Review Article

An overview of targets and therapies for glioblastoma multiforme

Gayathri Chandrasekar[1], Vinay Scheel Bansal[2], Manas Panigrahi[3], Satish S Kitambi[1,2]

[1]Department of Microbiology, Tumor and Cell Biology, Karolinska Institutet, Solna, Sweden, [2]Department of Translational Sciences, Institute for Healthcare Education and Translational Sciences, Secunderabad, [3]Department of Neurosurgery, Krishna Institute of Medical Sciences, Hyderabad, Telengana, India

For correspondence: Prof. Satish S Kitambi, Institute for Healthcare Education and Translational Sciences, 10-2-311, Plot 187, Str4, Cama Manor, West Marredpally, Secunderabad - 500 026, Telengana, India.
E-mail: satish.kitambi@klife.info

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ABSTRACT

Glioblastoma multiforme (GBM) affects individuals above 65 years of age and has low median survival rate. Due to limited treatment options, lack of effective diagnosis, and palliative care, there is an urgent need to develop new therapeutic strategies to combat GBM. This review provides an overview of the current clinical trial scenario with a special focus on new targets, repurposed drugs, and technologies in the field of GBM. The use of technological advances and artificial intelligence in diagnosis and imaging is also discussed. In addition, this review also highlights the need to design a dynamic palliative care strategy for end-of-life management of patients with GBM.

KEY WORDS: Cancer, care, drug, glioblastoma, glioma, treatment

INTRODUCTION

Glioblastoma multiforme (GBM) is a tumor of neuroectodermal origin that constitutes for more than 50% of all glioma with a high incidence rate among individuals of age group of 65 years and above [Figure 1a].[1] In general, GBMs are classified into three categories, IDH-1 wild type, IDH-1 mutant, and unclassified NOS group. A low median survival rate, aggressive nature of the tumor, and lack of proper therapeutics make GBM a deadly disease.[1,2] Histology of GBM is routinely used to quantify various morphometric features in order to classify GBM, predict survival rate, and design therapeutic strategy.[1,2] Histology is useful to assess features such as number of cell undergoing mitosis [Figure 1b], the vasculature of tumor [Figure 1c], pseudopalisading structures [Figure 1d], and various marker gene expression such as GFAP, Oligo2, ATRX [Figure 1a-g]. In addition to histology, various molecular markers such as vascular endothelial growth factor (VEGF), platelet-derived growth factor receptor (PDGFR), phosphoinositide 3-kinase (PI3K), epidermal growth factor receptor (EGFR), and EphA3 are routinely used [Figure 2]. These molecular markers also help in developing therapeutic strategies in designing specific small molecules against these molecular targets [Figure 2].

CURRENT TREATMENTS AND CLINICAL TRIAL SCENARIO FOR GLIOBLASTOMA MULTIFORME

The standard therapy for GBM involves tumor mass removal using surgical resection, which is followed by radiotherapy and chemotherapy treatments. However, a high rate of relapse, resistance development of the cancer cells, and severe deterioration of the patients quality of life make such treatments ineffective.[3,4] Recent development of tumor-treating fields (TTFields), such as Optune™,[5,6] has effectively raised the median lifespan of GBM patients along with their quality of life. However, more therapeutic options needs to be created to effectively combat this disease and for developing various personalized medicine protocols. The current clinical trial scenario, as indicated in clinical trial database (www.clinicaltrial.gov), shows 493, 543, and 63 active or completed trials in Phase I, II, and III, respectively [Figure 3]. Various technological developments such as TTFields, laser interstitial thermal therapy, and Gamma Knife [Figure 3] are also being evaluated. Most of the trials are in Phases I and II studies and show that more than 80% of the trials fail to reach Phase III. Majority of clinical trials are done with small molecules while antibody-based treatment occupies small numbers only [Figure 3], suggesting that the pharmaceutical sector is focusing mainly on small molecules to combat GBM.

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EMERGING TARGETS FOR GLIOBLASTOMA MULTIFORME

Treatment of GBM presents unique challenges as access of therapeutics to the tumor site is a daunting task.[3-5] Common treatment protocol follows initial maximal tumor resection followed by radiation and chemotherapy to provide the patient maximum chance of progression-free survival.[4] The presence of blood–brain barrier hinders easy access to the brain and hampers entry of 98% of small molecules, especially the ones that are larger than 400 daltons.[7] A very high number of cases show tumor progression and reoccurrence despite the above treatment procedure as the disease rapidly develops resistance to radio- and chemotherapy.[5,8] Hence, identification of new targets and technological advances is warranted in order to facilitate the development of novel targeted therapies.

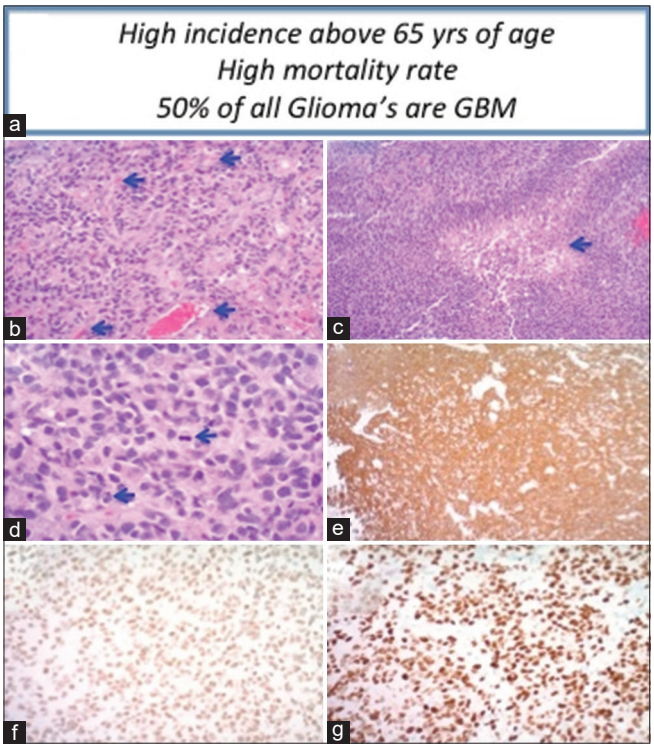

Figure 1: Modalities and histological features associated with glioblastoma multiforme. Modalities of glioblastoma multiforme (panel a), histological image panels show excessive vascularization (blue arrows in panel b), pseudopalisading structure (blue arrow in panel c), mitotic cells (blue arrow in panel d) and immunostaining with anti-GFAP, Oligo2 and ATX antibodies (panels e, f, and g respectively)

Various factors such as neoangiogenesis, tumor heterogeneity, site of tumor, and genetic and epi-genetic landscape of the tumor affect the prognosis of the patient and his or her response to therapy.[9-12] Large-scale analyses of GBM tumors have provided various key signaling pathways that are very important to tumor development, growth, resistance to therapeutics, and reoccurance. Molecular components belonging to three key pathways, the receptor tyrosine kinase (RTK)/Ras/PI3K, inhibition of p53, and retinoblastoma protein are found in almost 80% of GBM cases [Figure 2]. Therefore, a large part of the industries' initiatives in developing new GBM therapeutics are directed toward these three pathways [Figure 3].[12,13]

Several different RTKs such as PDGFR and PI3K have been explored as a single or combinatorial therapeutic strategy against GBM.[14] Amplification of PDGFRA is seen in more than 10% of GBM cases and is often co-expressed with EGFR.[15] Inhibitors of PDGFRA, imatinib, and sunitinib have been tried as monotherapy or in combination; however, they did not show improvement in overall progression-free survival.[16]

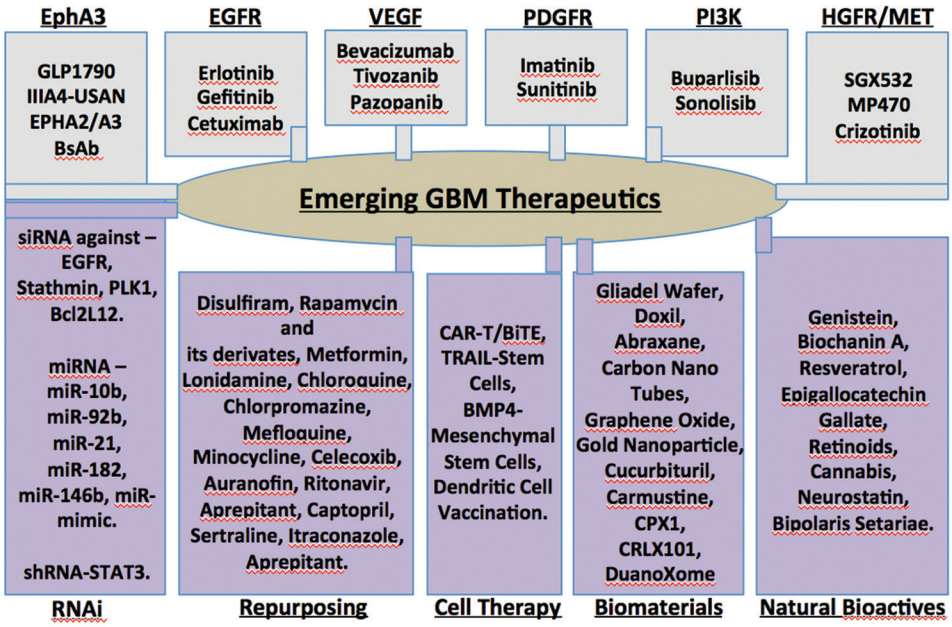

Figure 2: Emerging therapeutic targets for designing therapeutics against glioblastoma multiforme

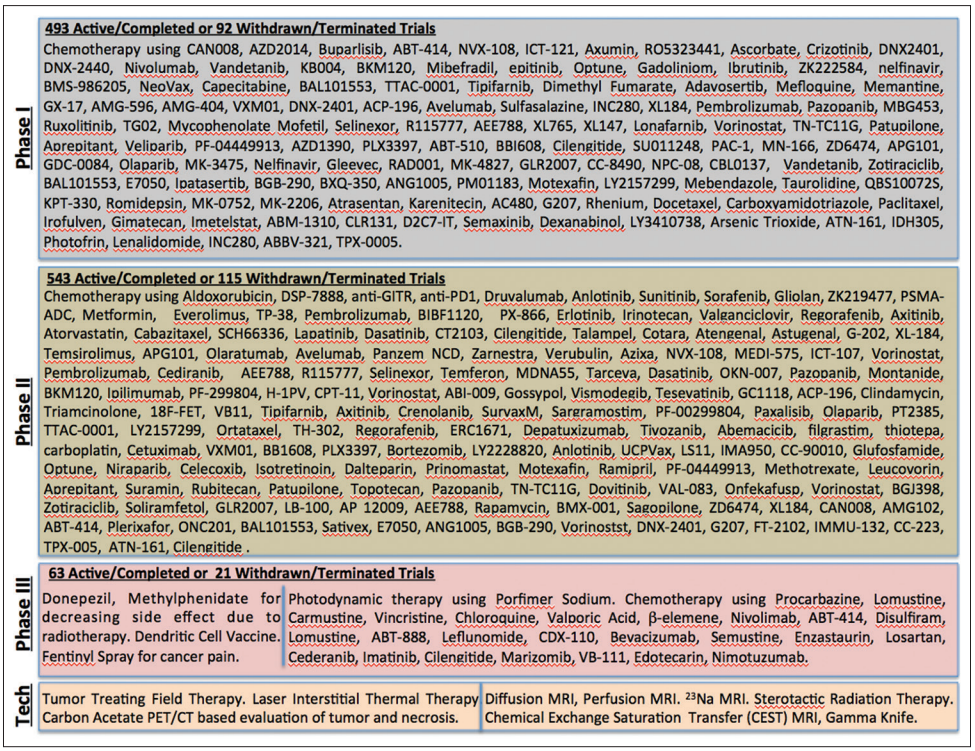

Figure 3: Clinical trial scenario of glioblastoma multiforme. Trials are divided into Phase I, II, III and technologies and data were obtained from US clinical trial registration database (www.clincaltrials.gov)

Various PI3K inhibitors have been developed, among them are buparlisib and sonolisib which showed promise in the preclinical stage; however, its efficacy in clinical settings has not been very impressive. However, due to implications of PI3K in various cancers, its tolerability and BBB penetrability has made it an interesting target for development of more variety of small molecules.[17,18]

The identification of stem-like cells has added a new dimension toward the complexity of this disease.[19] Analysis of such stem-like cells has identified EphA3 receptor to be overexpressed in close to 50% of recurrent GBM cases. Overexpression of this receptor has been demonstrated to be necessary to maintain stem-like state of GBM cells and is linked to tumourigenic potential of GBM cells.[20] EphA3 belongs to the ephrin receptor superfamily and plays an important role in the development of the nervous system. The overexpression of this receptor suggests that it could be a potential target to develop new therapeutics, especially targeting stem like undifferentiated GBM cells which has tumorigenic potential.[20] Efforts toward exploiting this receptor as a target have resulted in a small molecule GLPG1790, a monoclonal antibody that targets EphA3 globular ephrin-binding domain, and a bispecific antibody targeting EphA2/A3.[21] A chimeric antibody conjugated to maytansine (IIIA4-USAN) is also being tested.[22] These studies show the immense potential of targeting EphA3 in recurrent GBM cases.[20,21]

Another interesting receptor belonging to HER superfamily of RTKs is EGFR which are linked to poor prognosis and are typically found to be amplified or mutated in 40%–60% of GBM cases.[22,23] The overexpression or mutation of EGFR leads to an array of signaling cascades that are linked to enhance proliferation, angiogenesis, and inhibition of apoptosis. A variety of EGFR inhibitors have been developed and assessed preclinically and clinically, top performers among them are erlotinib, gefitinib, and lapatinib.[23] Erlotinib has shown promise in malignant GBM phenotypes and in cells that develop resistance to radiotherapy. Erlotinib has good efficacy in cells that in addition to overexpression of EGFR also express phosphatase and tensin homolog.[23] It also shows good efficacy when combined with temozolomide and radiotherapy. In contrast to erlotinib, gefitinib inhibits GBM cell migration and proliferation and exhibits antitumor activity irrespective of EGFR levels.[23] However, limited clinical effects and no survival benefits have been observed in several clinical studies when gefitinib was administered along with radiotherapy.[24] Efforts toward developing monoclonal antibody against EGFR has resulted in cetuximab which shows promise for treatment of patients with high-grade recurrent gliomas.[25]

Similar to EGFR, another target that shows high expression in GBM and is directly associated with poor prognosis, promotes proliferation, and angiogenesis is VEGF.[26] Activation of VEGF, especially in hypoxia conditions in tumor, increases angiogenesis and promotes cell proliferation. GBM tumors often have irregular vasculature and an overexpression of VEGF. Small molecule inhibitors such as tivozanib and pazopanib did not show promise as a monotherapy against GBM.

Monoclonal antibody therapy using bevacizumab produced a modest treatment response along with treatment-related adverse events, thereby discouraging its use in the treatment of GBM.[26,27]

Ligand of hepatocyte growth factor receptor (HGFR/MET) has been associated with poor prognosis in GBM patients.[28] An overexpression of this ligand is seen in a small percentage of patients and has been experimentally linked to tumor growth and angiogenesis. SGX-523, amuvatinib, and crizotinib are small molecules that have been developed against these targets and show promise in various preclinical studies for mono- or combinatorial therapy.[25]

Various phenotypic screening efforts in developing new approaches have been attempted,[29] and many targets that are not necessarily implicated in oncogenic transformation but enable the cells to proliferate have been identified. However, these efforts have not been translated into a successful clinical platform.[29,30]

Designing new therapies for GBM based on new targets is of utmost need, especially since this disease is very fatal. Although genomic mining and experimental studies have identified various new targets, clinical research indicates that patients might benefit with therapeutic designs that employ a combination of several targets.

DRUG REPOSITIONING FOR GLIOBLASTOMA MULTIFORME

Finding new use for existing drugs is an effective approach to reduce time and cost involved in drug discovery. Drug repurposing presents itself as safe, fast, and relatively inexpensive approach to GBM treatment. Success stories of repositioning new drugs can be seen with minoxidil, sildenafil, thalidomide, azidothymide, and many others [Figure 2].[31] Computational-based or activity-based repositioning of the drug are two approaches used routinely to identify drugs that can be repurposed.[31] In the computational repositioning approach, network algorithms mine datasets with information on drug-drug interaction, clinical data, molecular structure, catalytic and ligand binding sites, gene expression signatures, or side effects produced by drugs to regroup existing drugs for a new indication.[31] Many such freely accessible resource tools and databases such as GeneSigDB, MsigDB, DAVID, cMAP, PubMed, GEO, and array express are routinely used. Although this approach is cost-effective and quick, it still requires laboratory-based experimental confirmation before it is clinically validated. Activity-based approach is a more concrete approach as it relies on protein target-based screenings.[31]

Disulfiram, an ALDHI inhibitor used to treat alcohol abuse, was found to also inhibit known GBM targets like NK-Kb and MGMT which made it an interesting candidate for GBM therapy.[32] An antifungal drug rapamycin and its derivatives were also found to inhibit mTOR pathway which is also an interesting target to develop therapeutics against GBM.[33] Similarly, oral antidiabetic drug metformin was also found to inhibit AMPK and mTOR pathway in addition to other kinases such as SGK1, EGFR, which play a key role in GBM.[34] New insights into such mechanism of action allowed for lonidamine and chloroquine, which were earlier used to inhibit spermatogenesis and for malaria treatment, respectively, to be used for GBM treatment.[35] An antipsychotic agent chlorpromazine and other such dopamine receptor inhibitors have been found to inhibit KSP/Eg5 mitotic kinases which play a crucial role in cancer cell proliferation.[36] Clinical trials with these candidates have been very promising as either mono- or combinatorial therapy. Although there are clear advantages in drug repurposing, the lack of monetary incentives for redevelopment for new indication and patent issues have made drug repurposing an interesting alternate that could be exploited by mainstream pharmaceutical industry.

Various observational and epidemiological studies have indicated that many natural compounds and dietary compounds influence the development, progression, and metastasis of various cancer types. Investigative studies have shown that isoflavones, such as genistein, daidzein, and biochanin A, have potential properties to be used against treatment against GBM.[37] Polyphenolic compounds such as resveratrol and epigallocatechin gallate have been shown to be very effective against GBM in various preclinical studies. Naturally occurring retinoids have been found to enhance the efficacy of chemotherapy and radiotherapy in GBM. Other natural compounds such as cannabis and cannabinoids, neurostatin, and bipolaris setariae fungi-derived ophiobolin A have also produced promising preclinical results for treatment against GBM.[37]

TECHNOLOGICAL ADVANCES FOR GLIOBLASTOMA MULTIFORME IMAGING

Neuroimaging technologies for detecting the site, size, and shape of tumor play a crucial role in the initial diagnosis of GBM. Proper tumor visualization, delineation, and quantification are important for clinicians to plan surgical procedure, predict prognosis, and follow-up on treatment response.[38] Computed tomography or magnetic resonance imaging (MRI) are standard initial diagnostic approaches adopted for imaging where volumetric measurement was shown to be more accurate than one-dimensional (1D) or 2D measurements.[38] In addition, 3D acquisition instead of 2D MRI sequences reduces the variability relating to slice positioning dramatically. Tumor contrast enhancement was also achieved by T1 subtraction for better quantification with various commercial and open-source softwares. Advances in MRI imaging resulted in the development of diffusion and Perfusion MRI which could be effectively used to reflect the degree of malignancy and gauging response

to cytotoxic therapy and antiangiogenic therapy. With the development of many amino acid tracers, positron-emission tomography radiotracers have been effectively used to differentiate tumor growth from treatment-related changes. Techniques such as 23Na MRI and chemical exchange saturation transfer have shown promise for imaging in GBM.[38]

ARTIFICIAL INTELLIGENCE AND GLIOBLASTOMA MULTIFORME

Histological outcomes of tumor biopsy and the treatment design are done by the physician after manually curating observed datasets. However, this is time consuming and limited as the physician does not have access to a large number of datasets that allows him/her to make a more informed decision.[39] The advent of artificial intelligence (AI) has allowed the development of neural networking and deep learning algorithms that facilitates the extraction of salient features of vast clinical data that could be used to develop better diagnosis and treatment design.[39] The cloud-based AI computing done by IBM Watson for oncology has enabled physicians to integrate large amount of molecular/genetic, clinical, and imaging information into their treatment planning.[40] An integrated platform of AI and machine learning, such as OncoDynamiX (https://oncodynamix.com), already uses their proprietary multi-omics algorithm for drug discovery/development [Figure 4] and to predict cancer patients' response to specific drug treatment [Figure 5]. Various supervised and unsupervised learning algorithms are being developed for extensive use in neuroimaging of tumors to define its structure, location' and size/shape [Figure 5]. This not only allows a clinician to plan their surgical activities but also predict the grade, severity, automate histopathology, and clinical outcomes of the disease.[39,40] In addition, enhanced imaging programs allow clinicians to demarcate normal tissue, edema, and tumor region and predict site of recurrence.[39,40]

One such important application of AI in GBM is grading of the disease as it plays an important role in treatment planning and prognosis. Such machine learning-based grading techniques have been employed to identify features such as rim enhancement, hyperperfusion, and central necrosis that are often associated with Grade IV GBM when compared to other grades. Such algorithms employ a large number of images to make such predictions, hence are more accurate and reliable. In addition to grading, computational methods such as radiomics have been employed to predict genomic signatures such as IDH1 mutation, MGMT methylation in GBM, and deletion of a chromosomal arm. Such algorithms enable an analysis of gene expression and predict prognosis and treatment response.[40]

AI is increasingly used to simulate the simulation of patients' response post surgery and treatment. Such exercise allows to test various options of treatment regimens and its outcome, before selecting one that suits the patient. Such methodology allows for designing treatment and posttreatment follow-up and predicting survival outcomes.[39]

Major challenge of AI is that learning algorithms depends on the availability of large amount of standardized and annotated data sets. In addition, coordination and accumulation of a uniform dataset from multicenter clinical trials, clinician-AI interaction, and ethical and legal implications are challenges that need to be addressed to fully realize the power of AI for GBM therapy and care.[39,40]

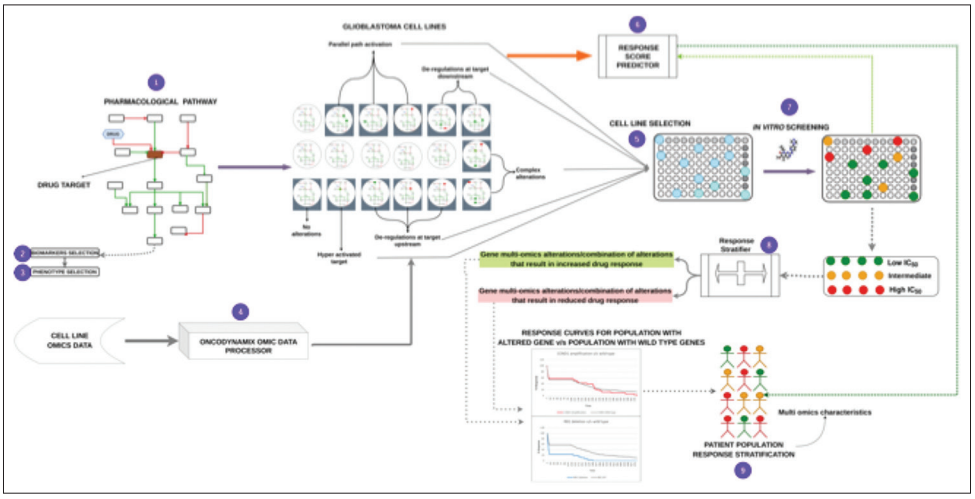

Figure 4: Applications of OncoDynamiX in drug discovery and development in oncology. The figure illustrates how OncoDynamiX can assist in selection of appropriate cancer cell lines and biomarkers in anti-cancer drug development in Glioblastoma. 1-5: Selection of glioblastoma cell lines representing alterations in pharmacological pathway, corresponding biomarkers, phenotypic endpoints integrated with multi-omics, 6: Prediction of response scores in cell lines and in patients, 7: Experimental verification of predictions, 8: Stratification of response of cell lines and patients to drug using multi-omics data, 9: Stratification of patients into responders and non-responders that enables selection of patients for showing successful treatment

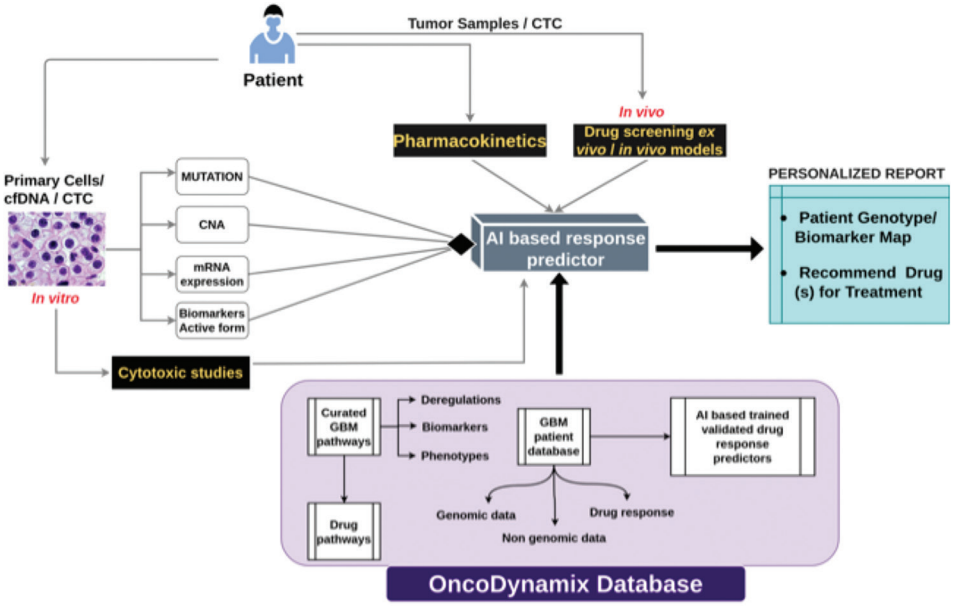

Figure 5: Applications of OncoDynamiX in personalized medicine in glioblastoma. The figure illustrates how OncoDynamiX can assist in identification of patients for personalized medicine in Glioblastoma. Samples from patients (cancer tumor cells, cell free tumor DNA, tumors, blood) are analyzed for gene alterations, multi-omics changes, pharmacokinetics, subjected to experimental assessments for anti-cancer activities in *in vitro* and *ex vivo* studies. The information generated from these studies is integrated with the OncoDynamiX glioblastoma patient data base and processed using artificial intelligence to generate patient specific report that has recommendations for drug or drug combinations to be used for the patient

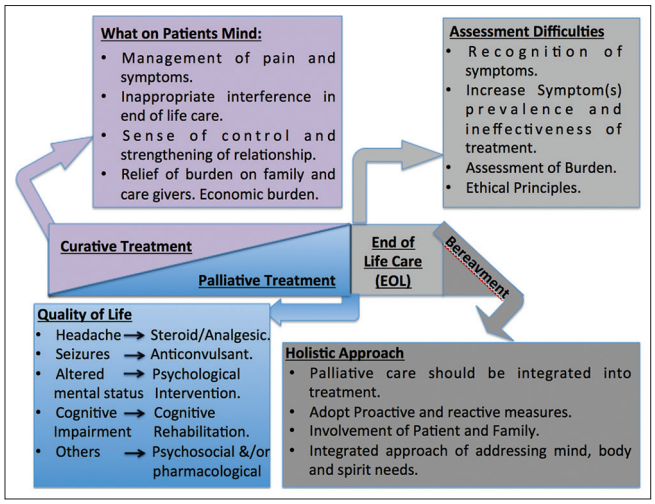

Figure 6: Diagrammatical representation of curative, palliative, and end-of-life care for glioblastoma multiforme

PALLIATIVE AND SUPPORTIVE CARE FOR GLIOBLASTOMA MULTIFORME PATIENTS

Patients with a rapidly progressing cancer like GBM exhibit dynamically evolving and unpredictable life-changing symptoms that affect their survival and quality of life [Figure 6]. These symptoms range from psychosocial to neurological leading to loss of patient autonomy.[41] In addition, the incurability of this disease, cost on health-care system, and caregiver burden (next of kin) advocate an early integration of palliative care into the treatment protocols adopted for GBM patients.[41,42] Treatment of GBM patients should not be merely directed toward prolonging life but also toward quality of life, especially when the patients' transition into end-of-life care (EOL) phase. Major component of palliative care is the symptom burden experienced by the patient, which can be addressed by palliative care protocols such as adopting psychosocial, pharmacological, or rehabilitation protocols to improve the quality of life.[41,42] Majority of patients showed symptoms of decrease in the level of consciousness followed by fever, dysphagia, seizures, and headache. The largest class of pharmaceuticals received by these patients were opioids followed by nonsteroidal anti-inflammatory drugs, anticonvulsants, and steroids.[43] Early, high-quality serious illness conversation which is very critical for GBM patients happens relatively late and infrequently reflects patients' goals and priorities. A randomized control trial on patients has shown that early integration of palliative care dramatically influences the quality of life, survival, mood of the patients, and caregiver burden.[41-43] A Dutch cohort study indicated that patients preferred an advanced discussion of their EOL preferences, but their physicians were not always aware of these preferences.[41-44] As the disease progresses into EOL phase, recognizing and assessment of symptoms becomes difficult as cognitive deficits increase hampering communication and decision-making difficult. Hence, it becomes very critical that during the EOL phase of the disease, organization of care that is governed by both ethical and treatment guidelines is important for improving the quality of life of patients and decreasing caregiver burden. The caregiver burden depends on the organization of care,

especially during EOL and place of death. In most of the cases, patients partners are the caregiver followed by children, family, and friends.[41-43] A study in Austria reported that sadness followed by fear, burnout, loss of interest, and irritation was common emotion experienced by caregivers.[44] In addition to the physical and emotional stress, caregivers also experienced social and financial problems. This highlights the risk of overburdening caregivers and emphasizes a need for support and counseling to caregivers to enable them to prepare for the disease trajectory. Most patients from the Netherlands and Italy died at home, patients from Anglo-Saxon regions died in hospice settings, whereas most of the patients from Austria died in hospital settings.[44] The place of death reflected the health-care costs incurred, and according to next of kins of the Dutch patients, patients who died at home died more often with dignity when compared to other settings. Hence, early discussion about organization of care during EOL and knowing a patient's preference are critical to ensure higher satisfaction with care and a more dignified dying process for patients with GBM.[41-44]

CONCLUSIONS

A multiple approach disease management model is needed for GBM. In addition to clinical evaluation of various new or repurposed molecules and technologies, efforts should be put in evaluating the quality of care during the progression and during EOL of this disease. Given the severe morbidity associated with this disease, the therapeutic strategy should consist of early diagnosis and molecular and histological evaluation for designing treatment protocol that suits the patients needs. The treatment protocol design should also take into account the palliative end-of-life care of the patients.

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Conflicts of interest

There are no conflicts of interest.

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