Chapter 4

Complementary And Alternative Therapies in the Brain Tumors

Burcu Biltekin[1]

Abstract

The brain tumor remains mostly fatal, highlighting the need for innovative treatments despite improvements in the surgery, radiation, and chemotherapy. The blood-brain barrier, redundant molecular pathways, and genetic heterogeneity have all hampered the utility of molecularly targeted drugs. As an therapeutic option and to reduce the symptoms, the frequency of Complementary and alternative medicine (CAM) has been increasing in brain tumors. CAM is operationally defined as any practice that aims at cure or at obtaining similar effects as evidence-based medicine, but without scientific evidence and without clinical trial data to support efficacy and safety. Mostly used type of CAM was biological base therapies including the herbal, diet supplementary, vitamin and minerals. The factors affecting use of CAM are the duration/situation of disease, educational level and history of CAM usage in society. In this chapter, a summary of CAM used as a targeted therapy for patients with glioblastoma is presented along with information on in vivo and in vitro studies and potential future therapeutic approaches.

HISTORY OF COMPLEMENTARY AND ALTERNATIVE THERAPIES

The first step in traditional and complementary therapy started in 1977 with the decision under the title of "Development of Research and Education in the Field of Traditional Medicine" (Şen 2022). Afterwards "Medical Plants" was published in 1978, "Traditional Medicine" in 1987, "Traditional Medicine and Modern Health Services" between 1981-1991, "Traditional Medicine Research and Evaluation Methodologies Guide" in 2000, and "The Legal Status of Traditional Medicine/Alternative and Complementary

1 Istanbul Atlas University Faculty of Medicine, Department of Histology and Embryology, ORCID: 0000-0002-8435-6797, burcu.biltekin@atlas.edu.tr

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Medicine in the World" in 2001. Afterwards, "Traditional Medicine Strategy 2002-2005" was published by WHO and the "Beijing Declaration" in 2009 to promote the safe and effective use of traditional medicine (Muslumanoglu & Tayfun, 2019). The WHO Directorate-General requested that the "WHO Traditional Medicine Strategy 2002-2005", to be updated as "WHO Traditional Medicine Strategy 2014-2023", based on the assessment of the developments of countries and the current challenges. Through this strategy, it is aimed an appropriate integration of complementary and alternative therapies into health services, to regulate and control these therapies in a way that can be applied globally (WHO, 2013).

By the establishment of traditional and complementary practices in the health care system since the 20th century, the National Center for Complementary and Alternative Medicine (CAM) was established in 1998, affiliated to the United States National Institute of Health, in order to ensure their controlled use in the field of modern medicine. The first step in Turkey was taken by issuing the Acupuncture Treatment Regulation in 1991, and it was aimed to perform acupuncture with scientific methods (Lafçı & Kaşıkçı, 2014). Traditional, alternative and complementary medicine practices were first legally entered into our law with the Decree Law No. 663. The authority to execute, supervise and regulate traditional, alternative and complementary practices has been given to the General Directorate of Health Services (Talhaoğlu, 2021). The perception of the term alternative medicine as an alternative to modern medicine has caused the practices to not be included in a scientific platform. By making a regulation in the "Regulation on Traditional and Complementary Treatment Practices" published in the Official Gazette dated October 27, 2014 and numbered 29158, the phrase "Alternative medicine" was removed and the phrase "Traditional and complementary therapy Practices" became acceptable (Resmi Gazete, 2014).

DEFINITION OF COMPLEMENTARY AND ALTERNATIVE THERAPIES

Alternative medicine has been accepted by the public as a health service that replaces the medical treatment but is not accepted by the modern medicine. This treatment approach has been defined as all treatment practices that are not accepted by modern medicine (Tabish, 2008). The complementary medicine, on the other hand, includes the applications to support and strengthen the treatment, alleviate symptoms and improve the patient's quality of life in addition to medical treatment (Gilmour et al. 2011).

TYPES OF COMPLEMENTARY AND ALTERNATIVE TREATMENT PRACTICES

The types of CAM can be summarized under three broad titles according to the researches of The National Center for Complementary and Integrative Health (NCCIH):

1. Natural substances (medicinal plants, probiotics, etc.)
2. Mental and physical medicine (meditation, acupuncture, etc.)
3. Practices based on physical manipulation (massage, osteopathy, etc.)

Complementary and alternative treatment methods are handled in three main groups as cognitive-behavioral therapies and manipulative approaches, nutritional approaches and herbal approaches. Nutritional and herbal approaches have been mainly used in cancer patients (Le Rhun et al. 2019).

COMPLEMENTARY AND ALTERNATIVE THERAPIES IN CANCER PATIENTS

Cancer patients are frequently searching for CAM therapies in an effort to extend life and reduce negative effects of the disease or chemo- or radiotherapies (Lerner and Kennedy, 1992). CAM use in cancer patients has been reported between 9% and 83%, highlighting the variability in use among patients with cancer (Eisenberg et al. 1993; Bennett and Lengacher, 1999). Heterogeneity of cancer may be partially attributed to the variations in CAM use. The estimated percentage of CAM users showed a definite upward trend over time, rising from 25% in the 1970s and 1980s to more than 32% in the 1990s to 49% after 2000 (Horneber et al. 2012). 1471 cancer survivors reported using CAM at a rate of 66.5% in 2007 (Mao et al. 2011). In a different study, 29% of people was reported using CAM in Germany between 2014 and 2016 (Firkins et al. 2018).

Phytotherapy is used in the sense of treatment with plants today. Evidences for the safety and efficacy of plants in cancer treatment is limited. Since the doses used in cancer treatment are not standardized, care should be taken in terms of the side effects and interactions with cytotoxic drugs. Patients should use this treatment in accordance with the recommendations of their physicians. Herbal products that are frequently used in cancer treatment are turmeric (curcumin), green tea, ginger, pomegranate and garlic (Gullett et al. 2010). Naturally-occurring agents from these herbal products have received considerable attention for the prevention and treatment of cancers. These natural agents are safe and cost efficient in contrast to expensive chemotherapeutic agents, which may induce significant side effects. One of

these products, the pomegranate (Punica granatum L.) fruit exhibits strong antioxidant activity and is a rich source of anthocyanins, ellagitannins, and hydrolysable tannins. Studies have shown that the pomegranate fruit as well as its juice, extract, and oil exert anti-inflammatory, anti-proliferative, and anti-tumorigenic properties by modulating multiple signaling pathways, which suggest its use as a promising chemopreventive/chemotherapeutic agent (Sharma et al. 2017).

COMPLEMENTARY AND ALTERNATIVE THERAPIES IN BRAIN TUMORS

Primary brain tumors (PBTs) are frequently accompanied by neurologic complications and a poor prognosis, hence CAM use may be widespread in this population and all three CAM categories mentioned before were evaluated for their efficacy with an improvement in their quality of life. However, the exact risks and side effects have not been properly investigated in patients with PBTs (Armstrong et al. 2006).

The prognosis of PBTs varies according to the general and neurological conditions of the patients, WHO grade and molecular subtype, and the available treatments. Meningiomas and gliomas represent the most common PBTs in adults. 56.6% of all gliomas are glioblastomas, the most malignant type of glioma (WHO grade IV) (Ostrom et al. 2018). The median survival for glioblastoma patients ranges from 4 to 16 months in clinical investigations (Stupp et al. 2017; Weller et al. 2017), whereas at 12 months for the general population (Gramatzki et al. 2016). WHO grade II and grade III gliomas have a better prognosis with median survival times changing 5-13 years. Therefore, the cancer patients and family members may apply for CAM more frequently in this prognosis of severe disease and limited effectiveness of evidence-based medicine. It is likely that patients with glioblastoma feel more pressure to combat their cancer than those with less malignant tumors, as seen by the association between a diagnosis of glioblastoma and higher CAM use compared to patients with lower WHO grade gliomas (Le Rhun et al. 2019).

Several studies have shown that CAMs including the phytochemical compounds, such as phenolic acids extracted from fruits and vegetables, exhibit various cytotoxic and anti-proliferative effects as those of chemotherapeutics (Zhao et al. 2017; Lee et al. 2014; Yang et al. 2015). One of these compounds, a dietary polyphenol called ellagic acid (EA, 2,3,7,8-tetrahydroxy-chromeno; C14H6O8) is found in nuts and fruits including pomegranates and berries. In various mammalian tissues, EA

promotes anti-inflammatory activities and demonstrates antioxidant capacity, anti-fibrotic and chemopreventative effects (Seeram et al. 2005). EA has been identified as a potential neuroprotective agent, but there are not enough reports to determine whether and how EA acts to protect neurons in humans (de Oliveira 2016). EA exhibits anti-tumour pharmacological properties, such as inhibition of tumour formation and growth via cell cycle arrest, induction of apoptosis (Edderkaoui et al. 2008), and suppression of angiogenesis (Narayanan et al. 1999). EA was also shown to have successful in vitro therapeutic efficacy when combined with chemotherapeutics in glioma cell lines via inhibiting cadherin switch, angiogenesis, inhibition of O6-methylguanine DNA methyltransferase expression, time-dependent inhibition of P-glycoprotein (MDR1), activating apoptotic protein, p53 and caspase-3, expression (Çetin and Biltekin, 2019; Çetin et al. 2019; Cetin and Biltekin, 2020; Cetin et al. 2022). Clinical research is needed to prove the short-term and long-term efficacy and safety of ellagic acid in brain tumors.

Another herbal product, turmeric has an antiapoptotic effect in the treatment of cancer patients. The turmeric also shows an antioxidant effect via the phenolic acid compounds it contains, and a cytostatic effect via its oxygenated aromatic structures. A major polyphenolic compound of turmeric, named curcumin or diferuloylmethane, was shown to eliminate cancer cells derived from a variety of peripheral tissues. Oral delivery of this food component has been less effective because of its low solubility in water. A soluble formulation of curcumin crosses the blood–brain barrier but does not suppress normal brain cell viability. In vitro and in vivo studies indicated that solubilized curcumin effectively blocks brain tumor formation and also eliminates brain tumor cells by activating proapoptotic enzymes caspase 3/7, by suppressing Cyclin D1, P-NF-kB, BclXL, P-Akt, and VEGF, all of which blocks proliferation, survival and invasion of cancer cells (Purkauastha et al. 2009). Turmeric is recommended to be used with caution as it may cause bleeding disorders (Toptaş, Ateş, & Alagöz, 2017).

Green tea produced from the leaves of the *Camellia sinensis* plant contains several phenolic compounds including phenolic acid, catechin, etc. (İpek et al, 2021). In studies, the protective effect of catechins against cancer is explained by mechanisms such as inhibiting cell proliferation, ceasing the cell cycle, suppressing active receptors, reducing the release of cytokines, suppressing mitotic stimuli, preventing mutagenicity and genotoxicity, activating detoxification enzymes and accelerating apoptosis of cancer cells (Hazafa et al. 2020). In case of overdose, symptoms such as nausea, insomnia, diarrhea, confusion can be observed. It increases cognitive performance, provides mental alertness, shows weight loss and diuretic effect. It reduces

the effect of warfarin with the effect of vitamin K it contains (Cheng, 2007). Green tea is rich in non-oxidized catechins among which epigallocatechin-3-gallate (EGCG) stands out as the most abundant and active ingredients (Yang et al. 2011). Chemotherapeutic drug combined with EGCG was shown to sensitize the glioblastoma cells to temozolomide by increasing the apoptosis, reducing tumor growth and decreasing the expression of GRP78, which is over-expressed in chemoresistant cancer cells (Chen et al. 2011).

Ginger is a tuberous plant that grows 15-25 cm under the soil and reaches 1.5 meters in height. It is widely used in the traditional treatment of nausea-vomiting and colds. Studies have proven that gingerol and chagoal in its content inhibit the growth of cancer cells, sensitize cancerous cells by halting the cell cycle, and have antimetastatic and anti-invasive activities by targeting the signaling pathways of different cells. In addition, nausea-vomiting, which is one of the most common symptoms of cancer treatments, has been shown to have an antiemetic effect in the use of ginger. In excessive consumption, it can lead to bleeding disorders by reducing the platelet value in the blood (Bayraktar, 2021). A natural product Zerumbone, which is a ginger sesquiterpenoid phytochemical have antimetastatic effects on glioblastoma by reducing matrix metalloproteinase (MMP)-2/-9 expression, downregulating the mRNA experission level of IL-1β and MCP-1, two genes contributing to MMPs expression, inhibiting expression of Akt and total p44/42 MAPK (Erk1/Erk2), all of which have roles in repression of migration, invasion, and metastasis (Jalili-Nik et al. 2021).

CONCLUSION

CAMs are frequently used by the patients with brain tumors. Underlying needs and expectations, as well as potential interactions with tumor-specific treatments, and financial and quality of life burden, should be discussed with patients and caregivers. More research into the possible therapeutic and/or toxicological effects of CAMs on brain tumors would be necessary to fully comprehend the circumstances under which these CAMS may be safely used by people as a neuroprotective drug.

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Chapter 5

Molecular Therapeutic Approach to the Head and Neck Carcinoma

Fatih Mutlu[1]

Abstract

Head and neck cancers, the 6th most common cancer worldwide, are genetically complex. Tobacco, alcohol and HPV are the main risk factors. Due to its complex formation mechanisms, there are difficulties in its treatment. Despite chemotherapy, radiotherapy and immunotherapy, no significant progress has been made in terms of disease-free survival, quality of life, recurrence and distant metastasis. For this reason, studies on effective targeted therapies for developmental pathways continue both experimentally and clinically.

There are many studies on classical targets like Phosphatidyl inositol 3-kinase/ Protein kinase B/ mammalian Target of Rapamycin pathway, Epidermal Growth Factor Receptor signaling, Vascular Endothelial Growth Factor Receptor signaling, Fibroblast Growth Factor Receptor signaling, and Mitogen Activated Protein Kinase/Extracellular Signal Regulatory Kinase signaling. Cetuximab, pembrolizumab and nivolumab have been approved and are among the molecules used in the clinic.

Beside classical targets, there are new studies on Hepatocyte Growth Factor signaling, Cyclin Dependent Kinase 4/6 inhibitor and Notch signaling.

It is estimated that the new molecules, which are expected to have less side-effect profiles compared to other treatment modalities, can be used either alone or in addition to the existing treatment. Reducing resistance to radiotherapy and reducing the serious side effects of chemotherapy are among the expected targets.

Although one of the goals of targeted therapies is to limit side effects to more specific effects, they can also create serious non-target side effects that can lead to treatment failure.

1 Kocaeli Üniversitesi Tıp Fakültesi, KBB AD, ORCID: 0000-0003-4831-9582, drfatihmutlu@gmail.com

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The increasing number of new patients, the inability to achieve significant success in treatments and serious side effects necessitate new studies.

MOLECULAR THERAPEUTIC APPROACH TO THE HEAD AND NECK CARCINOMA

Head and neck carcinoma is reported as the 6th most frequent cancer all over the world in 2020. Expected number of new cases in 2030 is increasing to 1.08 million. Squamous cell carcinoma is the leading pathologic type (~90%). The etiological agents are tobacco, alcohol and HPV. The majority of cause is tobacco and alcohol in oral cavity and larynx. HPV frequency is increasing by the time especially in oropharynx. Another etiological agent in head and neck carcinoma is the Epstein-Barr virus, the cause of nasopharyngeal carcinoma.

Treatment based on the stage of the carcinoma. Surgery, radiotherapy, chemotherapy, immunotherapy and targeted therapy are the options. The side effects, the poor quality of life, and the poor outcomes of the treatment modalities make scientists to search new targeted molecules. This chapter includes the historical options and the novel strategies for head and neck carcinoma. Every part includes pathway, in vivo studies and clinical studies.

EGFR

Epidermal Growth Factor Receptor (EGFR) is a transmembrane protein and a cell surface receptor. EGFR intracellular signaling cascades stimulates of proliferation of cell, angiogenesis, cell migration and metastasis. EGFR over expression is a adverse prognostic factor for head and neck squamos cell carcinoma. Amphiregulin and TGF- α production due to tobacco stimulates a complex activation of EGFR cascade. JAK/STAT, PI3K/AKT, MAPK, PLCγ/PKC, and Src pathways are downstreaming signaling cascades.

FDA approved only Cetuximab for the head and neck squamous cell carcinoma in 2006. Cetuximab alone or combination with other EGFR inhibitors (gefitinib, erlotinib) provided more tumor regression, delayed recurrence. Cetuximab achieved partial or transient tumor regression and increase the radiotherapy effect. But Cetuximab plus radiotherapy showed poor adherence to treatment, increased toxicity in comparison with Cisplatin plus radiotherapy. Combining Cetuximab with induction chemotherapy results seems to be controversial in taxan, cisplatin, and 5-FU group. But Cetuximab, paclitaxel, and carboplatin regimen point more hopeful outputs.

Panitumumab did not showed any improvement in addition to chemoradiotherapy. Nimotuzumab had a better effect on locoregional control

and no more adverse effect beside increasing mucositis. Zalutumumab had more skin rash.

Gefitinib had a significant response rate for overall survival for local-advanced head and neck squamos cell carcinoma. Lapatinib monotherapy showed superiority to placebo, addition to chemoradiotherapy revealed safe and effective progression free survival in local-advanced head and neck squamous cell carcinoma. Erlotinib in monotherapy or combination studies pointed out favorable anti-tumor activity in recurrent or metastatic disease.

In vivo material CP-358,774 is a novel selective inhibitor of EGFR. The EGF mediated mitogenesis is inhibited. GW2016 and ZD6474 are inhibitors of EGFR tyrosine kinase. Vandetanib inhibited tumor volumes in mouse adenoid cystic carcinoma. Gefitinib inhibits cell growth and proliferation by EGFR inhibition. Dacomitinib inhibits tumor volume and also increased radiotherapy activity. AC480 with radiotherapy significantly reduce the tumor size.

PI3K/AKT/mTOR PATHWAY

The PI3K/Akt/mTOR pathway is a central signaling current system that plays a role in important events such as cell cycle, cell survival, protein production, growth, metabolism, and angiogenesis. HPV positive head and neck cancer had more mutation of this pathway. This signaling pathway is also responsible in nasopharyngeal carcinoma.

BYL719, the PI3K inhibitor, had a remarkable antitumor effect on head and neck squamous cell carcinoma. BKM120 is another PI3K inhibitor act with inthibiting cell proliferation in in vivo. Taselisib monotherapy had an effect in cell proliferation in cancer cells. It completely stops proliferation but not decreasing tumor mass. LY294002 and copanlisib (BAY 80-6946) are also studied in anticancer models.

Buparlisip with cetuximab and buparlisip with paclitaxel showed improvement in outcomes. Alpelisib is another ATP-competitive PI3K inhibitor showed better results in local-advanced head and neck squamous cell carcinoma.

Perifosine, an AKT inhibitor, acts with blocking cell cycle. MK-2206 with cisplatin and ipatasertib showed antitumor effects. But they had serious hyperglicemia and ulcerative keratitis. Capivasertib broke saracatinib insensitivity of head and neck squamous cell carcinoma cells.

Temsirolimus and RAD001, the mTOR inhibitors, studies reported anticancer effects, like tumor shrinkage by inhibiting cell proliferation.

CC223, OSI-027, AZD8055, and CZ415 are monotherapy agents studied in vivo recent times.

PF04691502 is the inhibitor of mTOR and PI3K both. It increased the radiosensitization of nonmetastatic head and neck squamous cell carcinoma.

VEGF PATHWAY

Vascular endothelial growth factor (VEGF) is a poor diagnostic criteria, expressed highly in head and neck carcinoma. VEGF is responsible for the angiogenesis.

Bevacizumab is studied in many type of cancer. It did not inhibit proliferation in head and neck squamous cell carcinoma but increase the effect of Cisplatin when added. Lenvatinib, the inhibitor of VEGFR and FGFR, showed a similar result with bevacizumab. AEE788, Apitinib, SCH772984 with apitinib, ONC201, linifanib, pazopanib, cabozantinib, PTK787/ZK 222584, motesanib, and axitinib had good results in vivo.

Sorafenib with cisplatin and 5-FU had better outcomes in reccurence/metastatic nasopharyngeal carcinoma. Sunitinib monotherapy had increased risk for hemorrhage and some clinical outputs in recurrent or metastatic head and neck squamous cell carcinoma.

FGFR PATHWAY

BGJ398 and PD173074 had significant effect on head and neck squamous cell carcinoma in vivo. AZD4547 increase the efficacy of radiotherapy.

HGF/MET PATHWAY

Hepatocyte growth factor receptor (c-MET) acts in EGFR inhibitor resistance and tumorigenesis. In head and neck cancers, overexpression is common.

BPI-9016 M plays role in radiosensitization and tumor growth. PF-2341066 with cisplatin and Capmatinib with pitavastatin had a synergistic effect in head and neck squamous cell carcinoma.TR1801-ADC, PF-2341066, cabozantinib, and PHA665752 had a promising results in head and neck carcinomas.

MAPK PATHWAY

The essential pathway of differentiation, angiogenesis, cell proliferation, metastasis and resistance to therapy is the mitogen activated protein kinase

(MAPK). In head and neck carcinoma mutations of this pathway (BRAF, HRAS, KRAS, and ERK) can be seen about eighteen percent.

U0126, trametinib, selumetinib, AZD6244, and PD-0325901 had hopeful results in head and neck squamous cell carcinoma in vivo.

p53/RETINOBLASTOMA (RB) PATHWAY

TP53 is a tumor suppressor gene. Its mutation mostly seen in head and neck carcinoma. Genomic stability and DNA repair are the issues of TP53. A member of p53, TP63, had overexpression in 80% of head and neck squamous cell carcinoma. This shows poor overall survival.

OTHER TARGETED THERAPIES

Inhibitor of indolamine 2,3-dioxygenase (IDO1), epacadostat, showed significant tumor efficacy with pembrolizumab. For the resistance overcoming of platinum and cetuximab, palbociclib, CDK 4/6 inhibitor, pointed out hopeful results. Dalantercept, ALK1 inhibitor, make a significant effect on recurrent or metastatic head and neck squamous cell carcinoma patients.

As a summary; the expected improvement could not be achieved in head and neck squamous cell carcinoma during past decades. Some molecules also intend to increase sensitivity of other drugs and radiotherapy to have a better disease control Targeted therapies aim to demonstrate good results with fewer side effects. But off-target severe side effects can cause treatment failure.

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