficult challenges to the pharmaceutical industry. The compared low incidence of brain tumours may cause delays in drug development, there is a lack of patients recruited to clinical trials (12) and the expensiveness of the development phase is huge. In recent years, only 3-5% of the medicines developed reached the consumer because most of them could not cross the BBB *in vivo* (84) which is the main reason to the unsuccess of therapeutic agents applied in neurooncology not being diffused in the CNS. (85).

The BBB is not a static or physical barrier, it is a structure that results from the combination of various elements and the characteristics of the endothelial cells (EC) that form the blood vessels that vascularize the CNS and reduce permeability. The BBB prevents neurotoxic plasma components, pathogens, and blood cells to enter the brain, regulates the transport of small molecules inside and out of the CNS maintaining the delicate microenvironment, enabling the proper oxygenation of the tissues and nutrient exchange between them.

The tight junctions between ECs are structures formed by multiple specific transmembrane proteins, that interact via extracellular components, to form a highly resistant electrical barrier which will influence permeability (86). Transports that include ATP-binding cassette (ABC) transporters and solute carrier (SLC) transporters are also a factor affecting permeability. ABC transporters include the P-glycoprotein (P-gp), breast cancer resistance proteins (Bcrp) and multi-drug resistance proteins (Mrps). P-gp transports tend to permit the efflux of a diversity of compounds, but Mrps are mainly for anionic medicines, glucorinated, sulphated and glutathione-conjugated metabolites. Brcp and P-gp are known for acting in a synergistic manner. (87)

The BBB itself lacks pinocytic vesicular transport (85) however, there are specific transcytosis mechanisms that allow large molecules to cross it. They allow the re-routing of macromolecules away from the lysosome so some of them remain intact in peripheral endothelium which is believed to be a special feature of the BBB (88).

On top of all of this, the BBB contains other cellular components, astrocytes, pericytes, and an acellular basement membrane, limiting almost entirely the access to the CNS (85). All these components working together contribute to the steady state of the BBB (89) allowing small lipophilic molecules, oxygen and carbon dioxide to easily diffuse across the cell membranes, following their concentration gradients and the selective uptake of amino acids and glucose (85).

3 Tirosine kinase inhibitors (TKI)

3.1 The importance of protein tyrosine kinases (PTKs) in normal metabolic functions.

PTKs are molecules who were first identified 35 years ago as enzymes who catalyse the phosphorylation of tyrosine residues in specific target proteins. Of the 90 genes identified since that time, 32 PTKs are non-RTKs and 58 PTKs are RTKs (90).

The 58 RTKs, depending on the gene encoding the RTK like EGFR, MET or HER2/ErbB2, a different signalling pathway will be triggered (91). Mutations on these genes can reveal the genomic landscapes of human cancer (91). These RTKs initiate a cascade of signals from the exterior (92), intervening in crucial metabolic cellular processes like proliferation, cell survival, apoptosis and motility (93,94). C-Kit is a type III RTK and it plays an important part in cancer occurrence (95). It is considered a Stem Cell Factor (ScF), but early studies consider it an oncogene. It is expressed by fibroblasts and EC promoting migration, proliferation, survival and differentiation between hematopoietic progenitors, melanocytes and germline cells (95,96)

Non-receptor tyrosine kinases are proteins with an intracellular domain who have no direct role in receiving signals from the exterior, they are usually downstream of RTKs, and they subdivide in 10 families for example the Janus kinase (JAK), Src, Syk and the Bruton tyrosine kinase (BTK). They play an important role in various immune-related disorders (97,98)

3.2 Tumour regulating mechanisms involving PTKs

According to recent studies, RTKs are involved in multiple tumorigenesis-related events like angiogenesis, proliferation, immune evasion and metabolic adaptation (99). There are essentially four principal mechanisms who lead to constitutive RTK activation in human cancers: gain-of-function mutations, genomic amplification, chromosomal rearrangements, and autocrine activation (93).

A gain-of-function mutation in an RTK may lead to an abnormal downstream signalling pathway, escaping from the “checkpoints” that usually occur in physiological signalling. It was identified in some gastrointestinal stromal tumours in the c-kit RTK (93,100).

Overexpression is the major mechanism that leads to genomic amplification. It is found in a large number of RTKs: EGFR in non-small cell lung cancer (NSCLC) and breast cancer (101), MET receptor in NSCLC and colorectal cancer, HER2/ErbB2 in breast cancer, upper

gastrointestinal cancer (93) and metastatic prostate cancer (102). When overexpression occurs, the local concentration of the receptor increases, which results in increased RTK signalling overwhelming the regulatory negative feedback mechanisms (93).

Chromosomal rearrangements like translocations, deletions or gene amplifications usually lead to loss of function of tumour suppressing genes or activation of promoter genes. In thyroid cancer, RTK gene neurotrophic tyrosine receptor kinase (NTRK1), Rearranged during Transfection (RET) protooncogene and MET are sometimes rearranged (103). In a number of haematological cancers, like anaplastic large cell lymphomas (ALCLs), Anaplastic lymphoma kinase (ALK) fusion was notified (104).

Lastly, autocrine activation is a system of communication between cells where growth factors and cytokines are secreted and act as "messengers", leading to clonal expansion and self-activation, resulting in tumour growth. It is a well characterized occurrence for example in Scf-KIT autocrine loops (93) in the growth of small cell lung cancer (SCLC) (93,105).

Emerging mechanisms have been reported recently, which need further investigation, such as the role of microRNAs in the modulation of RTKs, signal attenuation by negative regulators and modulation of tumour microenvironment, behaviour regulation and growth of specific cells like macrophages, and targeting important RTKs to tumour microenvironment like vascular endothelial growth factor receptor (VEGFR) and vascular platelet derived factor receptor (PDGFR) (93,105)

3.3 Mechanism of action

Despite having different locations and functions, RTKs and non-RTKs share the same catalytic mechanism based on the phosphorylation of tyrosine residues on target proteins using ATP. This phosphorylation triggers the different signalling pathways (19). When the ligand binds to the extracellular domain, it promotes receptor dimerization which results in autophosphorylation of specific tyrosine residues. The now activated receptor recruits interacting proteins that bind to several phosphorylation sites. These proteins will subsequently be able to phosphorylate other proteins activating signalling pathways which consequently leads to biological responses (20,90). TKIs reversibly or irreversibly bind to the ATP-binding pockets of the respective tyrosine kinase, either to their active or their inactive conformation. Afatinib, ibrutinib, and osimertinib are the only TKIs who bind irreversibly to the ATP-binding site (19,106). A simplified mechanism of action of TKIs can be found in Figure 5.

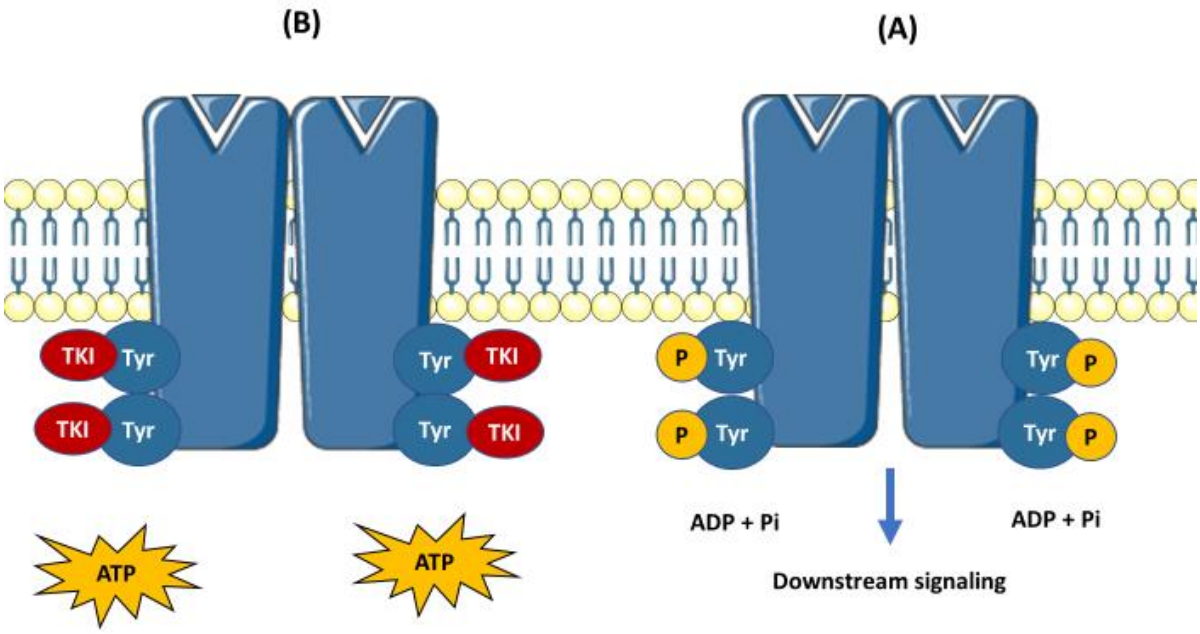

Figure 5 Mechanism of action of TKIs. Ref: (A) Activated RTK in normal physiological conditions, (B) Activated RTK with TKI action. This image was designed with elements from https://smart.servier.com/.

3.4 Toxicity and common side effects

Side effects are caused by the molecule not reaching the intended target because of the multiple barriers of the CNS (107).

TKIs present variations in their pharmacokinetics and toxicity profile, however most of them cause skin toxicity, like folliculitis, in more than 50% of patients. EGFR-TKIs are known for causing TKI-associated keratitis but proto-onco B-Raf (BRAF), JAK, and VEGFR pathways also make patients more susceptible to this problem (106,108). TKIs that present the broadest spectrum of side effects are erlotinib and gefitinib. EGFR-TKIs can cause rash, hair loss, neurogenic inflammation (in erlotinib may be severe), diarrhoea and nausea. In gefitinib the effects are usually mild to moderate, hepatotoxicity only occurs rarely and it is resolved by therapy discontinuation (109,110).

Lorlatinib, is an ALK-TKI, brain-penetrating which the most common side effects are hypercholesterolemia, hypertriglyceridemia, edema, peripheral neuropathy and other CNS side effects (111). A study has shown that other ALK-TKIs like alectinib, crizotinib and ceritib may develop adverse reactions in a higher grade in patients with ≥ 65 years old, unlike young patients. There were observed big differences regarding fatigue with alectinib and ceritinib, diarrhoea, nausea, creatinine elevation with crizotinib and ceretinib, vision disorders with crizotinib, myalgia with alectinib, transaminase elevation and fluid retention with all agents. Alectinib is the one that presents the lower rate of high-grade side effects (112).

Thyroid related adverse effects are also common. Hypothyroidism is one of them, and some authors believe that it is the cause of TKI-related fatigue. The mechanism why hypothyroidism occurs in patients treated with TKI is still unclear, however it is believed that it might be due to one of these reasons: induced thyroiditis, inhibition of thyroid peroxidase, regression of the gland vascular bed induced by treatment, non-deionization clearance, immune mediated destruction, or transmembrane transport of thyroid derived hormones (113). Sunitinib is the most described TKI relating hypothyroidism. 18% of the patients dealt with sorafenib showed hypothyroidism occurrences. Imatinib and motesanib were also correlated with hypothyroidism (114).

Laryngeal manifestations are possibly lethal side effects of the treatment with TKIs although there are not many studies corroborating it. Other side effects reported in other regions are head, neck and facial edema (including palpebral edema), shortness of breath, oral lesions, xerostomia, epistaxis, nasopharyngitis, gastroesophageal reflux disease (GERD), and hoarseness (115).

Recently it was reported long-term side effects in patients with CML. Cardiopulmonary comorbidities are now impacting treatment choice in patients with malignancies because of the development of cardiovascular side effects. The mechanism to how this effect undergoes is yet to be confirmed (116–118). Imatinib, dasitinib and nilotinib are chosen as a first-line, while ponatinib and bonutinib are used in relapsed or intolerant patients (117). Patients treated for renal cell carcinoma (RCC) have also showed drug-induced hypertension while being treated with multikinase inhibitors (MKIs) sorafenib and sunitinib although this might occur due to the patient selection (106,119).

Since side effects can be caused by the not reaching of the molecule to the intended target, nanomedicine enables the distribution of the medicine to their original target in an adequate concentration without the loss of their volume or activity, therefore it can reduce the potential incidence of side effects and toxicity-related events and avoid acquired drug resistance. The combination of TKIs and nanomedicine should be explored in the future not only for therapeutics, but also for theragnostics - combining therapy and pharmacokinetic imaging *in situ* which enables long-term monitoring, consequently resulting in a reduction of occurrences adverse effect-related and improvement of treatment planning and prognostics (107).

In conclusion, we can assume that TKIs are generally a well-tolerated class (106).

3.5 Mechanisms of resistance

Most cancer patients have disease regression after using TKIs, but acquired resistance still remains a difficult challenge to overcome in cancer targeted therapy (120). TKIs have a variety of mechanisms for drug resistance. In this monograph we are just going to dig deeper into the ones that are most important to the theme in question.

The T790M mutation is of great importance because it is a mechanism that leads to acquired resistance in first- and second-generation EGFR-TKIs, and is found in 50%–60% of the cases (120,121) The T790 residue is found within the ATP-binding pocket of the EGF-RTK and therefore mutation in this residue will increase TKI resistance by increasing protein affinity for ATP, decreasing the effectiveness of TKIs. It is seen in most patients with NSCLC treated with erlotinib or gefitinib (121).

The amplification of the c-MET gene is related to 20% NSCLC patients with TKI resistance. MET is activated through the hepatocyte growth factor (HGF). The amplification of this gene will potentiate growth, survival, and invasion pathways via Src, PI3K, and RAS family members. Combination therapy with TKIs appears to be a promising method to conquer such resistance (120,121).

Amplification of ALK fusion gene copy number it is thought to be one of the resistance mechanisms to crizotinib and brigatinib. Giving a second-generation ALK inhibitor seems to be effective to overcome this problem. Epithelial-mesenchymal transition (EMT) appears to be correlated with this mechanism (122). EMT is a process characterized by the loss of epithelial cell junctions and the gain of mesenchymal markers, by loss of polarity and attachment to the basement membrane and gaining of ability to invade and migrate (120,123).

Other mutations have also been reported but at a lower frequency. Resistance mediated by non-genetic changes has also been described like the up-regulation of the insulin-like growth factor 1 receptor (IGF-1R), fibroblast growth factor receptor (FGFR), HGF, and the ligand for MET (121).

The IGF-1R overexpression is present in many tumours because it regulates cell growth, and it is involved in proto-oncogene activation and transcription. IGF-1R activates RAS/RAF/MAPK and PI3K signalling pathways. Activation of the IGF-1R leads to EGFR-TKI resistance by regulation of the metabolism, proliferation, and apoptosis of tumour cells by a continuing activation of the PI3K-AKT signalling pathway, consequently leading to AKT activation. The loss of the tumour supressing gene PTEN can also promote AKT activation which will

eventually lead to tumour activation and cell survival. Inhibiting the IGF-1R seems to the delay the EGFR-TKI resistance. The AKT signalling pathway is frequently associated with acquired resistance to EGFR-TKI treatment in NSCLC activating other resistance mechanisms spoken before (120,124).

Point and rare mutations are a problem that needs to be addressed in the future specially regarding the EGFR because of their ability to provoke variable clinical response in patients and induce resistance. Evaluating the existence of this mutations in other receptors is urgent, and develop new therapies to address this mutations is absolutely necessary (125).

A simplified scheme of the pathways described above can be found in Figure 6.

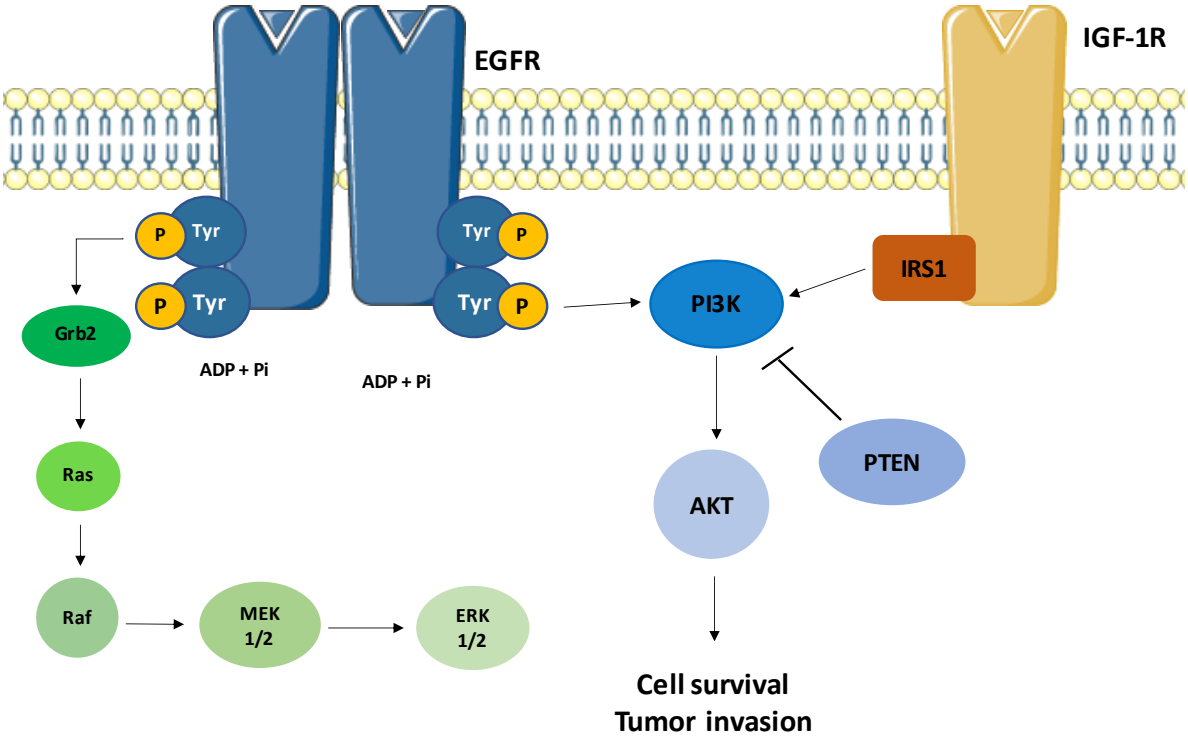

Figure 6 Simplified scheme of the IGF-1R pathway and its link to the EGFR pathway causing resistance. This figure was made using elements from https://smart.servier.com/

4 Therapeutic value of TKIs in neurooncology

4.1 Dacomitinib, cabozantinib and regorafenib in primary and recurrent glioblastoma

4.1.1 Dacomatinib

Dacomitinib (Vizimpro®) is a second-generation irreversible TKI targeting the EGFR, Human epidermal growth factor 2 (HER2) and HER4. It can also be called a pan-HER TKI. The EGFR is one of the most promising targets, because it is mutated and/or overexpressed in nearly half of the GBs (126,127). Dacomitinib is used to treat patients with NSCLC in a late stage or advanced disease (127), and when in comparison with gefitinib it showed improvements on progression-free survival of patients with NSCLC EGFR-positive (128). Studies show that dacomitinib significantly reduced the phosphorylation of EGFR and the GB cell progression and survival, also being able to inhibit the growth of GB cells that expressed EGFR mutations *in vitro* (129). A study performed in January 2021 confirmed that, despite most patients did not benefit with the treatment with dacomitinib, several individuals had a meaningful clinical response, meaning dacomitinib has the ability to penetrate through the GB tissue. (130). Another phase II trial performed in 2017 showed that as a single-agent, dacomitinib has a limited response in recurrent glioblastoma with EGFR-amplifications (131). More studies need to be performed in order to identify biomarkers that indicate if patients will respond to this medicine or not, a study in particular indicated the RNA signature in extracellular vesicles might be a good option (130).

4.1.2 Cabozantinib

Cabozantinib (Cometriq®) is an orphan medicine. It means it was developed for a small number of individuals that have a rare disease, life-threatening or chronically debilitating, and it was probably developed with the help of financial incentives. It was approved by the EMA in 2014 for the treatment of medullary thyroid cancer, originated in the calcitonin-producing cells, and it is used in non-resettable cancer that has metastasized to other parts of the body (132). This medicine is taken orally and is a VEGFR2, MET, and AXL-TKI. A clinical trial performed in 2018 showed evidence of cabozantinib significantly improving the overall survival of patients with recurrent GB (133). Another trial that happened in 2018 indicated that cabozantinib was linked to a clinical response in patients with recurrent GB who were naive for the antiangiogenic-therapy. In this trial the clinical targets weren´t achieved, but side effects were

reversed by adjusting doses, specifically reducing them (134). Cabozantinib also showed evidence of being effective combined with other therapies. A trial performed in 2016 indicated that administering 40 mg of cabozantinib daily with radiotherapy and temozolomide, and post-radiotherapy with temozolomide in HGG recently diagnosed was generally well-tolerated, and no significant pharmacokinetic interactions with temozolomide were reported. Since the acquired resistance to EGFR-TKIS has become a significant issue and given the fact that MET, VEGFR2 and VEGFR1 are elevated in GB, cabozantinib should be considered as a treatment option for these patients in the future (135).

4.1.3 Regorafenib

Regorafenib (Stivarga®) is an MKI used for the treatment of metastatic colorectal cancer, gastrointestinal stromal tumours and hepatocellular cancer (136). GB multiforme is the most aggressive type of primary CNS tumour in central nervous, and it is frequently associated with poor prognosis and unfavourable treatment outcomes, presenting high risk of progression and/or recurrence. A case report dated this year reported a great response to treatment with regorafenib, during three months, in a patient with GB multiforme with rapid progression after completing the treatment with radio-chemotherapy with only one cycle of adjuvant temozolomide (137). According to a study performed in 2020, regorafenib is capable of inducing autophagy in glioblastoma cells by inducing growth arrest on GB multiforme cells by promoting autophagosome accumulation through blocking of the autophagosome-lysosome fusion, showing better efficacy than the first-line treatment, temozolomide (138). A retrospective bicentric analysis made in 2019 acknowledged the treatment with regorafenib showed partial response with a progressive free survival of 2.1 months and the overall survival was 4.1 in the whole cohort. Dermatological side effects were present in only 30% of the patients compared to the ones treated with lomustine in the REGOMA trial, which also included patients in an earlier stage of the disease and was associated with more favourable clinical outcomes. This concludes that due to the lack of effective treatments for malignant glioma, regorafenib might be an option for treatment but not a very effective one (139). Regorafenib also did not prove to be an effective treatment for high grade astrocytoma (140). More studies are needed to define the role of regorafenib in glioblastoma (139)

4.2 Ponatinib for the treatment of neuroblastoma

Ponatinib (Iclusig®) is a MKI indicated as a third-line treatment for CML patients, in particular the ones that develop the gatekeeper mutation T315I, which promotes resistance against the

first- and second-line drugs imatinib, nilotinib, dasatinib and bosutinib (141,142). Ponatinib was initially reported as a potent, orally bioavailable MKI active against the breaking point cluster receptor (BCR) - ABL mutants therefore it become indicated for the treatment of CML. It was reported to inhibit Src and members of the VEGFR and PDGFR families of RTKs (143). Abnormal activity in tyrosine kinases has been reported in the development of NB and recent studies have shown that ponatinib inhibits cell multiplication and promotes apoptosis in NB cells in a dose dependent manner by blocking FGFR1 PI3K/AKT/mTOR and JAK/STAT3 signal pathways. Although some authors believe that ponatinib has antiangiogenic effect in NB and inhibits different tyrosine kinases, they weren´t able to mark them as part of a precise mechanism of action (144,145). These findings acknowledge the effects of ponatinib in NB cells and referred to them as a good onset for using small molecule inhibitors as treatment strategy for patients with NB (144). This medicine is subjected to additional monitoring and it was designated orphan medicine (141).

4.3 Foretinib for the treatment of sonic hedgehog medulloblastoma

MB SHH is the most well documented subtype of MB, an embryonal tumour of the brain (146). Foretinib is an orally bioavailable MKI that targets c-MET and has demonstrated having an antitumor activity in preclinical models of a number of cancer types (147) one of them being MB SHH since c-MET and PDGFRβ are highly expressed in this tumour (147,148). Fresh studies also demonstrated that foretinib has the advantage of being able to cross the BBB on its own and that it can be used safely in intrathecal therapy, inducing tumour regression and treating established metastasis (147). However, there have been reports of foretinib acquired resistance by pathways involved in the metabolism of proteins, specifically in the ubiquitin-mediated protein degradation, in primary tumour sites (148).

4.4 Gefitinib, Crizotinib, Brigatinib and Afatinib in NSCLC´s brain metastasis

4.4.1 Gefitinib

Gefitinib (Iressa®) is a medicine with oral bioavailability and is a reversible EGFR-TKI (109). It is approved for the treatment of metastatic and non-metastatic NSCLC with active mutation on EGFR (149). Some retrospective studies showed patients with BM could benefit from gefitinib, however the concentrations on CSF were not high, this medicine being an active substrate of P-gp, limiting its active penetration through the BBB (150). One way to overcome this problem might be coming up with strategies to inhibit P-gp/BCRP in patients to improve

delivery to the brain (151). There is no standard treatment to achieve total remission of NSCLC brain metastases, however recent studies have shown the therapeutic benefit can be boosted by adding a second form of treatment (152,153). Studies have shown that using WBRT in crescent doses can help disrupt the BBB and help gefitinib to penetrate (153). A meta-analysis concluded the use of gefitinib/erlotinib with WBRT can have better results than WBRT alone and well tolerated (154) however erlotinib proved not to have a significant added benefit despite being safe for patients to take being its use merely investigational, however more studies need to be done on the matter (155,156). Another problem is the appearance of acquired resistance. Chemotherapy and EGFR-TKIs are thought to act synergistically by inducing apoptosis and suppressing Aky and extracellular signal–regulated kinase phosphorylation, which may delay the appearance of acquired resistance. Clinical trials demonstrated that there were benefits in adding pemetrexed and carboplatin to the treatment of gefitinib but it may also increase toxicity, namely nephrotoxicity and myelosuppression (152).

4.4.2 Crizotinib

The first EGFR-TKIs like gefitinib were approved for use in NSCLC prior to the knowledge of activating EGFR mutations. After the discovery of this mutations, the clinical utility of EGFR-TKIs was optimized opening a new era of molecular therapy in NSCLC. After this the ALK rearrangement was reported in 2007 in NSCLC, and simultaneously crizotinib entered phase I of clinical development as a MET inhibitor (157). Crizotinib (Xalkori®) is a MKI with activity against ROS1, MET and ALK approved by the EMA in 2012 for NSCLC ALK-positive and ROS1-positive, because it increases life quality on patients with ALK rearrangement without the disease getting worse and it is the only treatment available for ROS1-positive patients (158,159). It was demonstrated that patients who have BM derived from NSCLC show improvement while being treated with crizotinib but patients that exhibit intracranial progression might not benefit from continued treatment (160). Progression of pre-existing/developing intracranial lesions might be related to acquired resistance to crizotinib (158). New molecules have been developed in order to overcome the problem of acquired resistance like ceritinib (161) and brigatinib (162). This medicine also presents low penetration through the BBB, so WBRT and crizotinib combined treatment might be a solution but more investigation is required to see the mechanisms involved (163). This is a well-tolerated medicine with mild to rare side effects like transient visual disorders, gastrointestinal toxicities, fatigue, rare alanine transaminase elevations, and even rarer pneumonitis (1.6%) and

confirmatory studies of the benefits of combining chemotherapy with crizotinib are still ongoing (157).

4.4.3 Brigatinib

Brigatinib (Alunbrig®) is a second-generation MKI, much like crizotinib, with an activity against ALK, ROS1, IGF-1, FLT3 and EGFR deletion and point mutations, and it is indicated for the treatment of NSCLC in patients that have never received treatment with an ALK-TKI or previous treatment with crizotinib (162,164). Brigatinib has shown good results, compared to the ones treated with crizotinib, and it was even demonstrated that it can outperform the latter on patients ALK-TKI-naive (162,165), which is explained by the increased penetration of the BBB that brigatinib has over crizotinib, allowing it to have an enhanced activity against BMs and leptomeningeal disease (166). Emergent and highly resistant G1202R mutation is common and is present in 21%, 29% and 43% of patients according to a study performed in 2019, in cases where resistance to ceritinib, alectinib and brigatinib, was acknowledged, respectively. This medicine is taken orally, and low doses should be given to patients with liver or kidney impairment toxicities. While visual and gastrointestinal/ hepatic toxicities are associated with crizotinib and ceretinib respectively, pulmonary complications are more associated with brigatinib which are serious and dose-limiting side effects (164,167).

4.4.4 Afatinib

Afatinib (Giotrif®) was approved by the EMA in 2013 for the treatment of patients with NSCLC, EGFR-mutated, in an advanced stage of the disease when no other treatments with TKIs have been applied or when the cancer is of the squamous cell type but does not respond to platinum-based regimens (168). A multicentred observational study based on real world evidence demonstrated that administering afatinib as a first-line treatment for patients with EGFR positive NSCLC improves long-term survival and has added clinical benefit, with attainable management of side effects (169). Side effects are correlated with the dose given which may have an impact on the intra and extracranial activity of afatinib (170). A retrospective multicentred study was able to demonstrate that dose reduction does not seem to have an impact in managing the CNS disease when afatinib was administered alone or with other treatments (171). In 2020 it was approved the start of a paediatric investigational plan for afatinib regarding the treatment of CNS tumours and other malignant neoplasms of the lymphoid tissue and the haematopoietic tissue (172).

4.5 Osimertinib: Treating leptomeningeal metastases in NSCLC

Osimertinib (Tagrisso®) was approved by the EMA in 2016 as a first-line treatment of patients with metastatic NSCLC. It is an irreversible third generation TKI for when patients present mutations on the EGFR exons 19 or 21 L858R. Patients with these mutations have very limited treatment options. In patients who have the T790M mutation the medicine can be given after other treatments (174,175). It is administered orally once a day until disease progression or unacceptable toxicity, with or without food (175). Leptomeningeal metastases occur when there is an aggressive spread of tumour cells to the CSF and leptomeninges alongside the invasion of the subarachnoid space (176). Despite other therapeutic options like stereotactic radiosurgery, WBRT or intrathecal chemotherapy are indicated for multiple or singular brain metastases, they are not associated with better prognosis (176,177). Studies show this medicine efficiently crosses the BBB regardless of the T790M mutational status so one of the advantages of this medicine is that it can be given after patients have acquired resistance to other TKIs and that is more effective than other current alternatives like erlotinib, afatinib, gefitinib, or dacomitinib (178). The most common side effects of osimertinib are diarrhoea, rash and itching, stomatitis and decreased platelets and white blood cells (174,179). This medicine was subjected to accelerated assessment and it is under additional monitoring (174). Patients should look out for the identified risks like the appearance of intestinal lung disease (IDL), cardiac failure and Stevens-Johnson syndrome (179,180).

4.6 TKIs in the treatment of brain metastases from breast cancer and melanoma

Breast cancer is one of the neoplasms that spreads most to the brain after lung cancer. According to a retrospective study performed in 2019 there is a 25% chance of people with advanced breast cancer developing BM, occurring nearly 2-3 years after the initial diagnosis (181). The most frequent kinds of breast cancer brain metastases (BCBM) are brain parenchymal metastases, intracranial dural metastasis and leptomeningeal carcinomatosis (182). Treatments available for BCBMs consist in stereotactic radiosurgery, surgery with postoperative and preoperative radiation therapy, WBRT, and targeted treatment. The targeted treatment available is based on trastuzumab containing regimens, which diversify between using trastuzumab alone or in combination with pemetrexed, pertuzumab or another taxane, trastuzumab emtansine, and TKIs (183). Lapatinib (Tyverb ®), which was approved by EMA in 2008 is indicated for the treatment of HER2-positive breast cancer and it is a dual HER1 and HER2-TKI (183,184). It is

a small and lipophilic agent which makes it very easy to cross the BBB, however the concentrations of lapatinib in the CNS were variable from patient to patient, but when capecitabine was added the response rate increased (183,185). Tucatinib (Tukysa ®), is an HER2-TKI and an investigational medicine, pending approval, with low molecular weight and an increased effectiveness when compared to lapatinib and neratinib (186,187). It is indicated for the treatment of HER2-positive breast cancer in combination with trastuzumab and capecitabine because it improves overall survival despite having a prominent side effect, diarrhoea (187,188).

The treatment of melanoma brain metastases (MBM) is arguable and consists in surgical and/or stereotactic radiosurgery, and WBRT (189). Overall survival for these patients, if they do not receive treatment, is approximately three months (190). Advances in the genomic field in the last few years have led to the identification of melanoma exclusive mutations, for example, neuroblastoma RAS viral oncogene homolog and v-Raf murine sarcoma viral oncogene homolog B, enabling the development of mutation-targeting agents (190). In cutaneous melanoma, arising in non-chronically sun-damaged skin, mutations generally occur in the tyrosine kinase BRAF, in melanoma arising from chronically sun-damaged skin, KIT mutations are more frequent. A retrospective study performed between 2006 and 2015 of gene mutations in 823 patients with MBM shows that BRAF-positive patients survive longer than BRAF-negative patients after diagnosis (191). Novel agents have revolutionized the treatment of MBM, increasing patients overall-survival and long-term survival (189). The management of MBM continues to evolve, but novelties are based in immunotherapy, despite the CNS being an immune-privileged site. Combination therapy with other techniques can overcome this problem (192). TKIs have shown impressive clinical responses in advanced melanoma, however, they display a long range of side effects (191). Vemurafenib is a medicine active against BRAF-mutant intracranial metastatic melanoma (193) and it seems to stabilize the disease but its role in preventing brain metastasis from appearing is controversial (194).

5 BTK inhibitors and other future perspectives

Regarding neurooncology in general, the COVID-19 pandemic has affected clinicians all over the world and the way treatment is administered to patients. During the COVID- 19 pandemic, we should explore if delaying repeat scanning, and outpatient visits in patients in stable conditions who are asymptomatic can be used in the clinician's advantage. Patients with brain tumours who have acquired COVID-19 infection will become a new challenge for neurooncologists. Symptomatic patients with COVID-19, will probably withhold any systemic chemotherapy, unless entirely non-immunosuppressive, for a question of prudency, and to evaluate the need for steroids until patients have fully recovered from COVID-19. Postponing resection or biopsy of primary brain tumours with stable neurological symptoms should also be considered as the use of hypo-fractionated radiotherapy in situations where it will not compromise the clinical outcomes and patient survival. The most complicated situation is the one of patients with brain tumours that tested positive for COVID-19 but are asymptomatic. A careful evaluation of risk and benefit is necessary, and moderate delays of systemic chemotherapy may be a preferred option (195).

TKIs that were already used before in other pathologies are starting to show their relevance when it comes to brain tumours (18,196). The BTK is a central piece in the B cell receptor signalling pathway that plays a role in B cell maturation, differentiation, and proliferation. BTK inhibitors are used in the treatment of B cell lymphomas (197), including mantle cell lymphoma, chronic lymphocytic leukaemia and Waldenström's macroglobulinemia (198), but since the expression of BTK was observed in solid tumours, its involvement is under investigation which led to the beginning of early phase I/II clinical trials in which monotherapy with BTK inhibitors are evaluated in advanced ovarian, colorectal, prostate and brain cancer patients (199). Ibrutinib (Imbruvica®) is a BTK inhibitor which irreversibly and selectively binds to BTK, preventing the maturation and proliferation of B cells when administered once a day. It intervenes in the BCR signalling and NF-κB signalling (down-regulation), in order to rapidly increase apoptosis (198,200). Ibrutinib has delivered good results in patients with primary CNS lymphoma exhibiting a 94% clinical response when administered alone, 83% showing partial remission of the disease (201). Clinical trials have shown that ibrutinib might be an option for patients who won´t respond to methotrexate (MTX), which is the gold-standard treatment for this disease, despite the high incidence of fungal infections especially when combined with different

chemotherapy regimens (202). Ibrutinib also exhibited an antitumor effect inducing autophagy via Akt/mTOR signalling pathway in GB cells (200).

Ruxolitinib (Jakavi®) is an inhibitor of JAK1 and JAK2 and it is used to treat myeloproliferative disorders, namely myelofibrosis, and polycythaemia vera in adults who are resistant or do not respond to the treatment with hydroxyurea (203,204). Recent studies have shown ruxolitinib can be used for the treatment of solid tumours like breast, lung, ovarian and brain tumours. The JAKs phosphorylate the signal transducers and activators of transcription (STAT) transcription factors present on tyrosine residues, promoting STAT dimerization and resulting in a downstream activation of various target genes which are also expressed in response to interferon gamma (IFN-γ) and interferon alpha (IFN-α). Mutated forms of JAKs can cause constitutive activation of the STATs transcription factors that promote a malignant phenotype. Studies have shown by inhibiting the JAK/STAT signalling pathway, through targeting the IFN-α and IFN-γ, it is possible to inhibit the activation of genes correlated to glioma invasion. More studies need to be conducted on the matter (204,205).

CAR-T cells (Yescarta®) is an unprecedented medicine and a sort of adoptive cell therapy used for immunotherapy. Approved by the EMA in 2018 for the treatment of follicular and diffuse B cell lymphoma (206) it has shown promise in treating several paediatric brain tumours despite this trials being in a very early stage. Current obstacles that need addressing for this therapy are finding the best way of delivery, overcoming the tumour microenvironment heterogeneity and developing different targets to increase efficacy (207).

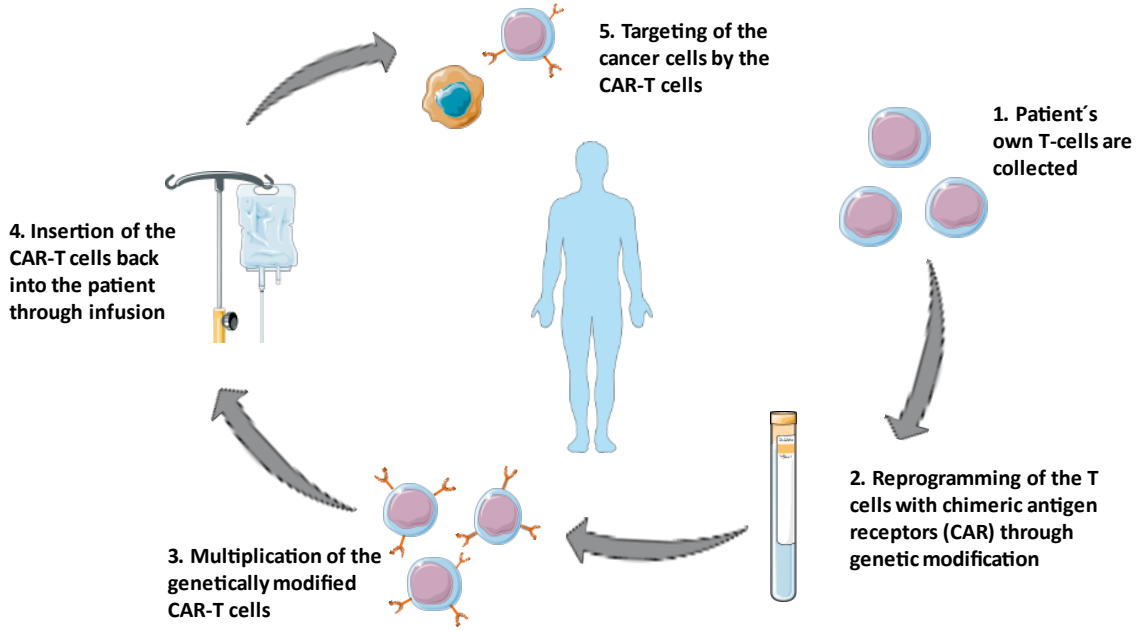

Figure 7 Simplified scheme of CAR-T cells immunotherapy. Ref: Adapted from Baylor, Scott &White Health Medical Professionals, accessed on May 23. This image was designed with elements from https://smart.servier.com/.

New TKIs have proven to deliver promising outcomes in the treatment of numerous brain tumours (208). Lorlatinib has raised the attention of investigators because of its efficacy against both systemic and intracranial lesions in preclinical and phase I/II studies regarding ALK-positive NSCLC (209).The NTRK gene suffers chromosomal rearrangements in a wide variety of solid tumours including NSCLC (210). NTRK inhibitors entrectinib and larotrectinib were approved by EMA in 2020 and 2019 respectively for the treatment of solid tumours NTRK gene fusion-positive (211,212). They have presented good results in phase I and phase I/II trials for the treatment of NSCLC brain metastases and primary brain tumours (213,214). NTRK gene fusions have been identified in a number of solid tumours including primary brain tumours and extracranial solid tumours (215). These chromosomal abnormalities lead to the expression of an oncogenic protein called the tropomyosin receptor protein (TRK) which is highly relevant (216).

6 Conclusion

Neurooncology is a recent discipline and has undergone rapid growth in recent years. The development of artificial intelligence and the incorporation of machine learning in diagnostics and therapeutic decision has increasingly allowed to arrive at a correct diagnosis, allowing the application of more targeted and more effective therapies.

The classification of tumours implemented by the WHO in 2016 is the one that is now in force, and that for the first time integrates molecular parameters in the classification of tumours. The development of these technologies and their application in therapy, including processes such as neurosurgery, can be decisive in the prognosis of these patients.

Treating a neurooncological disease represents a big challenge because often the resources, human and material, to perform an appropriate treatment are unavailable or non-existent. Access to the central nervous system is already structurally complicated due to the multiple barriers that make this microenvironment privileged as the existence of the blood-brain-barrier. Thus, therapeutic options are limited so it is necessary to carry out studies to understand the mechanisms that consolidate the blood-brain-barrier in order to find new effective therapeutic alternatives.

Kinase inhibitors have been used in the clinic in various pathologies for some time, such as diabetes and other types of cancer. The ones that are most used in therapy are tyrosine kinase inhibitors although new ones are now proving their relevance in clinic.

These medicines have already shown to be effective, however they have problems regarding the occurrence of side effects when the target is not reached. Another problem that has been reported is the acquired resistance to these inhibitors, making therapeutic success almost impossible. Thus, it is necessary to find delivery mechanisms at the site of action that allow the therapeutic action to the correct extent, but also to develop new alternatives and mechanisms to overcome the resistance problem.

Taking all of this into account, I believe that kinase inhibitors may become a very relevant therapeutic alternative in patients with tumours in the central nervous system, although further studies need to be carried out to ascertain their effectiveness, either in monotherapy or in combination with other methods.

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