A Systematic Review on the Efficiency and Safety of Chemotherapies in the Treatment of Astrocytoma

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A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of
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Declaration

It is hereby declared that

1. The thesis submitted is my own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis titled "A systematic review on the efficiency and safety of chemotherapies in the treatment of astrocytoma" submitted by Moumita Saha (17146048) of Spring, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy on 15th June, 2022.

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Ethics Statement

This is to certify that this project titled “Efficiency and Safety of Chemotherapies in the Treatment of astrocytoma” is submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the School of Pharmacy, Brac University. It constitutes my own work under the supervision of Mohd. Raeed Jamiruddin, Assistant Professor, School of Pharmacy, Brac University and I have given appropriate credit where I have used language, ideas or writings of another. This project does not involve any human or animal trials. No animals were used or harmed in this project.

Abstract

Astrocytoma or low grade gliomas are most deadly primary brain tumor and leading cause for poor quality life in brain cancer patients. In addition, the traditional treatment for astrocytoma has been unchanged for decades, consisting only surgery followed by radiotherapy. Although the benefits of chemotherapy in the treatment of astrocytoma have been suggested yet their efficacy is still unknown. The standard Temozolomide based chemotherapies, are widely used with radiation or in combination with monoclonal antibody also PARP inhibitor, mTOR inhibitor, tyrosine kinase inhibitor and Quinone agent alone or in combination are used treating astrocytoma patients. In this systemic review , a search of PubMed, google scholar, www.clinical trials.gov, national cancer institute, mayo clinic was conducted in order to find the data. Progression free survival, overall survival, treatment on time, adverse events of drugs used for the treatment of astrocytoma were systemically identified. The study included total 9 trials (3 phase I, 5 phase II and 1 phase III trials) for a total of 742 patients who received chemotherapies alone or in combination. According to available data some drug combinations are routinely utilized in the treatment of astrocytoma, there is still a lack of relevant and sufficient information and data, temozolomide-based treatments are still controversial.

Keywords: Astrocytoma, chemotherapy, alkylating agent, radiotherapy, mTOR inhibitor

Dedication

Dedicated to my Beloved Parents and My Respected Supervisor Dr. Mohd. Raeed Jamiruddin Sir.

Acknowledgements

All honors belong to Almighty for strengthening me with patience to complete my project work along with the courses necessary to complete Bachelor of Pharmacy (B.Pharm) program.

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Table of Contents

List of Figures

List of Acronyms

mCRC	Metastatic colorectal cancer
CIN	Chromosomal instability
MSI	Microsatellite instability
HNPCC	Hereditary non-polyposis colorectal cancer
CIMP	CpG Island Methylator Phenotype
PlGF	placental growth factor
VEGFR1	vascular endothelial growth factor receptor 1
PDGFR	platelet-derived growth factor receptor
VEGFR2	vascular endothelial growth factor receptor 2
VEGF-A	vascular endothelial growth factor-A receptor
VEGFB	vascular endothelial growth factor-B receptor
VEGF	vascular endothelial growth factor
ORR	Objective response rate
PFS	Progression free survival
OS	Overall survival
EGFR	epidermal growth factor receptor
IgG2	Immunoglobulin 2

Chapter 1

Introduction

Astrocytoma is a cancer that starts in astrocytes, which are star-shaped glial cells in the cerebrum. A glial cell called an astrocyte that helps to maintain the function of nerve cells. Astrocytic tumors are formed of glial cell tumors called gliomas. It's the most frequent type of glioma, and it mainly affects the brain and rarely the spinal cord.

Astrocytoma are the most widespread and malignant cancer tissues of the brain in adults. Glioma nomenclature is determined by the glial cell of origin . Gliomas of astrocytic origin, oligodendrogliomas of oligodendrocytes, and ependymomas of ependymal cells are referred to as astrocyte gliomas and glioblastomas, respectively. Patients being exposed to ionizing radiation, are more prominent to form glioma. Cowden, Turcot, Lynch, Li-Fraumeni, and Neurofibromatosis type I are some of the hereditary syndromes that increase the likelihood of having a glioma (Hirtz et al., 2020). Since decades of clinical trials for patients with benign, to most malignant astrocytoma are present yet it is difficult to diagnose (Ammirati et al., 2014). Its treatment is still challenging. Formerly, chemotherapy alone failed to treat astrocytoma but lately combination of chemotherapy, or novel agent with chemotherapy or standard chemotherapy with PARP inhibitor or chemotherapy with radiotherapy has been developed as an efficacious treatment for astrocytoma by increasing median survival rate which is a significant global concern in the cancer (Ammirati et al., 2014; Baxter et al., 2020; Peereboom et al., 2010). Combination of chemotherapeutics can be stated as an extensive category of treatments aiming to enhance chemotherapy and radiation sensitivity along with limited toxicity (Baxter et al., 2020; Kaley et al., 2020). The objectives of this study are to overview the low grade glioma of brain and spinal cord, Astrocytoma, to study the different chemotherapeutic drug combinations, to analyze the progression free survival, overall survival

rate and time on treatment also to study the adverse effects of those chemotherapeutic drugs for astrocytoma.

Chemotherapy is the treatment strategy that holds great potential in order to fight cancer. For individuals with advanced brain cancer, it offers a unique and effective therapeutic approach. However, chemotherapeutic treatment options, on the other hand, are limited to substances that penetrate the blood–brain barrier and are associated with potential side effects. (Garcia et al., 2020). To get a clear understanding of chemotherapy for astrocytoma, this systemic review provides an overview about the concept of astrocytoma, its chemotherapeutic drug combinations used in the management and analyzing the PFS and OS along with the adverse events. Nowadays, multiple chemotherapy options are available for astrocytoma treatment such as HIMRT with concurrent and adjuvant TMZ, antineoplastic, PARP inhibitor including TMZ, mTOR inhibitor with AKT inhibitor, mTOR inhibitor with conventional TMZ base chemo radiotherapy, HCQ in combination with radiotherapy and TMZ, combined bevacizumab with radiotherapy and TMZ, combined therapy with Imatinib and Hydroxyurea which demonstrated promising responses in clinical trials. Therefore, this systemic review was conducted to help the reader to understand about the different chemotherapeutic strategies available for Astrocytoma and responses to these treatment modality in clinical trials, and also to discuss the overall and progression free survival, time on treatment and adverse effects of chemotherapeutic drug combinations.

The majority of astrocytoma patients are over the age of 40, apart from grade 1 tumors, which are more common in children. Furthermore, the older the patient, the more likely the astrocytoma would be of a greater grade. Astrocytoma, a type of cancer can happen all through the CNS, counting within the following places: the cerebellum, the cerebrum, the diencephalon, the brain stem, the spinal line. Low grade astrocytoma occurs due to the overexpression of platelet derived growth factor- a (PDGF-a) and mutation of P-53. While high grade

astrocytoma show mutation of two tumor –suppressor genes, RB genes and P-16. Neurologic side effects from astrocytoma development depend first on the location and degree of tumor development within the CNS including brain fog, fatigue, blurry vision, vocal difficulties, diminishing mental capabilities, foot stiffness, drowsiness and abdominal discomfort, physical disability, convulsions, sensory anomalies and ataxia (National Cancer Institute, n.d.). The diagnosis of astrocytoma is based on an intensive clinical assessment, characteristic physical discoveries, a cautious patient history, and specialized tests.

1.1 Types of astrocytoma

Astrocytoma is categorized as grade 1 (most benign) to grade 4 (most malignant) by the World Health Organization (WHO) depending on how quick they are developing and the probability that they will spread (invade) to nearby brain tissue. They are Childhood Brain Stem Glioma: when a glioma located at the cerebrum which is the part where brain is connected to the spine. It is usually a high grade tumor most common in child. Grade 1 involves a finite growth of cancer cell within the cerebellum that also develops gradually another one is Pleomorphic Xantoastrocytoma most habitually starts within the occipital lobes and most typically associated to convulsions. SEGA (Subependymal Giant Cell Astrocytoma) is perhaps the most prominent in children and teenagers (Astrocytoma-NORD, n.d.). Diffuse Astrocytoma (Grade 2) is indeed an intrusive cancer with no obvious separation from the surrounding brain (Astrocytoma-NORD, n.d.). Grade 3, Anaplastic Astrocytoma seems to be a more dangerous advancement than lower grade astrocytoma, that already obtained invasive characteristics (Astrocytoma-NORD, n.d.). Grade 4 includes Glioblastoma (GBM) has been the most dangerous, aggressive, and prevalent form to astrocytoma (60 percent). It is distinguished anatomically by exceptionally atypical tissues, growth, zones with necrotic tissue, as well as the arrangement with unused arteries. Glioblastoma either appear like a threatening progression of a preexisting low class astrocytoma (as a rule in 10 percent of cases) or benign specifically

like grade 4 tumor (90 percent of cases). This situation occurs more frequently among younger people though it also occurs more frequently after the age of 60. In any case, the above cancer cells could be a potent cancer with articulated central nervous system attack as well as death, while also exceptionally quick movement (Astrocytoma-NORD, n.d.).

1.2 key terms in the treatment of astrocytoma

PFS: According to the National Cancer Institute, PFS refers to the time a patient lives with a condition, such as cancer, during and after treatment, without the disease worsening. PFS is one approach to determine how well a new medication performs in a clinical study. Survival without progression is also known as progression-free survival".

OS: According to NCI, the percentage of participants in a study or treatment group who are still alive after being diagnosed with or starting treatment for a condition, such as cancer, after a specific period of time. The five-year survival rate is the percentage of participants in a study or treatment group who are alive five years after their diagnosis or treatment begins. Also known as the survival rate.

Follow up Time: According to National Cancer Institute, assessing a person's health throughout time after therapy that also includes tracking the health of persons who take part in a clinical study or clinical trial for a set period of time, both during and after the study.

Adverse Effect: According to NCI, an unanticipated medical condition that arises during the course of medication or other therapy treatment. Adverse reactions can be minor, moderate, or severe, and they might be caused by something other than the drug or therapy being administered.

Chapter 2

Combination of chemotherapeutic drugs used in Astrocytoma

There are several chemotherapeutic drug combinations that are available for the treatment of astrocytoma. These drug combinations involve alkylating agent with high dose radiation, microtubule inhibitors like chemotherapeutic agent, alkylating agent with PARP inhibitors, mTOR inhibitors AKT inhibitors, mTOR inhibitor with conventional TMZ based chemo radiotherapy, HCQ with chemoradiotherapy, combined BV with chemoradiotherapy, tyrosine kinase inhibitor with HU. So, these drug combinations are different and their outcomes regarding overall survival, progression free survival and minimal adverse effects are different.

2.1 Temozolomide (TMZ) and Hypo fractionated intensity modulated radiotherapy (HIMRT):

Temozolomide is a new oral alkylating drug and have shown therapeutic potential of a range of aggressive malignancies, including primary brain tumors. Temozolomide is also related to a low rate of severe adverse occasions (Koukourakis et al., 2009). The methods by which temozolomide improves glioblastoma cell radiation response, have discovered that temozolomide improves radiation sensitivity by enhancing the degree of radiation-induced double-strand DNA damage in O6-methylguanine-DNA methyl transferase (MGMT)-negative glioblastomas. Depletion of MGMT with O6-benzylguanine considerably improves the anticancer effect of concurrent radiation + temozolomide in MGMT-positive glioblastomas. Furthermore, a recent study found that patients with glioblastoma who had combined treatment with TMZ and radiation therapy had considerably improved overall survival than those who received radiation therapy alone after a five-year follow-up. Hypo fractionation has the

following advantages: (a) shorter treatment times, which are clearly beneficial to patients with terminal diseases; (b) lower costs; and (c) radiobiological advantages such as increased cell killing associated with higher dose per fraction and reduced accelerated repopulation. Because of its ability to be extremely conformal, IMRT can treat targets close to vital structures while reducing the amount of radiation deposited on structures at risk while maintaining coverage of the target. However, the increased dose heterogeneity and integral dose associated with IMRT may theoretically increase the radio necrosis rate (Ammirati et al., 2014). Common adverse effects of TMZ + HIMRT therapy include- fatigue, constipation, hypertension, dry skin, high ALT,vision change, thrombocytopenia (Carlson et al., 2015).

2.2 Ixabepilone

The epithilones are microtubule-stabilizing compounds produced by cellulose-degrading myxobacteria fermentation. These new drugs elicit cell-cycle arrest at the G2/M transition and death by promoting tubulin polymerization and improving microtubule stability. Despite the fact that Ixabepilone has increased BBB penetration and is not a p-glycoprotein substrate, it has anticancer effect against many juvenile brain tumor models but no activity against recurrent HGGs. Ixabepilone's median PFS and OS in a phase I/II trial and pharmacokinetic study were 1.5 and 5.8 months, respectively. Ixabepilone shows no anticancer activity in recurrent high grade glioma due to dose-limiting toxicity in both phase I and phase II studies and the death of all patients (Peereboom et al., 2010).

2.3 3-Dimensional Conformal Radiation Therapy and Temozolomide and Veliparib:

Veliparib is a poly ADP-ribose polymerase (PARP) inhibitor protein that has cytotoxic activity against tumor cells when combined with an alkylating agent and radiation therapy. It works by directly adding additional alkyl groups to the bases of DNA via the N7 position on guanine residues, which inhibits DNA replication, cell division, and cell death. Although these factors

show beneficial anticancer activities but due to resistance they show poor patient outcome (Rose et al., 2020).

2.4 Perifosine and Temsirolimus:

A protein kinase B(PKB) or AKT inhibitor, Perifosin with mammalian target of Rapamycin(mTOR) inhibitor, Temsirolimus works against these malignancies like lower to higher grade astrocytoma by signaling through the PAM(PI3K/AKT/mTOR) pathway. A protein tyrosine kinase (PTK), an epidural key regulator, activates phosphatidylinositol 2-kinase (PI3K), which activates AKT, which activates mTOR, in the PAM pathway. AKT and mTOR play a role in tumor cell invasion and proliferation while also inhibiting apoptosis. Perifosine and Temsirolimus, on the other hand, inhibit AKT and mTOR, respectively (Crespo et al., 2016).

2.5 Everolimus and Temozolomide and Radiation:

Everolimus, a mTOR inhibitor, works through the phosphatidylinositol-3 kinase (PI3K)/Akt pathway when combined with traditional TMZ-based chemo radiation. It is a small molecule kinase inhibitor which is effective in penetration BBB of highly diffusive tumor like glioblastoma (Heffron, 2018)

2.6 Hydroxychloroquine and Temozolomide and Radiation:

Hydroxychloroquine is a 4-aminoquinoline agent combining with conventional TMZ-based chemo radiotherapy to treat glioma patients(GB) (Liu et al., 2019). Autophagy inhibition of this agent involves the digestion of a cells own organelles, proteins and other cellular debris in the lysosome and provides anticancer activity. In addition, HCQ is used over CQ because in combination with TMZ and radiation shows less toxicity in long term dosing (Collins et al., 2018).

2.7 Bevacizumab and Temozolomide :

Bevacizumab is a VEGFA-targeting monoclonal antibody (vascular endothelial growth factor). Although BV has shown limited toxicity and maximal tolerability when paired with TMZ and radiation, it is utilized alone or in conjunction with other chemotherapy agents.

2.8 Temozolomide:

Temozolomide is a DNA alkylating drug that causes apoptosis and cell cycle arrest in G2/M. It is converted to the active molecule MTIC at physiologic pH, which has a shorter half-life. When MTIC is broken down, it produces 5-amino-imidazole-4-carboxamide (AIC) and methylhydrazine. The cytotoxicity of TMZ is caused by the presence of methyl groups at the N7 and O6 sites on guanines and the O3 site on adenines in genomic DNA. Alkylation of the O6 site on guanine during subsequent DNA replication results in the insertion of a thymine instead of a cytosine opposite the methylguanine, potentially resulting in cell death. This treatment improves survival rates, with the only side effect being myelosuppression. It was approved by the US Food and Drug Administration (FDA) for the treatment of refractory anaplastic astrocytoma in adults, as well as newly diagnosed adult glioblastoma (GBM) patients. In a Phase I clinical trial, the suggested dose of TMZ was 750–1000 mg/m2 taken orally 5 days per week for 4 weeks.(Lee, 2016).

2.9 Imatinib mesylate and Hydroxyurea:

The ATP competitive inhibitor imatinib mesylate inhibits the activity of tyrosine kinases in a range of proteins, including ABL, BCR-ABL, c-KIT, and platelet derived growth factor receptors. Imatinib has also shown promise as a therapy for GBM in preclinical studies.

Imatinib and hydroxyurea, a ribonucleotide reductase inhibitor, were used in two phase II studies to examine the efficacy and safety of a novel GBM therapeutic strategy. This combination appeared to be well tolerated and showed long-term anticancer effectiveness in the patients in these studies (n 63 in total). Because both imatinib and hydroxyurea were ineffectual in the treatment of GBM when used separately, this combination offered an unexpected therapeutic benefit. As a result, studies suggest that cross-interactions between these treatments and their passage through the cerebral barriers could boost drug transport into the brain, hence increasing their efficacy. Hydroxyurea showed no effect on imatinib brain penetration after short or long-term coadministration. Imatinib had no effect on hydroxyurea's first transit through the BBB in mice. It's unclear whether imatinib decreases the activity of a hydroxyurea efflux transporter in brain distribution equilibrium. More study on preclinical tumor models is needed to better understand this link because the permeability qualities of the cerebral endothelium are likely changed in capillaries that irrigate the GBM tumor. Finally, the absorption of imatinib and hydroxyurea into tumor cells, as well as their possible interactions, should be studied (Bihorel et al., 2006).

Chapter 3

Methodology:

A comprehensive review based on chemotherapy in the treatment of astrocytoma was performed by utilizing various research papers, academic published journals and relevant websites such as cancer.net, nhs.uk, cancerresearchuk.org. Initially, a search of clinical trial was conducted on chemotherapies for astrocytoma based on completed results. After that another search of PubMed and Google Scholar was conducted to find out the original studies of the clinical trials for this review. Multiple articles from different journals were used to collect the information for this systemic review. The journals include PubMed, Elsevier, ScienceDirect, Springer, etc. Then an outline was prepared to conduct the review in a systemic way. The articles for the systemic review were explored utilizing key words such as astrocytoma, chemotherapy, low-grade glioma, glioblastoma, recurrent glioblastoma. The search was limited to retrospective case series rather than randomized clinical trials, Clinical trials (randomized controlled trials), meta-analysis, review article and systemic review articles were included in the search, as well as papers published in English. Data and relevant information were also collected from the clinicaltrials.gov website. The clinical trial ID numbers were- NCT00841555, NCT00045708, NCT01514201, NCT01051557, NCT00553150, NCT00486603, NCT00590681, NCT00313729, NCT00154375. The percentage of adverse effects of different drug combinations were taken from the 'study results' portion of the trial. Abstracts from prominent cancer conferences that appeared in PubMed search results were also taken into consideration. The reference lists of included trials and large systemic reviews were also examined for additional relevant trials.

3.1 Inclusion criteria:

Inclusion criteria for this study included the following: (1) astrocytoma patients, (2) clinical trials (randomized controlled trials from phase I-III), meta-analysis and systemic reviews (3) patients who received chemotherapy, chemotherapy along with radiation therapy (4) patients exposed to several drug combinations associated with chemotherapy, (5) clinical trials that reported mean average survival rate (OS) and progression free survival rate (PFS) from the beginning of therapy.

3.2 Exclusion criteria:

Trials that did not provide outcomes for OS, PFS or time to progression were excluded from the study due to lack of sufficient information, Only the most recent publication of a series published by the same institution in various years was incorporated in the analysis to eliminate the possibility of overlapping patients.

3.3 Selection of trials:

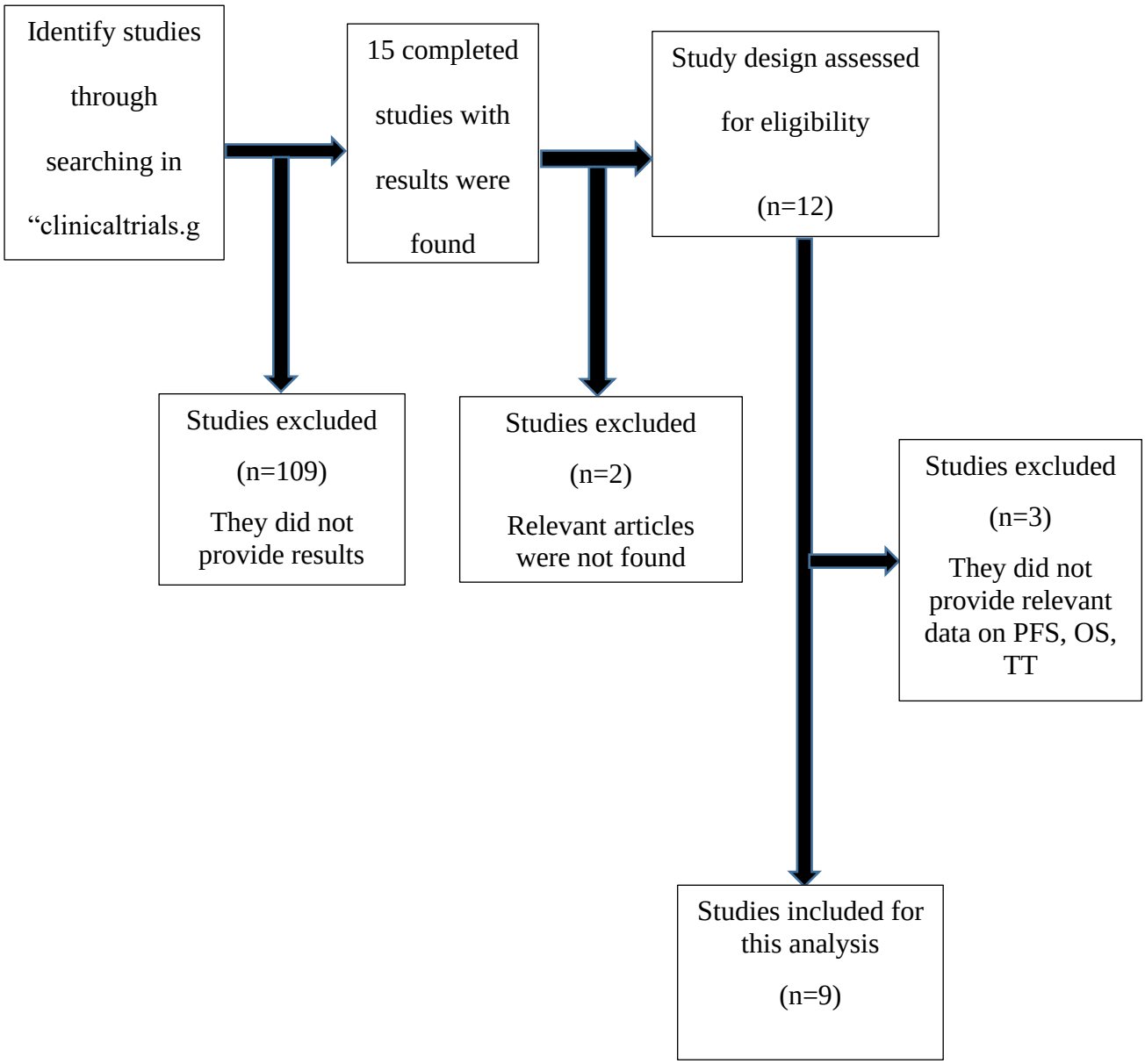
Total 9 trials were finally selected for this study where several drug combinations are associated with temozolomide, Hypo fractionated intensity modulated radiotherapy, 3-Dimensional Conformal Radiation Therapy, Veliparib, Ixabepilone, Perifosine and Temsirolimus, everolimus, hydroxychloroquine, and Radiation therapy, Bevacizumab, Imatinib mesylate and Hydroxyurea.

3.4 End points:

Summarization and cumulation of the over-all survival rate (OS), median progression free survival rate (PFS) and adverse effects from different drug combinations from the published literature was the primary end point of this analysis. The secondary end point was to assess and

contrast the efficacy of various combination treatments and analyze the reported toxicities and adverse effects associated with chemotherapy.

3.5 Flowchart for the included trials:



Chapter 4

Result:

The study included 9 trials comprising 742 patients who received the combined and single treatments (Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea) that are used in treating Astrocytoma.

4.1 Characteristics of Included Trials:

Table. 1 Combinations of Drug & Therapy and Characteristics of Included Trials:

SL No	Drug combination	Study completation date	Year/Phase	Study purpose	No of Patients	Median Age	ClinicalTrials.gov Identifier
1	**Temozolomide + Hypofractionated intensity modulated radiotherapy**	25-Nov-14	Phase 1	Treatment	9	67 years	NCT00841555
2	**Ixabepilone**	May-10	Phase 2	Treatment	23	54 years	NCT00045708
3	**3-Dimensional Conformal Radiation Therapy +Temozolomide+ Veliparib**	28-Mar-18	Phase 2	Treatment	53	6.6 years	NCT01514201

4	**Perifosine + Temsirolimus**	30-Sep-20	Phase 1	Treatment	35	52 years	NCT01051557
5	**Everolimus +Temozolomide+ Radiation**	15-Nov-19	phase 2	Treatment	100	61years	NCT00553150
6	**Hydroxychloroquine+ Temozolomide+ Radiation**	Jan-14	phase 1 and phase 2	Treatment	92	58 years	NCT00486603
7	**Bevacizumab and Temozolomide**	Sep-14	phase 2	Treatment	70	57.4 years	NCT00590681
8	**Temozolomide**	12-Jun-17	phase 2	Treatment	120	#N/A	NCT00313729
9	**Imatinib mesylate + Hydroxyurea**	Aug-08	phase 3	Treatment	240	51years	NCT00154375

Table 1: It depicted the characteristics of the included trials of this review. It showed that, 2 phase I trial, 1 phase I and II trials, 5 phase II trials, 1 phase III trial were included in this analysis for a total of 742 patients treated with chemotherapy combination or alone for the treatment of astrocytoma. The type of total 9 studies was interventional and the primary purpose was treatment. The number of patients in each trial was ranged from 9 to 240 and the age was ranged from 18 years to older. The clinical trial identifiers from which the data was collected were also showed in this table.

4.2 Efficacy of The Combined Regimens:

Table 2: Responses to The Treatments

SL No	Drug combination	Median Age	Median PFS	Median OS	Median follow up time	Author, year
1	**Temozolomide + Hypofractionated intensity modulated radiotherapy**	67 years	3.9 months	12.7 months	10 months	(Ammirati et al., 2014)
2	**Ixabepilone**	54 years	1.5 months (95%CI, 1.3-2.3)	5.8 months (95% CI, 5.0–8.6 months)	#N/A	(Peereboom et al., 2010)
3	**3-Dimensional Conformal Radiation Therapy +Temozolomide+ Veliparib**	6.6 years	#N/A	24 months	6.3 months	(Baxter et al., 2020)
4	**Perifosine + Temsirolimus**	52 years	2.7 months [95%CI: (1.8, 9.2)]	10.4 months [95% CI (7.2, 16.7)],	8.9 months	(Kaley et al., 2020)
5	**Everolimus +Temozolomide+ Radiation**	61years	6.4 months (95% CI: 5.4, 9.0)	15.8 months (95% CI: 13.0, 20.3),	17.5 months	(Ma et al., 2015)
6	**Hydroxychloroquine+ Temozolomide+ Radiation**	58 years	#N/A	15.6 months (95% CI: 13 to 17.0)	#N/A	(Taylor et al., 2014)

7	**Bevacizumab and Temozolomide**	57.4 years	13.6 months	19.6 months	24.2 months	(Lai et al., 2011)
8	**Temozolomide**		50 months	115 months	6.9 years	(Wahl et al., 2015)
9	**Imatinib mesylate + Hydroxyurea**	51years	#N/A	#N/A	#N/A	(Dresemann et al., 2010)

Table 2 depicted the efficacy of the combined regimens which were included in this review. The responses such as median OS (overall survival rate), median PFS (progression free survival rate), median follow up time or time on treatment of the patients to the treatment of all the trials were extracted if they were available.

4.2.1 Median progression free survival rate:

Median progression free survival time of patients receiving 9 chemotherapeutic drugs is depicted by the following graph:

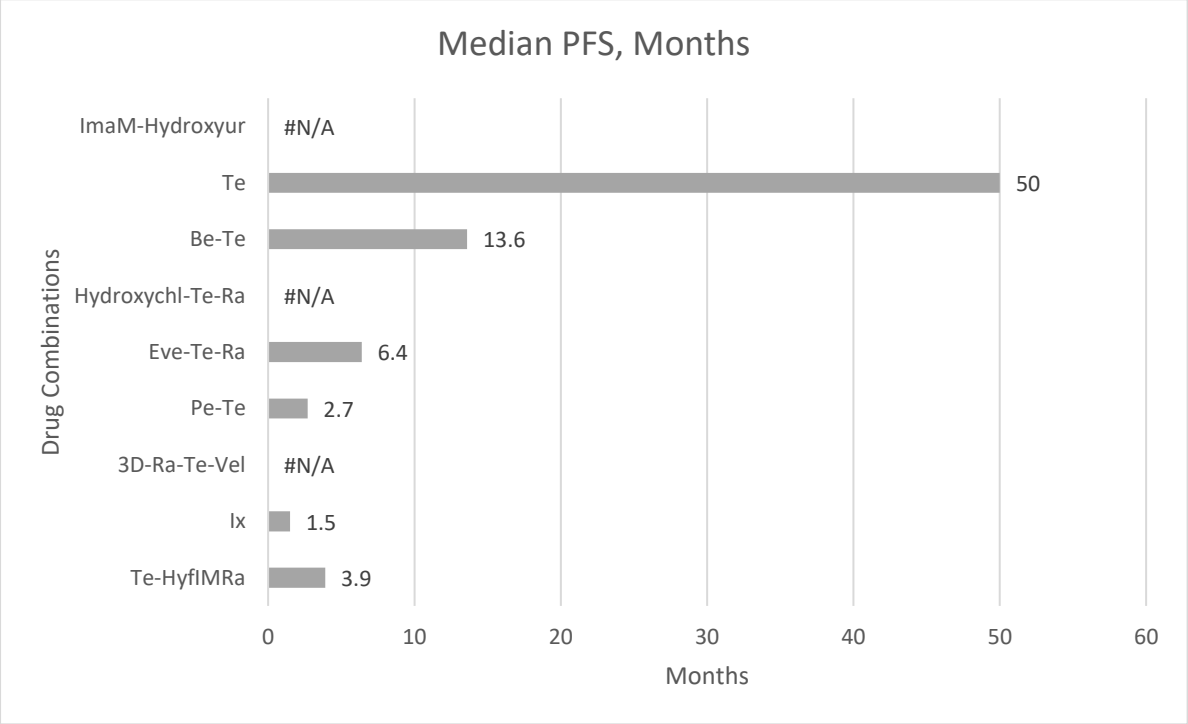


Figure 1: In this figure, Progression free survival(PFS) rates of patients receiving chemotherapeutic treatment alone or in combination for astrocytoma have mentioned. This graph represents that, Temozolomide alone has shown the highest PFS(50 months) in comparison to other chemotherapeutic drugs. On the other hand, Ixabepilone has shown the lowest PFS (1.5 months). However, patients who received combinations of chemotherapeutic drugs such as Bevacizumab + temozolomide, Everolimus+Temozolomide, temozolomide+ HyfIMRa and Perifosine+ temozolomide has shown PFS of 13.6 months, 6.4 months, 3.9 months and 2.7 months respectively, also taken into consideration for this systemic review. In addition, median PFS were not found for Hydroxycholoquine +Temozolomide + radiation, 3D confrontal radiation + Temozolomide + Veliparib and Imatinib mesylate + hydroxyurea combinations.

4.2.2 Median Overall survival rate:

Median overall survival time of patients receiving 9 chemotherapeutic drugs is depicted by the following graph:

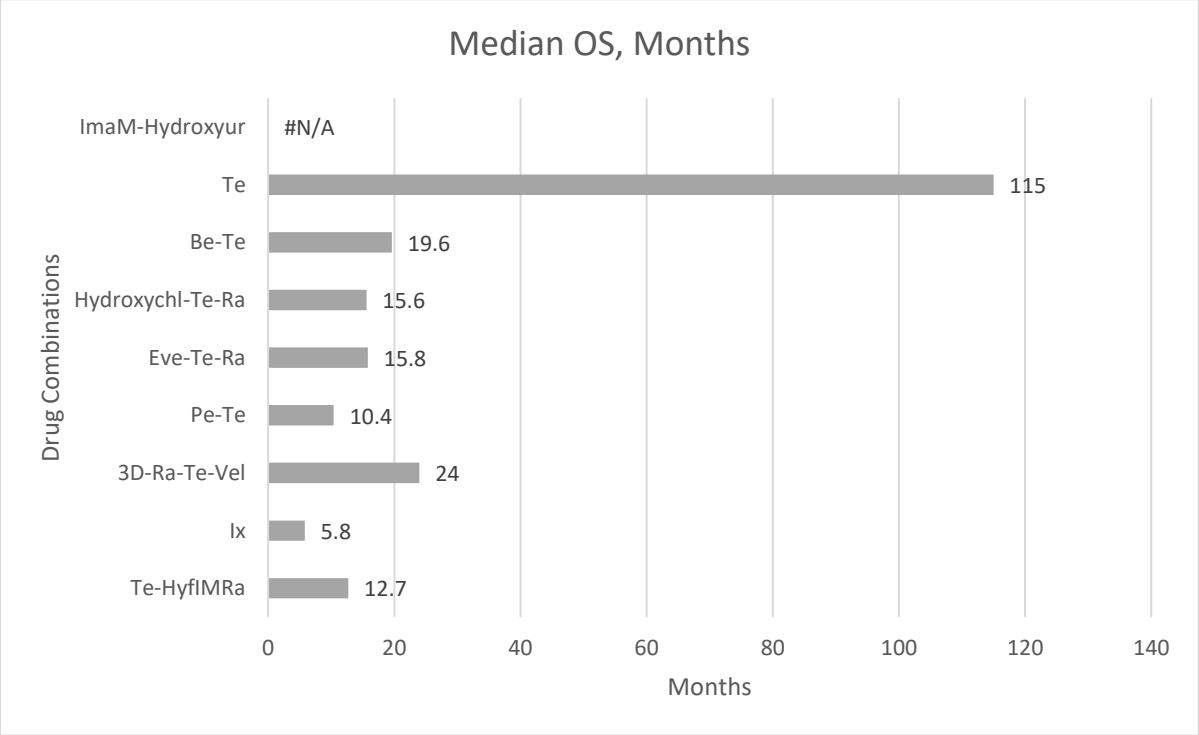


Figure 2: In this figure, overall survival (OS) rates of patients receiving chemotherapeutic treatment alone or in combination for astrocytoma have mentioned. This graph represents that, Temozolomide alone has shown the highest OS (115 months) in comparison to other chemotherapeutic drugs. On the other hand, Ixabepilone has shown the lowest OS (5.8 months). However, patients who received combinations of chemotherapeutic drugs such as 3D confrontal radiation + Temozolomide + Veliparib Bevacizumab + temozolomide, Everolimus+Temozolomide, Hydroxycholoquine +Temozolomide + radiation, temozolomide+ HyfIMRa and Perifosine+ temozolomide has shown OS of 24 months, 19.6 months, 15.8 months, 15.6 months and 12.7 months, 10.4 months respectively, also taken into consideration for their significant outcome. In addition, median OS were not found for Imatinib mesylate + hydroxyurea combination.

4.2.3 Median time on treatment:

Median time on treatment of patients receiving 9 chemotherapeutic drugs is depicted by the following graph:

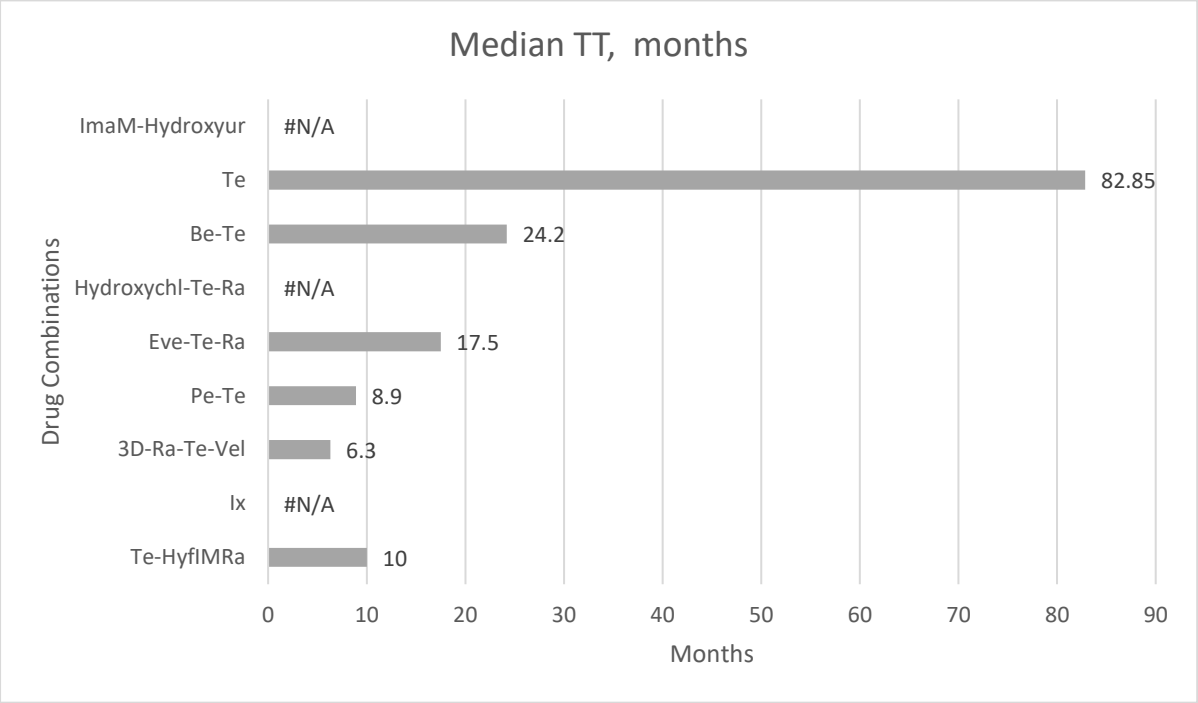


Figure 3: In case of median time on treatment or follow-up time, the patients who received Temozolomide alone had longest median time on treatment, 82.85 months and the patients who received 3D- radiation-Temozolomide-Veliparib had the shortest which was 6.3 months. Median follow up time of other combination of drug and therapy were also taken to the consideration in this analysis. For the combination of Imatinib mesylate + hydroxyurea, Hydroxycholoquine +Temozolomide + radiation and Ixabepilone, median time on treatment were not found.

4.3 Toxicity of the treatments :

Table 3: Serious Adverse Effects Rate & Mortality Rate of the Combined Regimens

SL No	Drug combination	Serious Adverse Effects Rate	Mortality Rate	ClinicalTrials.gov Identifier
1	**Temozolomide + Hypofractionated intensity modulated radiotherapy**	0/3 (0.00%)	#N/A	NCT00841555
2	**Ixabepilone**	1/19 (5.26%)	0/19 (0.00%)	NCT00045708
3	**3-Dimensional Conformal Radiation Therapy +Temozolomide+ Veliparib**	19/47 (40.43%)	40/47 (85.11%)	NCT01514201
4	**Perifosine + Temsirolimus**	4/6 (66.67%)	6/6 (100.00%)	NCT01051557
5	**Everolimus +Temozolomide+ Radiation**	32/101 (31.68%)	#N/A	NCT00553150
6	**Hydroxychloroquine+ Temozolomide+ Radiation**	53/76 (69.74%)	0/76 (0.00%)	NCT00486603
7	**Bevacizumab and Temozolomide**	3/62 (4.84%)	#N/A	NCT00590681
8	**Temozolomide**	17/120 (14.17%)	#N/A	NCT00313729
9	**Imatinib mesylate + Hydroxyurea**	49/85 (57.65%)	#N/A	NCT00154375

Table 3: It depicted the toxicities of the treatments. The serious adverse effect rate and the

mortality rate of the included trials were illustrated in this table.

4.3.1 Serious Adverse Effect Rates:

Among the total of 9 trials, patients who received Hydroxychloroquine + Temozolomide + Radiation combination had exhibited higher serious adverse events which was 69.74% (according to NCT00486603). Most common treatment-related adverse events : thrombocytopenia, leucopenia, rash maculo-papular, nausea, vomiting, fatigue, ALT, AST, hyperbilirubinemia. As well as patients receiving the combination of Bevacizumab + Temozolomide + Hypofractionated Intensity-Modulated Radiation Therapy had exhibited lower adverse events of 0.00% (according to NCT00841555).

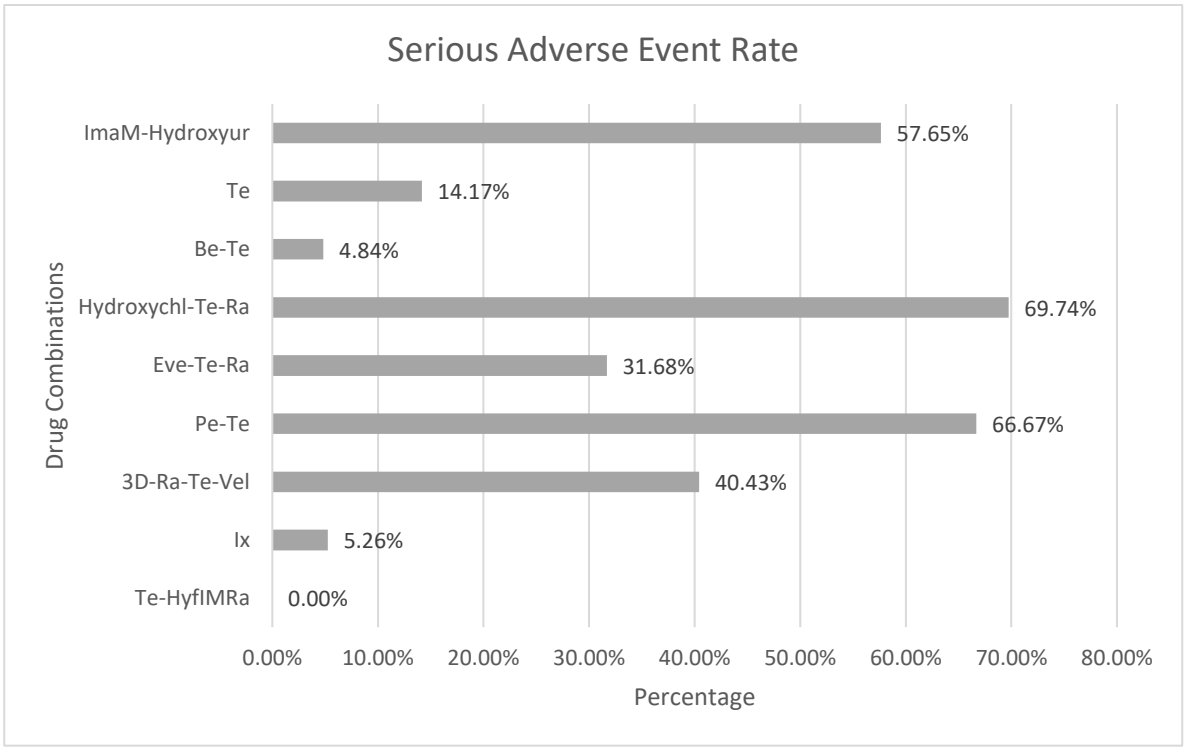
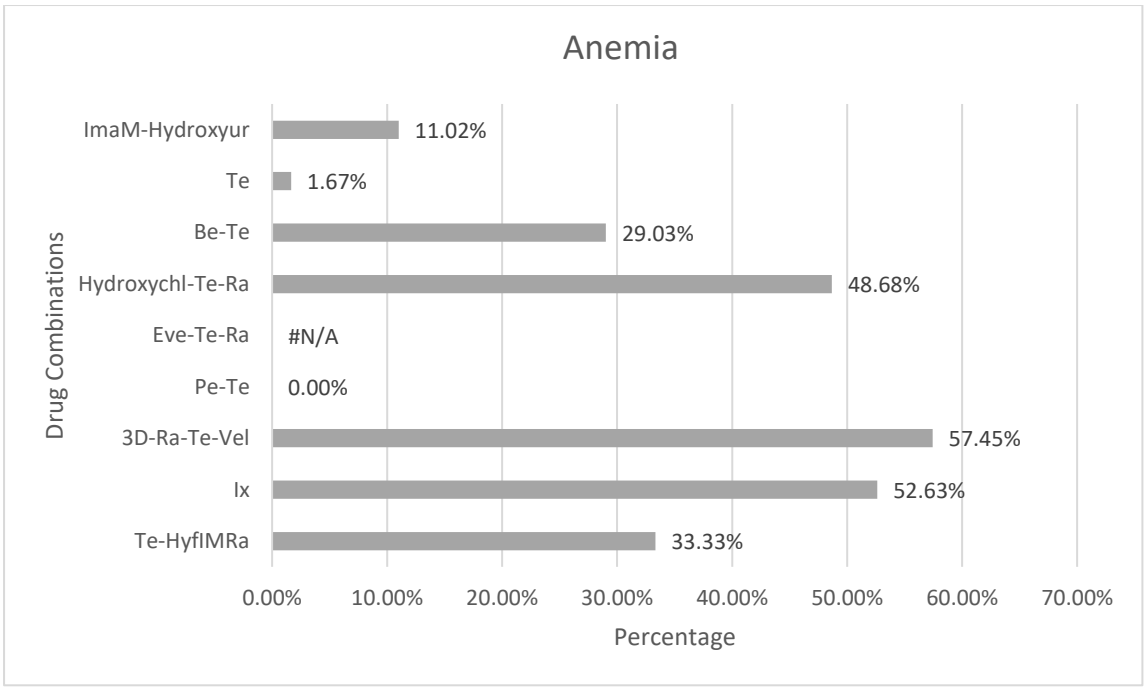


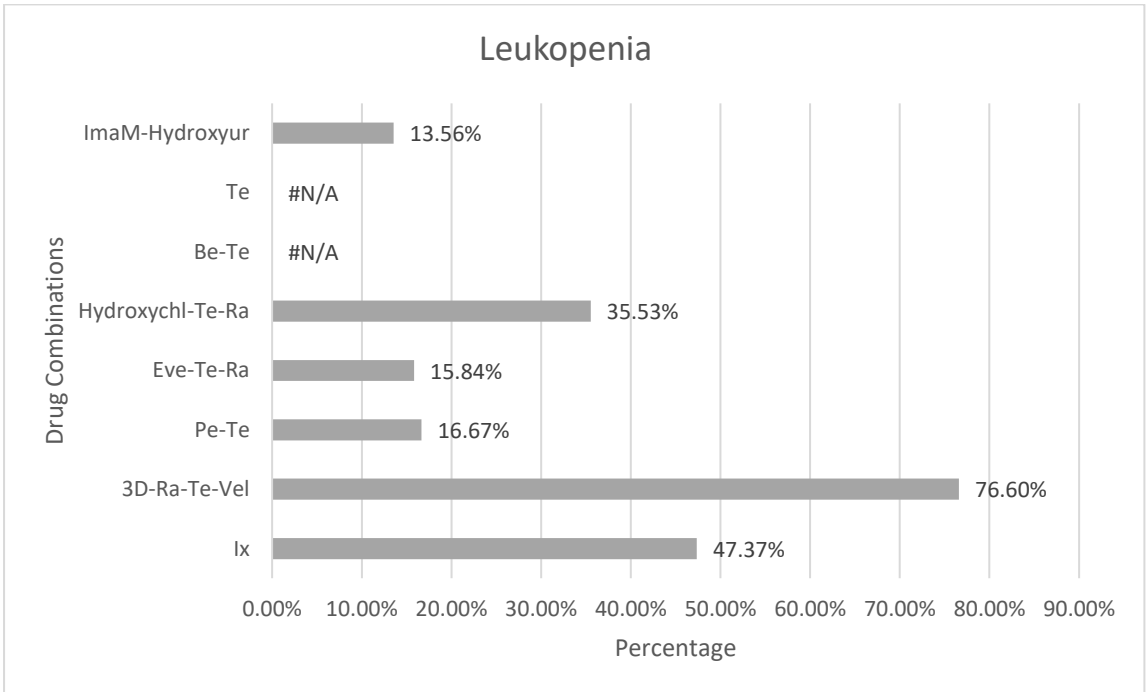
Figure 4: Serious adverse event rates for different chemotherapeutic drug and combinations. The different chemotherapies alone and in combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy(Te-HyfIMRa), Ixabepilone(Ix), 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib(3D-Ra-Te-Vel), Perifosine + Temsirolimus(Pe-Te), Everolimus + Temozolomide +

Radiotherapy(Eve-Te-Ra), Hydroxychloroquine + Temozolomide + Radiotherapy(Hydroxychl-Te-Ra), Bevacizumab + Temozolomide(Be-Te), Temozolomide(Te), Imatinib Mesylate + Hydroxyurea(ImaM-Hydroxyur). The values are presented as percentage in the graph.

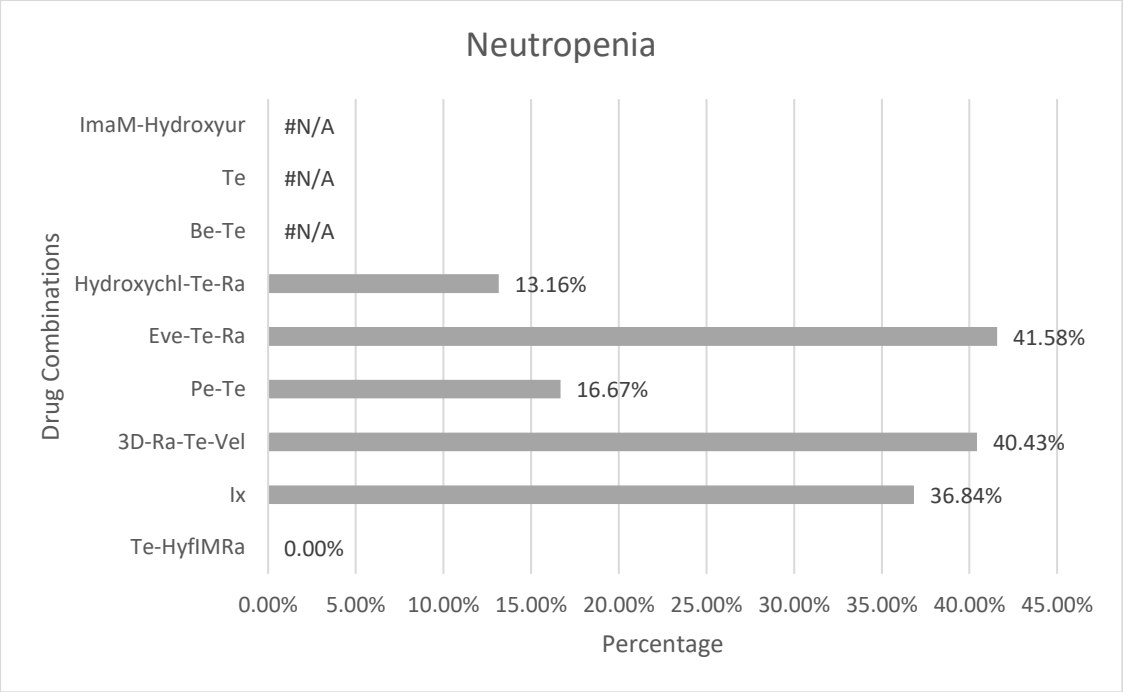
5(A)


Anemia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyfIMRa
11.02%
1.67%
29.03%
48.68%
#N/A
0.00%
57.45%
52.63%
33.33%
Drug Combinations
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%
Percentage

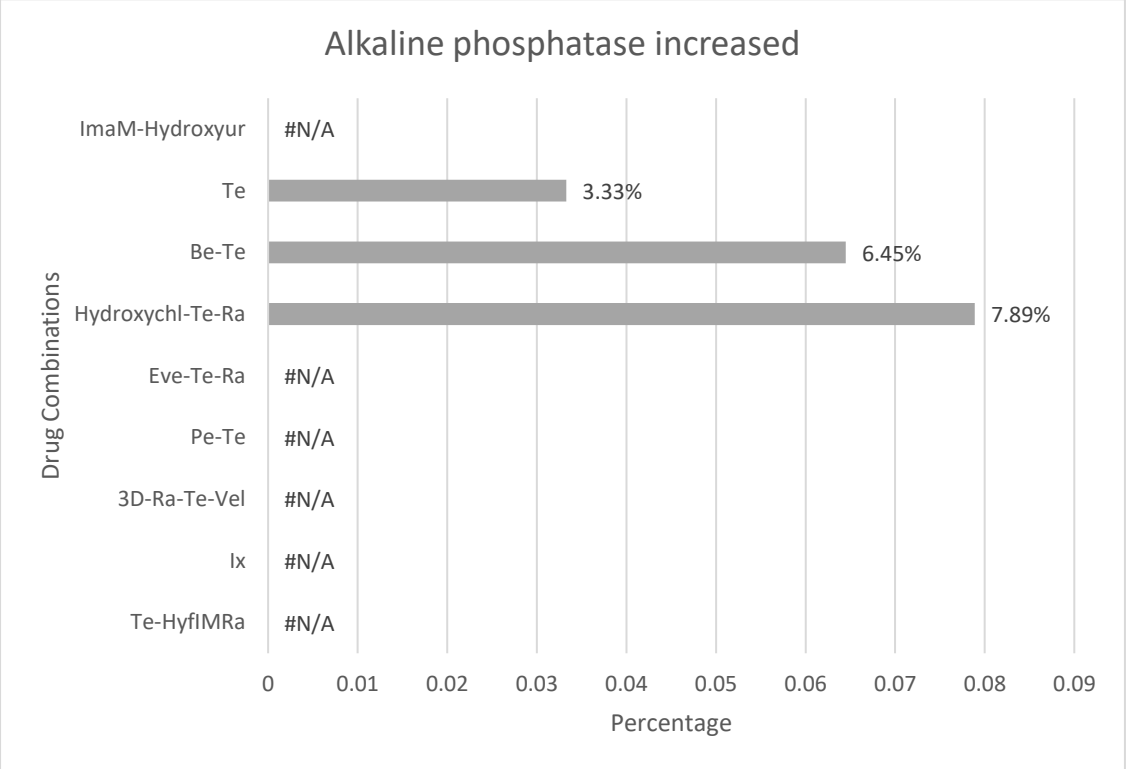
5(B)


Leukopenia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
13.56%
#N/A
#N/A
35.53%
15.84%
16.67%
76.60%
47.37%
Drug Combinations
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%
80.00%
90.00%
Percentage

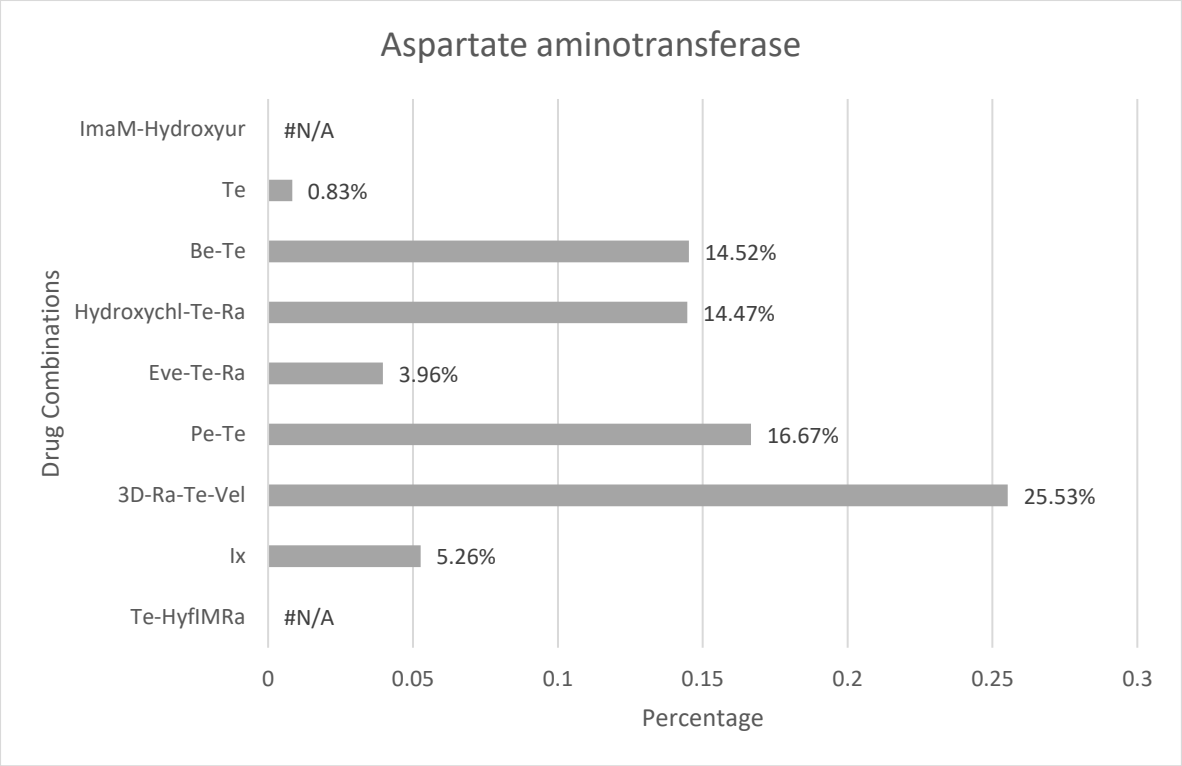
5(C)


Neutropenia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
13.16%
41.58%
16.67%
40.43%
36.84%
0.00%
Drug Combinations
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00% 35.00% 40.00% 45.00%
Percentage

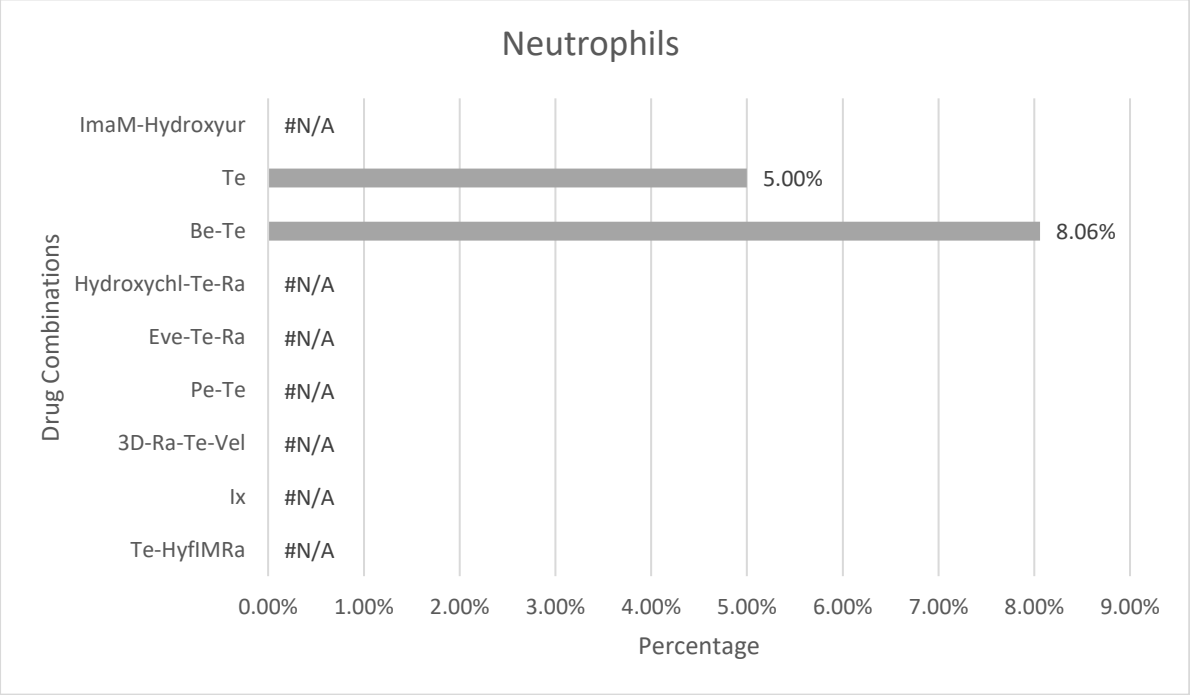
5(D)


Alkaline phosphatase increased
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
3.33%
6.45%
7.89%
#N/A
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0 0.01 0.02 0.03 0.04 0.05 0.06 0.07 0.08 0.09
Percentage

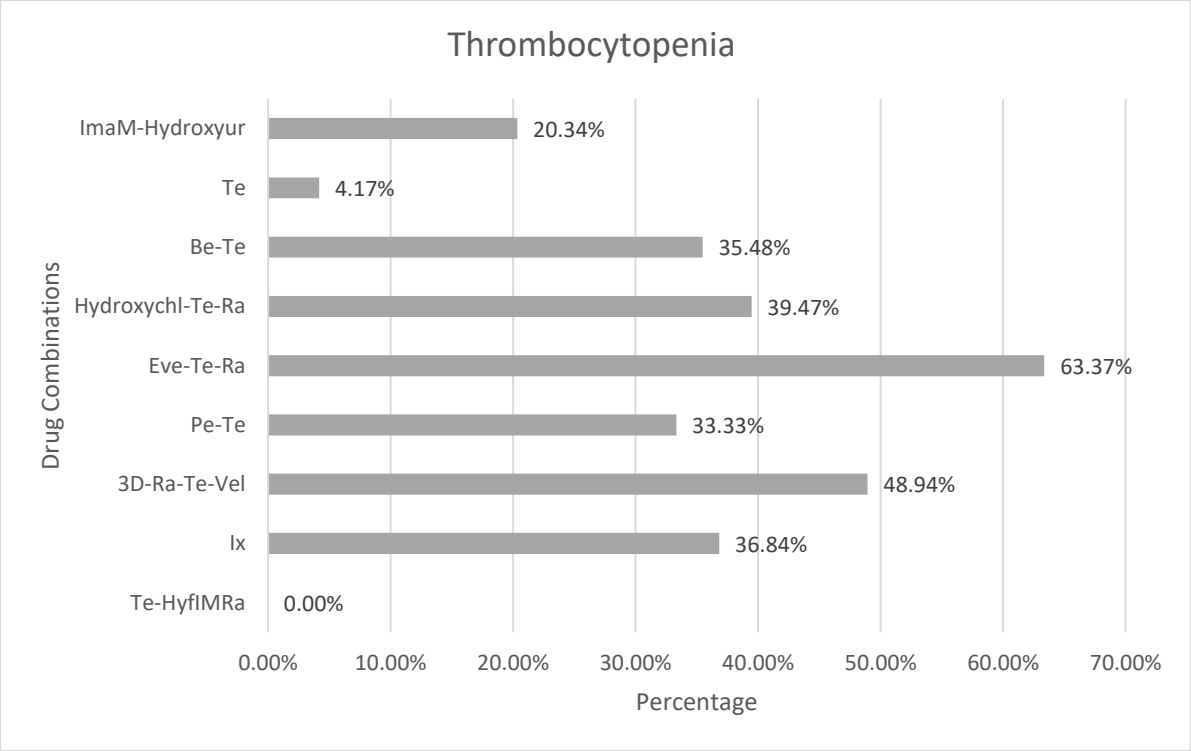
5(E):


Aspartate aminotransferase
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
0.83%
14.52%
14.47%
3.96%
16.67%
25.53%
5.26%
#N/A
Drug Combinations
0
0.05
0.1
0.15
0.2
0.25
0.3
Percentage

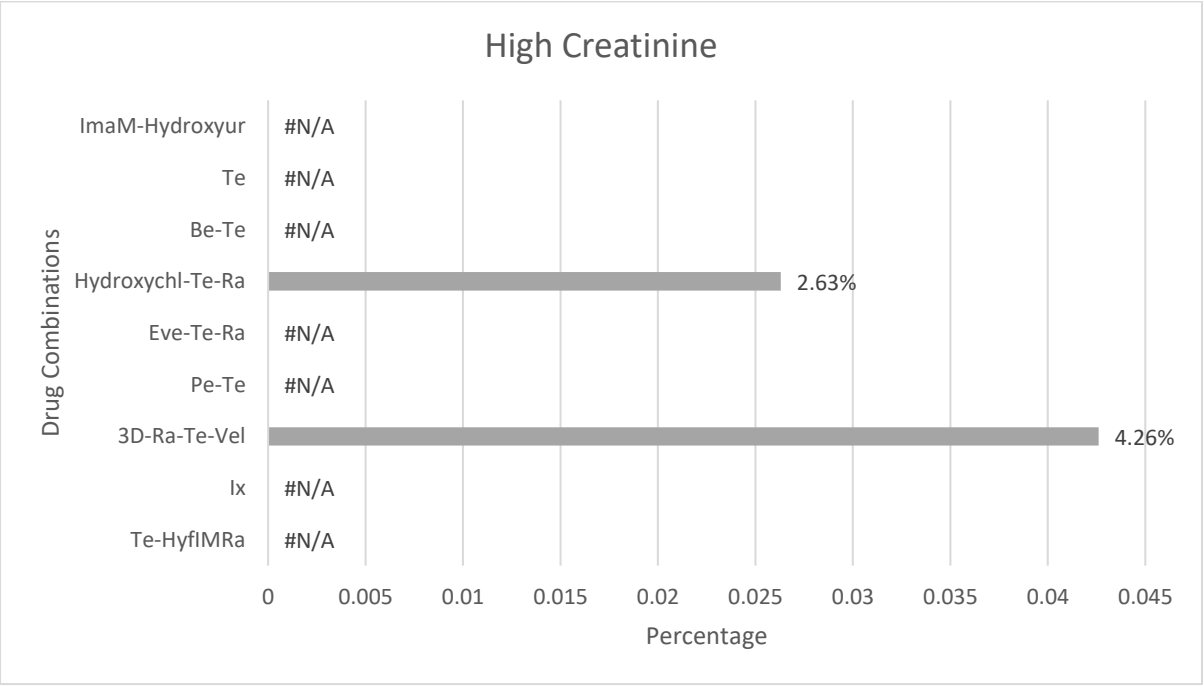
5(F):


Neutrophils
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
5.00%
8.06%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0.00%
1.00%
2.00%
3.00%
4.00%
5.00%
6.00%
7.00%
8.00%
9.00%
Percentage

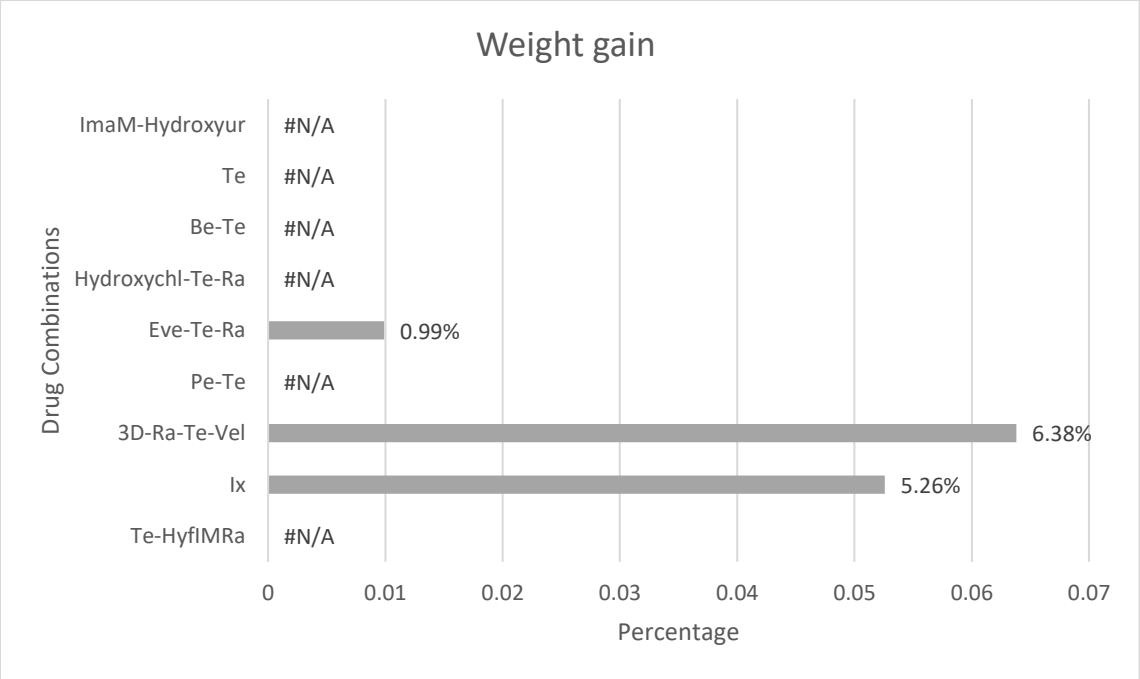
5(G):


Thrombocytopenia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
20.34%
4.17%
35.48%
39.47%
63.37%
33.33%
48.94%
36.84%
0.00%
Drug Combinations
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%
Percentage

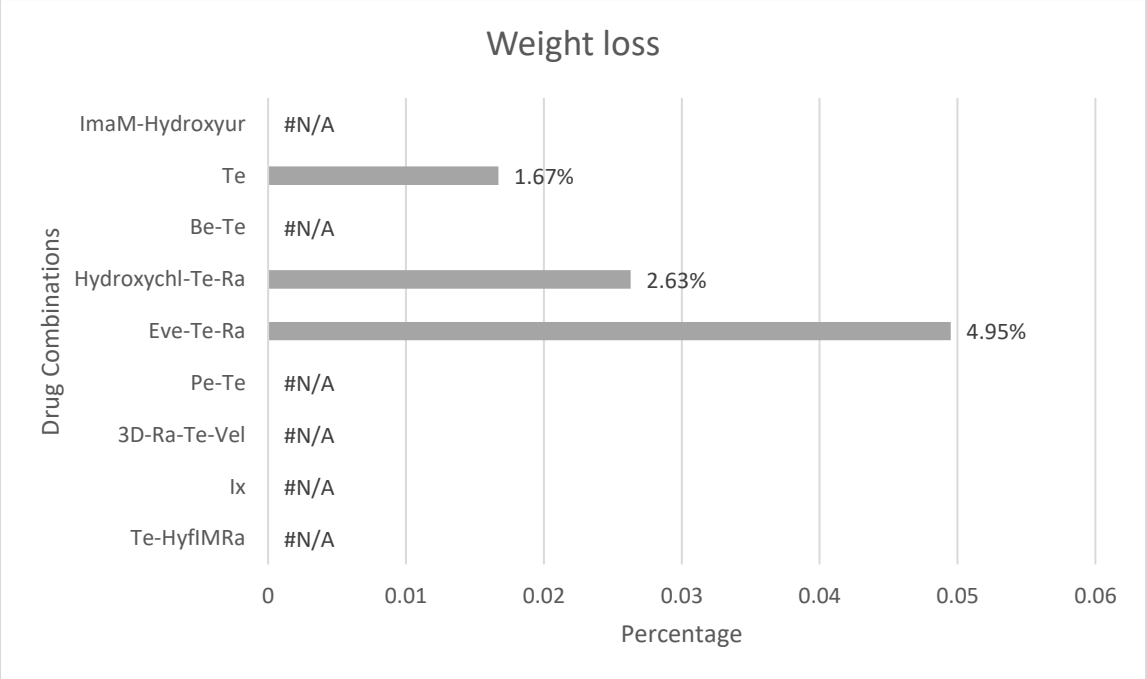
5(H):


High Creatinine
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
2.63%
#N/A
#N/A
4.26%
#N/A
#N/A
Drug Combinations
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04
0.045
Percentage

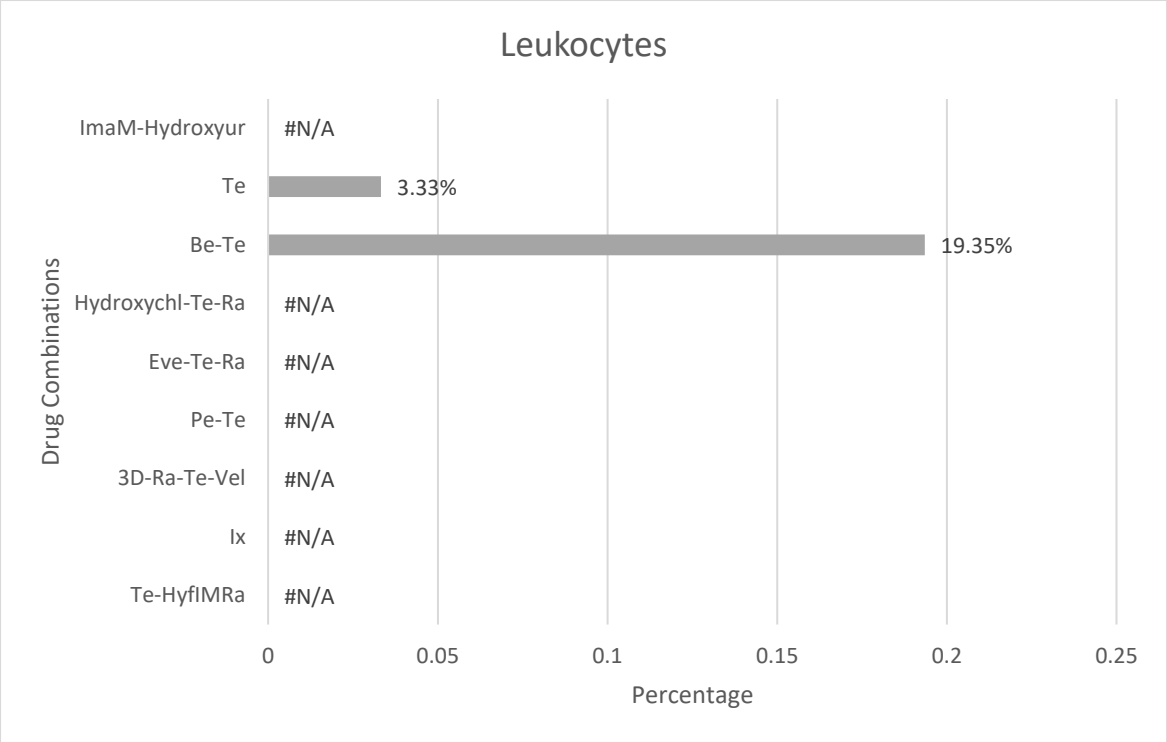
5(I):


Weight gain
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
#N/A
0.99%
#N/A
6.38%
5.26%
#N/A
Drug Combinations
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
Percentage

5(J):


Weight loss
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
1.67%
#N/A
2.63%
4.95%
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0
0.01
0.02
0.03
0.04
0.05
0.06
Percentage

5(K):


Leukocytes
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
3.33%
19.35%
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0
0.05
0.1
0.15
0.2
0.25
Percentage

5(L):

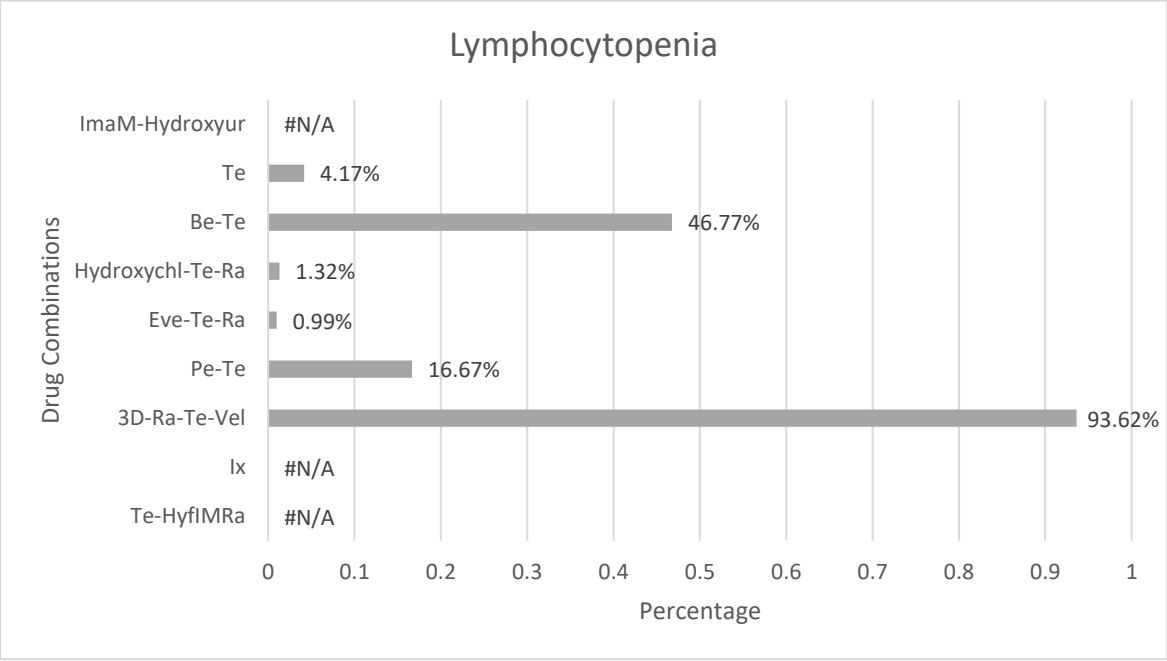
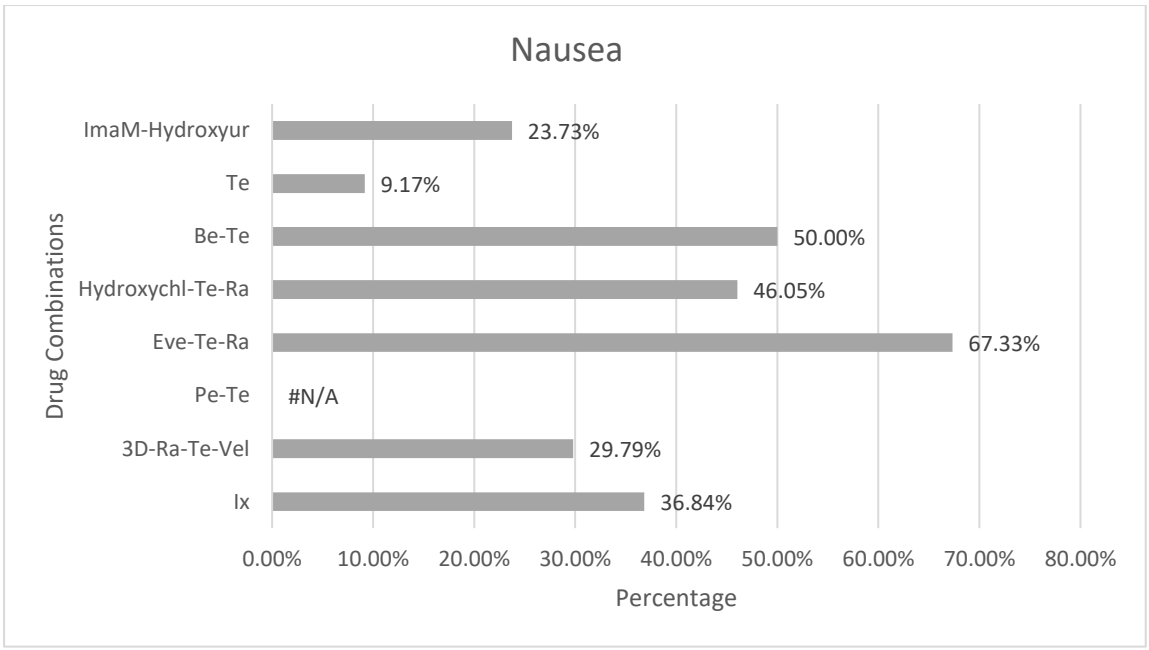

Lymphocytopenia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
4.17%
46.77%
1.32%
0.99%
16.67%
93.62%
#N/A
#N/A
Drug Combinations
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1
Percentage

Figure 5: Percentage of blood and lymphatic system disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

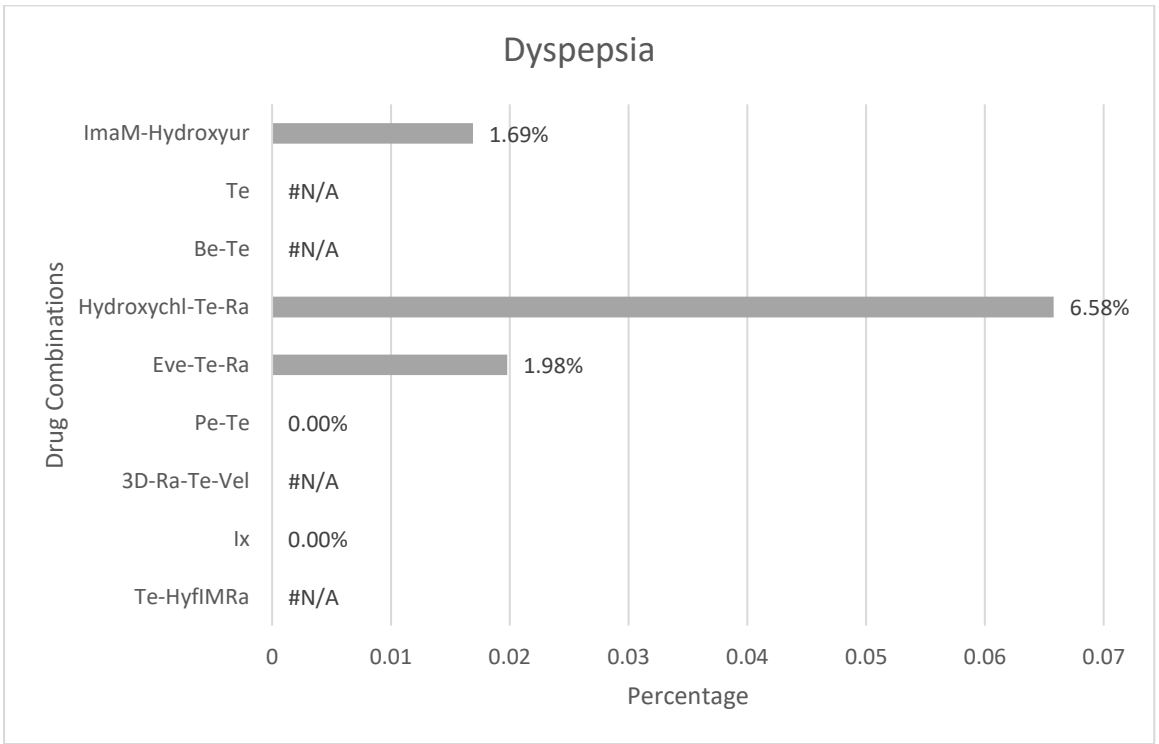
Blood and lymphatic system related disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Anemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of anemia was observed 57.45% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (B) represents percentage of Leukopenia in patients receiving chemotherapeutic drug combinations. The highest rate of leukopenia was observed 76.60% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination; (C) represents percentage of Neutropenia observed in patients receiving chemotherapeutic drug combinations. The highest rate of neutropenia was observed 41.58% in patients receiving Everolimus + Temozolomide + Radiotherapy combination. (D) represents percentage of increased Alkaline phosphatase observed in patients receiving chemotherapeutic drug combinations. The highest rate of increased alkaline phosphatase was observed 7.89% in patients receiving Hydroxychloroquine + Temozolomide + Radiotherapy combination. (E) represents percentage of Aspartate Aminotransferase (AST) observed in patients receiving chemotherapeutic drug combinations. The highest rate of aspartate aminotransferase was observed 25.53% in patients receiving 3-Dimensional Conformal

Radiation therapy + Temozolomide + Veliparib combination. (F) represents percentage of Neutrophils observed in patients receiving chemotherapeutic drug combinations. The highest rate of neutrophils was observed 8.06% in patients receiving Bevacizumab + Temozolomide combination. (G) represents percentage of Thrombocytopenia observed in patients receiving chemotherapeutic drug combinations. The highest rate of thrombocytopenia was observed 63.37% in patients receiving Everolimus + Temozolomide + Radiotherapy combination. (H) represents percentage of High creatinine observed in patients receiving chemotherapeutic drug combinations. The highest rate of high creatinine was observed 4.26% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (I) represents percentage of Weight gain observed in patients receiving chemotherapeutic drug combinations. The highest rate of weight gain was observed 6.38% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (J) represents percentage of weight loss observed in patients receiving chemotherapeutic drug combinations. The highest rate of weight loss was observed 4.95% in patients receiving Everolimus + Temozolomide + Radiotherapy combination. (K) represents percentage of Leukocytes observed in patients receiving chemotherapeutic drug combinations. The highest rate of leukocytes was observed 19.35% in patients receiving Bevacizumab + Temozolomide combination. (L) represents percentage of Lymphocytopenia observed in patients receiving chemotherapeutic drug combinations. The highest rate of lymphocytopenia was observed 93.62% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination.

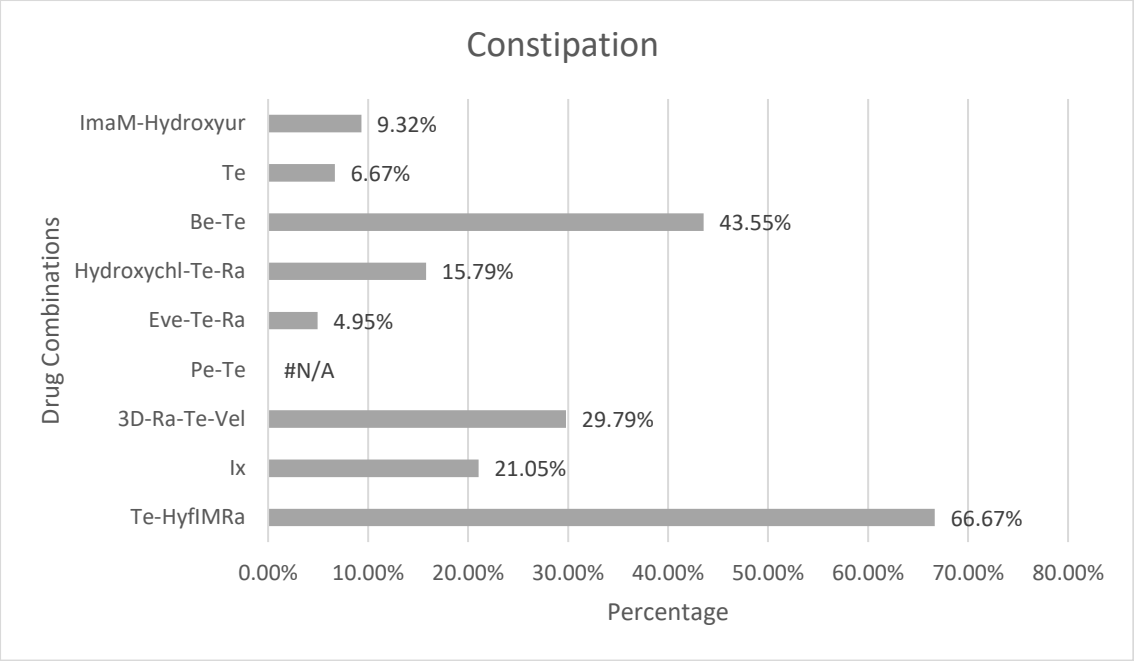
6(A):


Nausea
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
23.73%
9.17%
50.00%
46.05%
67.33%
#N/A
29.79%
36.84%
Drug Combinations
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%
80.00%
Percentage

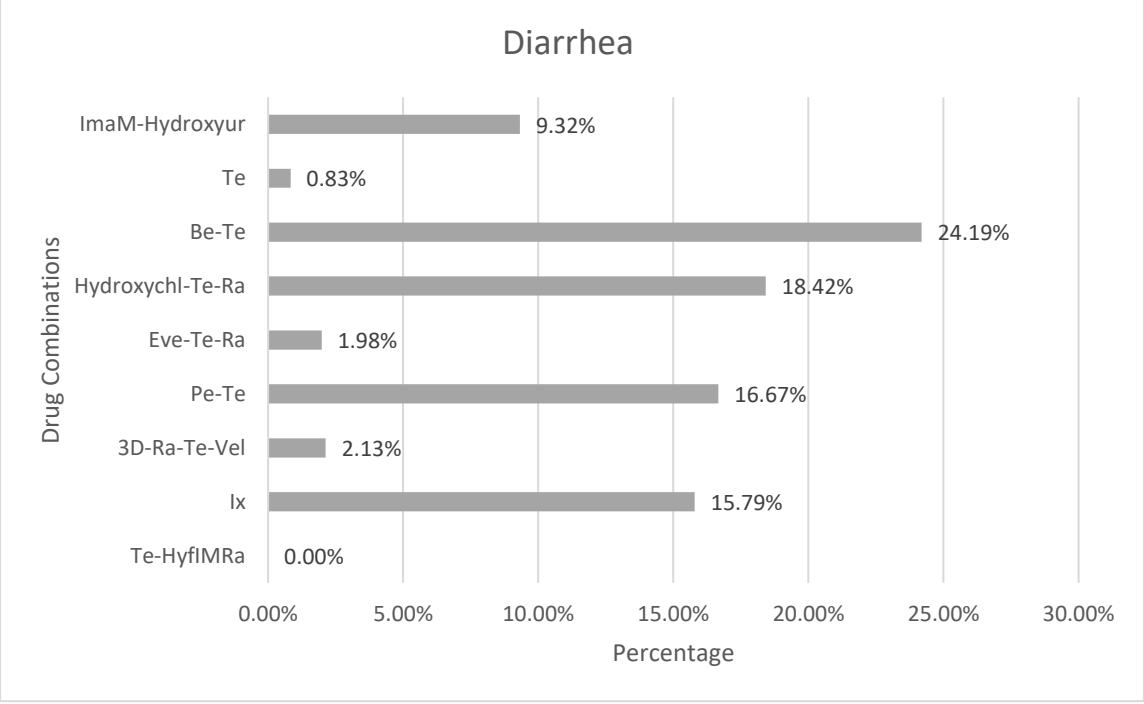
6(B):


Dyspepsia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
1.69%
#N/A
#N/A
6.58%
1.98%
0.00%
#N/A
0.00%
#N/A
Drug Combinations
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
Percentage

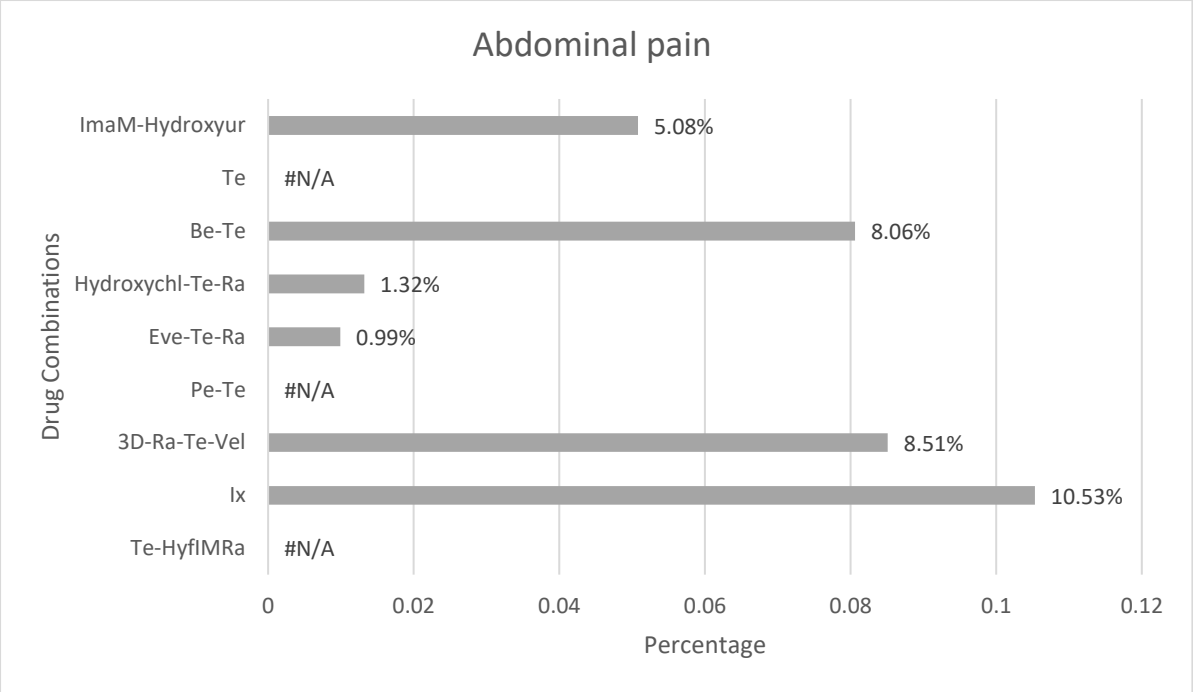
6(C):


Constipation
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyfIMRa
9.32%
6.67%
43.55%
15.79%
4.95%
#N/A
29.79%
21.05%
66.67%
Drug Combinations
0.00% 10.00% 20.00% 30.00% 40.00% 50.00% 60.00% 70.00% 80.00%
Percentage

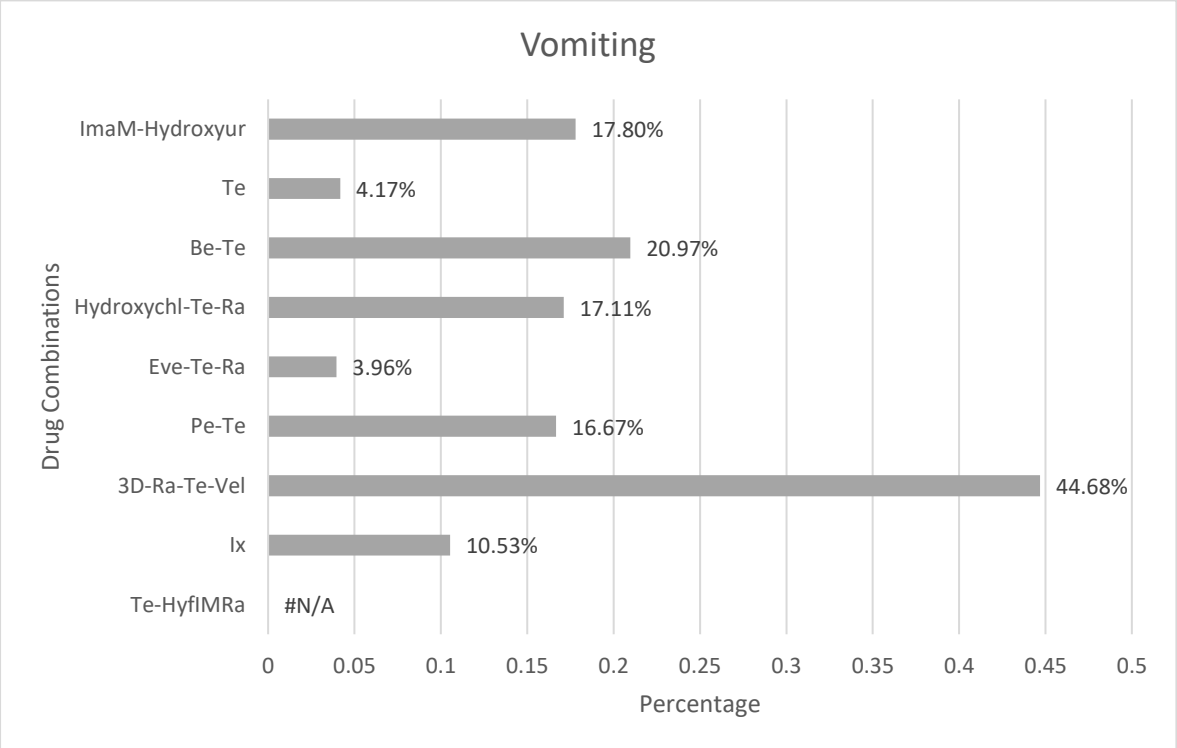
6(D):


Diarrhea
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyfIMRa
9.32%
0.83%
24.19%
18.42%
1.98%
16.67%
2.13%
15.79%
0.00%
Drug Combinations
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00%
Percentage

6(E):


Abdominal pain
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
Drug Combinations
5.08%
#N/A
8.06%
1.32%
0.99%
#N/A
8.51%
10.53%
#N/A
0
0.02
0.04
0.06
0.08
0.1
0.12
Percentage

6(F):


Vomiting
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
Drug Combinations
17.80%
4.17%
20.97%
17.11%
3.96%
16.67%
44.68%
10.53%
#N/A
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
Percentage

6(G):

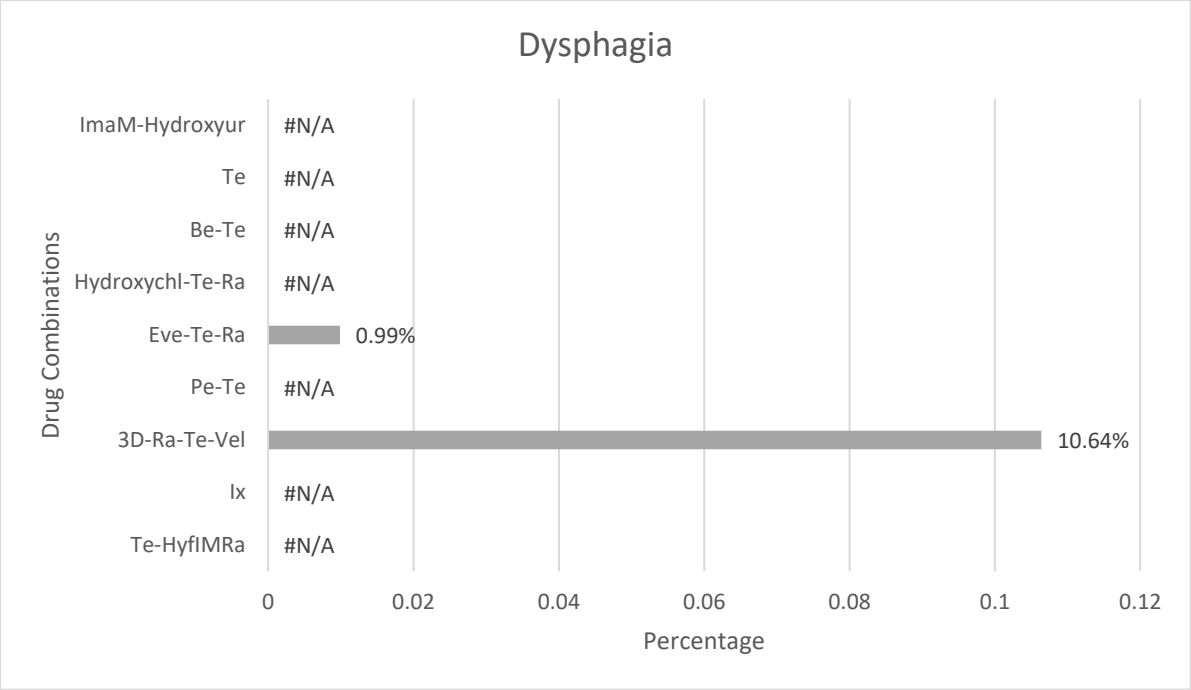
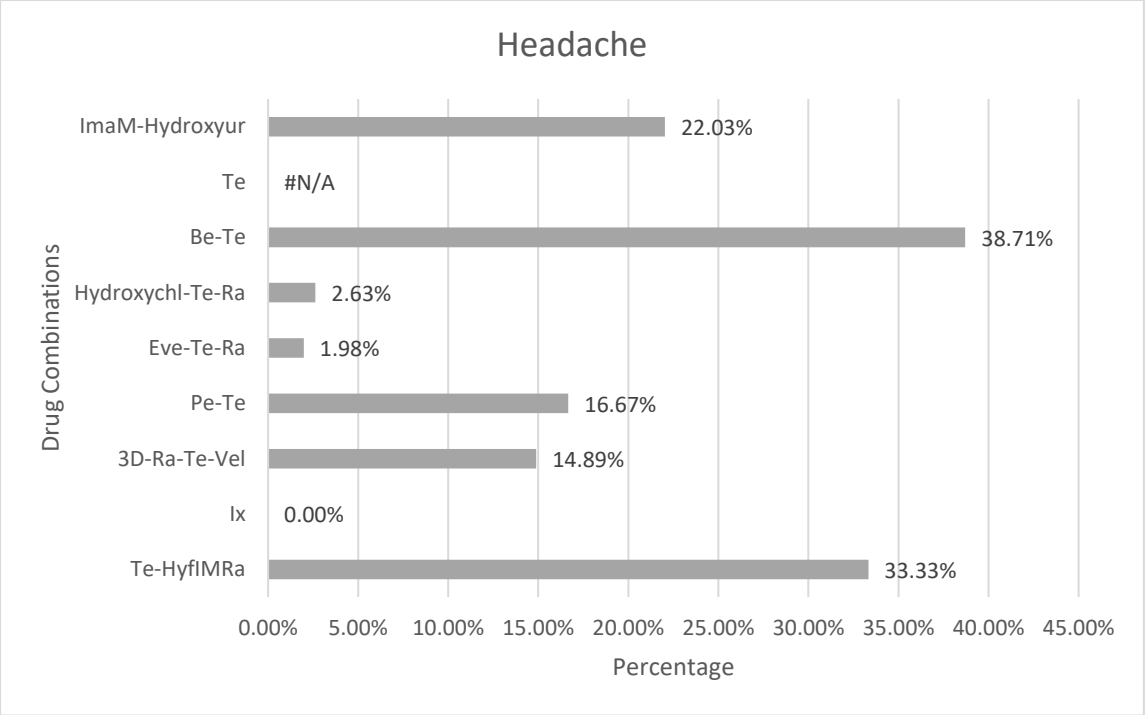


Figure 6: Percentage of Gastrointestinal disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

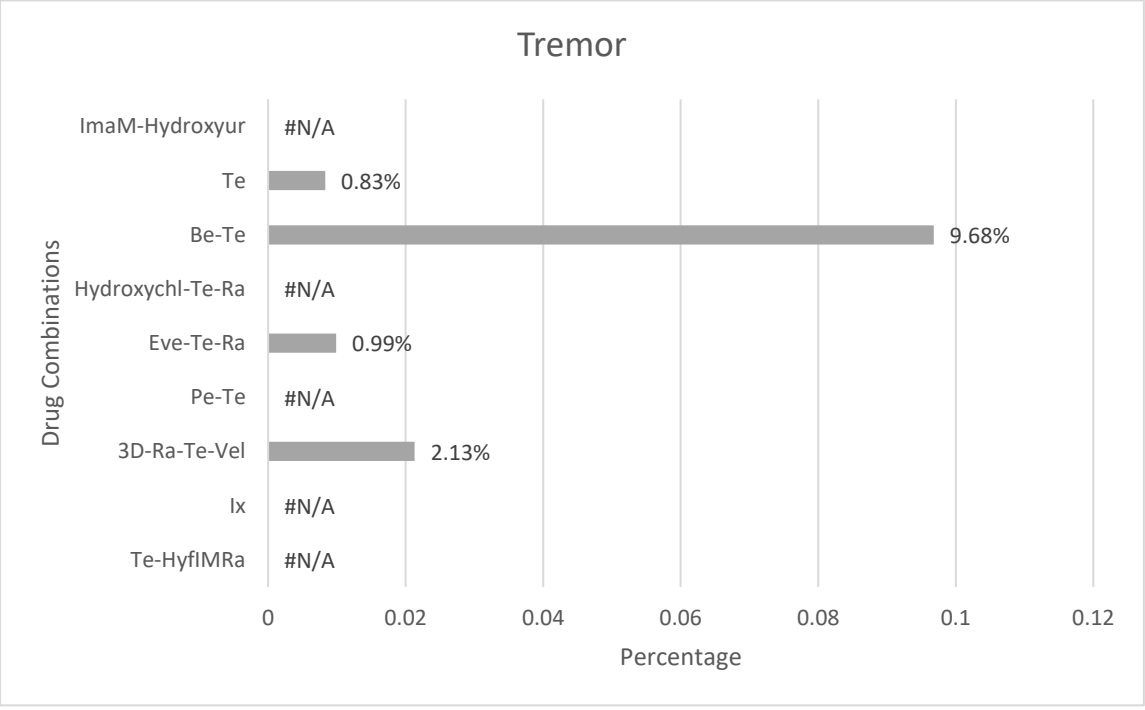
Gastrointestinal disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Nausea observed in patients receiving chemotherapeutic drug combinations. The highest rate of nausea was observed 67.33% in patients receiving Everolimus + Temozolomide + Radiotherapy combination. (B) represents percentage of Dyspepsia observed in patients receiving chemotherapeutic drug combinations. The highest rate of dyspepsia was observed 6.58% in patients receiving

Hydroxychloroquine + Temozolomide + Radiotherapy combination. (C) represents percentage of Constipation observed in patients receiving chemotherapeutic drug combinations. The highest rate of constipation was observed 66.67% in patients receiving Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy combination. (D) represents percentage of Diarrhea observed in patients receiving chemotherapeutic drug combinations. The highest rate of diarrhea was 24.19% in patients receiving Bevacizumab + Temozolomide combination. (E) represents percentage of Abdominal pain observed in patients receiving chemotherapeutic drug combinations. The highest rate of abdominal pain was observed 10.53% in patients receiving Ixabepilone chemotherapy. (F) represents percentage of Vomiting observed in patients receiving chemotherapeutic drug combinations. The highest rate of vomiting was observed 44.68% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (G) represents percentage of Dysphagia observed in patients receiving chemotherapeutic drug combinations. The highest rate of dysphagia was observed 10.64%. in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination.

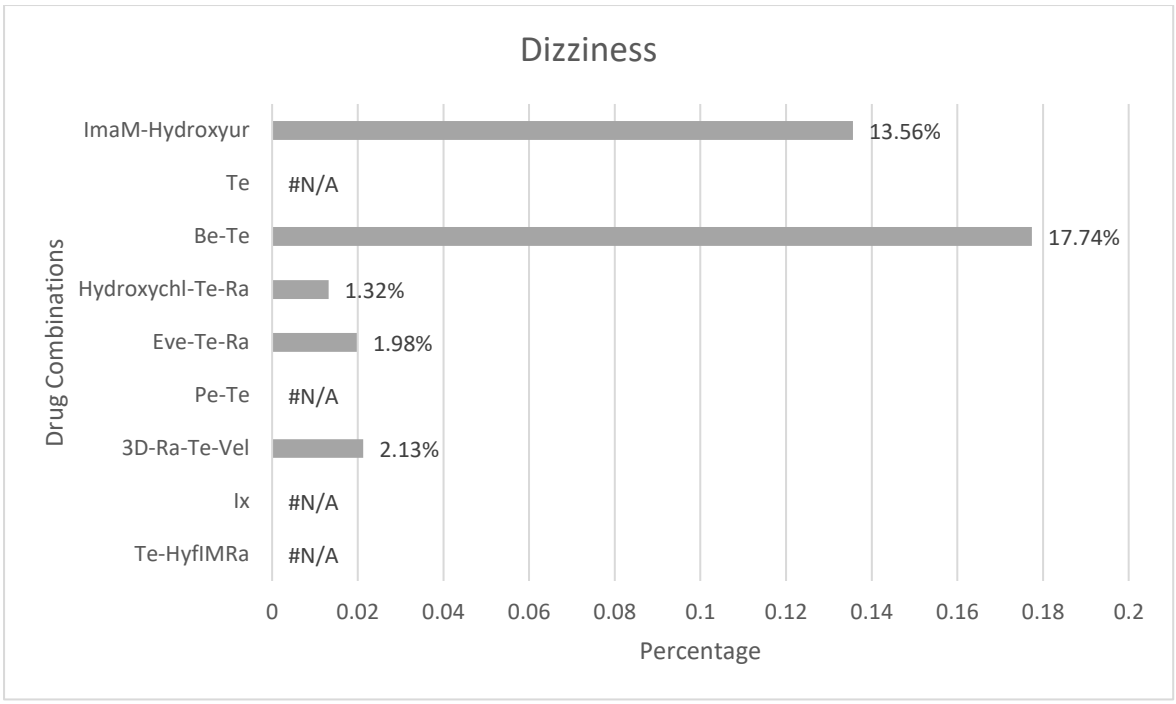
7(A):


Headache
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
22.03%
#N/A
38.71%
2.63%
1.98%
16.67%
14.89%
0.00%
33.33%
Drug Combinations
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00% 35.00% 40.00% 45.00%
Percentage

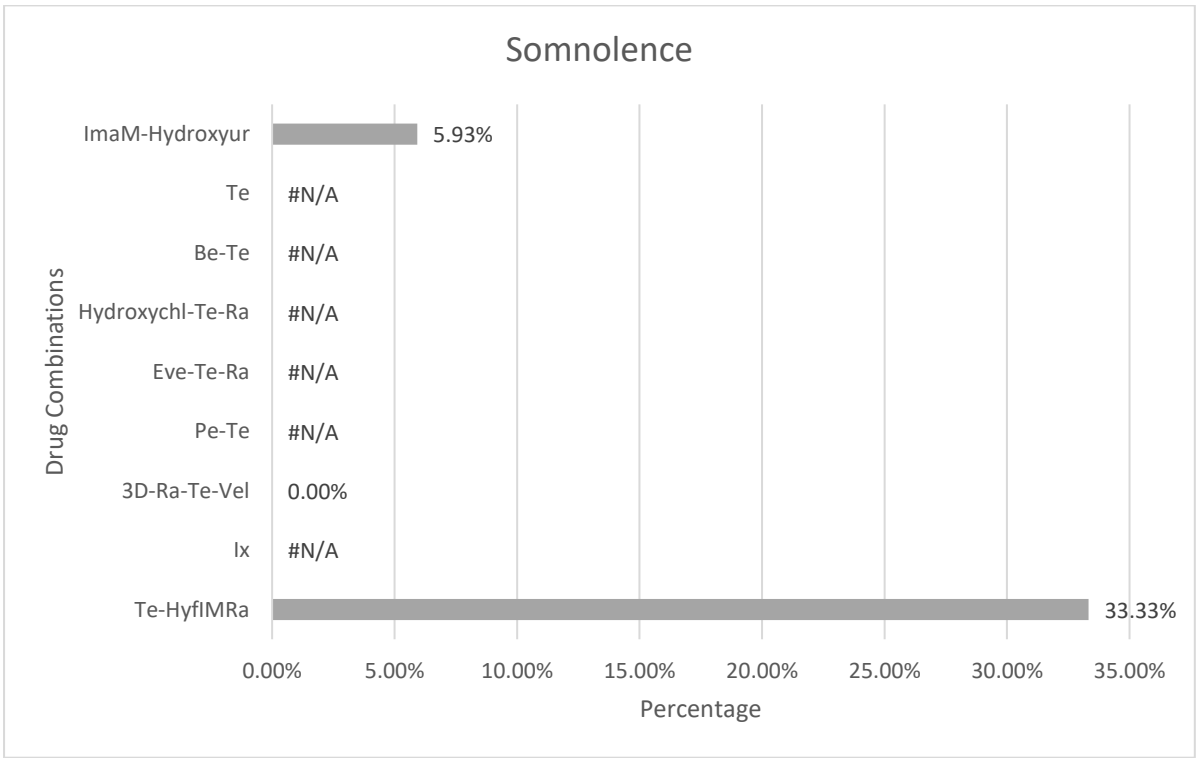
7(B):


Tremor
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
0.83%
9.68%
#N/A
0.99%
#N/A
2.13%
#N/A
#N/A
Drug Combinations
0 0.02 0.04 0.06 0.08 0.1 0.12
Percentage

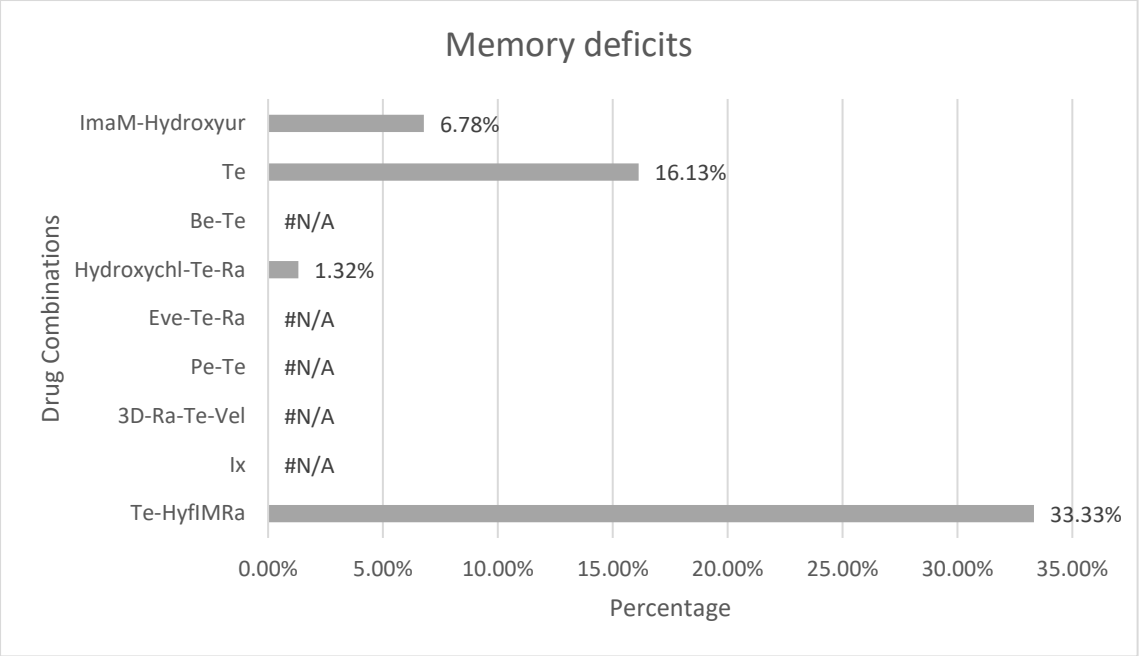
7(C)


Dizziness
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
13.56%
#N/A
17.74%
1.32%
1.98%
#N/A
2.13%
#N/A
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
0.18
0.2
Percentage

7(D):


Somnolence
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
5.93%
#N/A
#N/A
#N/A
#N/A
#N/A
0.00%
#N/A
33.33%
Drug Combinations
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
35.00%
Percentage

7(E):



7(F):

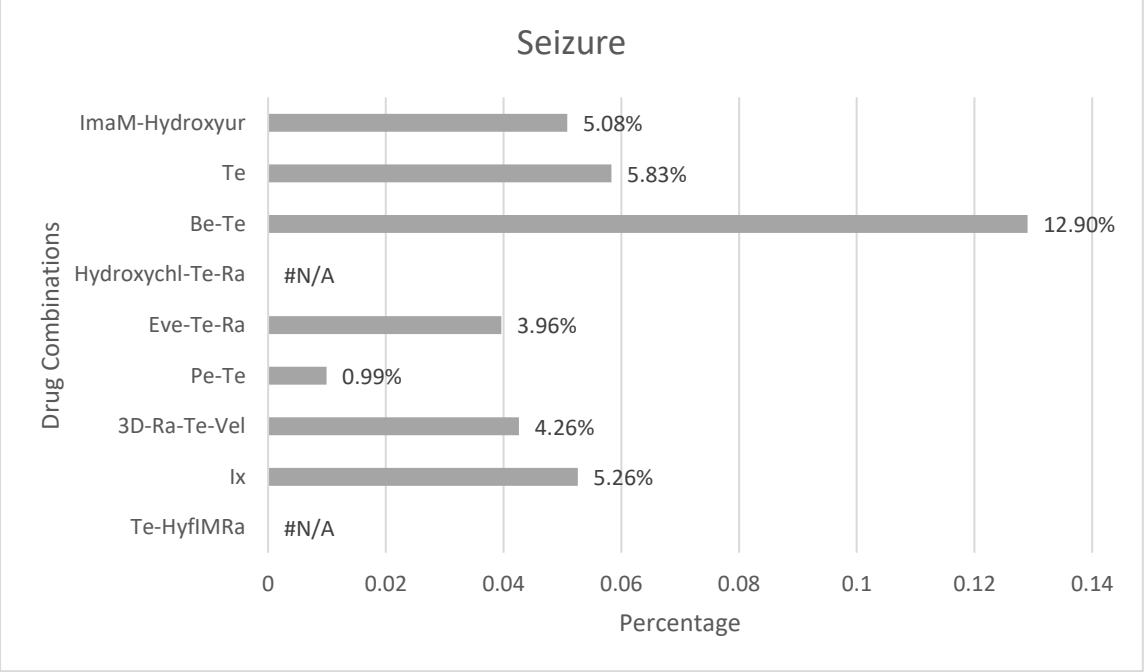
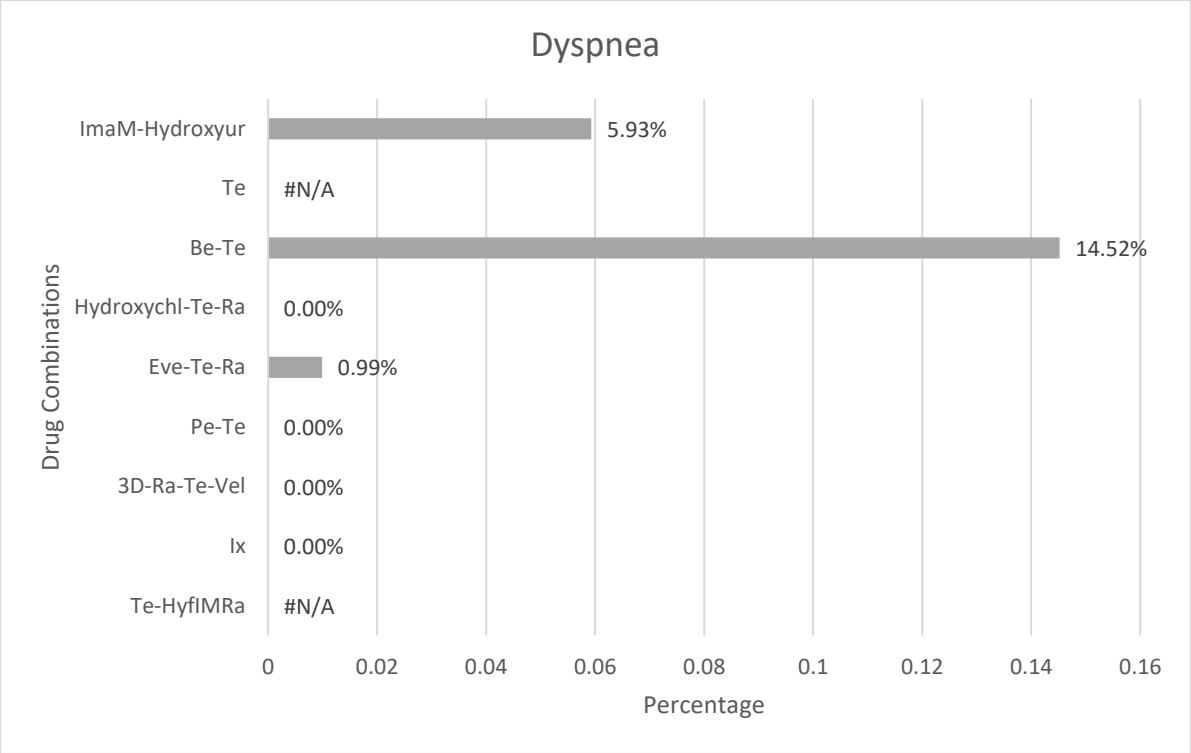


Figure 7: Percentage of Nervous system disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that

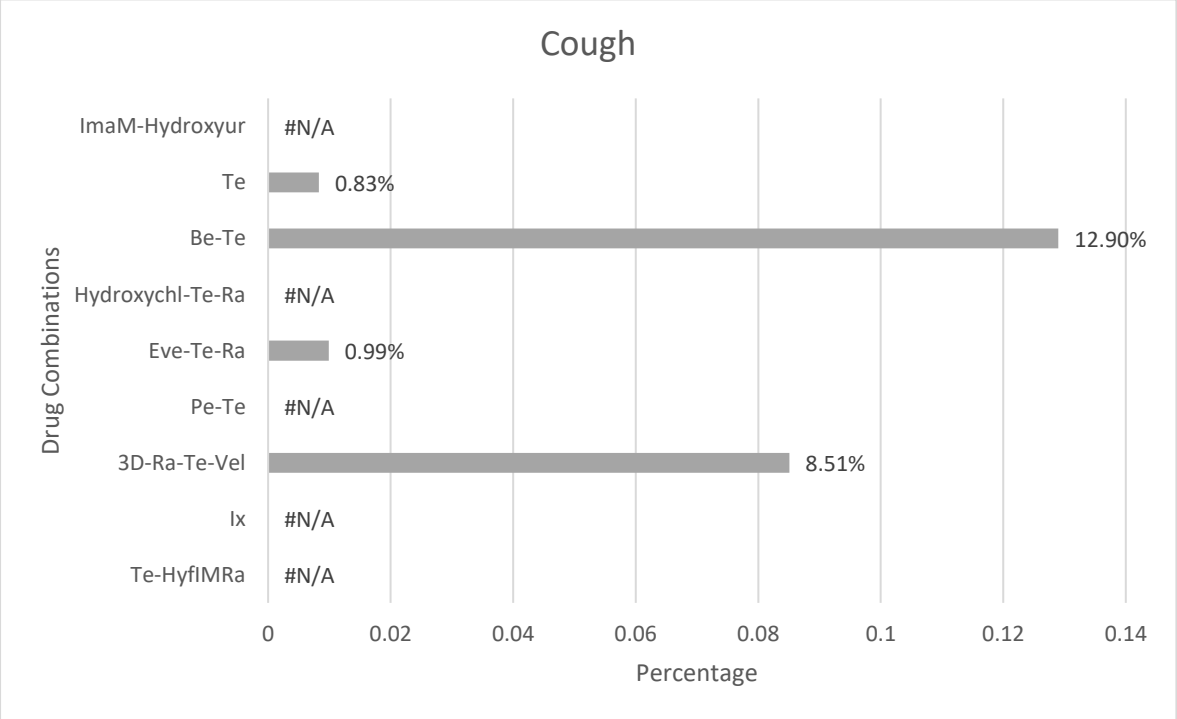
were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Nervous system disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Headache observed in patients receiving chemotherapeutic drug combinations. The highest rate of headache was observed 38.71% in patients receiving Bevacizumab + Temozolomide combination. (B) represents percentage of Tremor observed in patients receiving chemotherapeutic drug combinations. The highest rate of tremor was observed 9.68% in patients receiving Bevacizumab + Temozolomide combination. (C) represents percentage of Dizziness observed in patients receiving chemotherapeutic drug combinations. The highest rate of dizziness was observed 17.74% in patients receiving Bevacizumab + Temozolomide combination. (D) represents percentage of Somnolence observed in patients receiving chemotherapeutic drug combinations. The highest rate of somnolence was observed 33.33% in patients receiving Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy combination. (E) represents percentage of Memory deficits observed in patients receiving chemotherapeutic drug combinations. The highest rate of memory deficits was observed 33.33% in patients Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy combination. (F) represents percentage of Seizure observed in patients receiving chemotherapeutic drug combinations. The highest rate of seizure was observed 12.90% in patients receiving Bevacizumab + Temozolomide combination.

8(A):


Dyspnea
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
5.93%
#N/A
14.52%
0.00%
0.99%
0.00%
0.00%
0.00%
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
Percentage

8(B):


Cough
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
0.83%
12.90%
#N/A
0.99%
#N/A
8.51%
#N/A
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
Percentage

8(C):

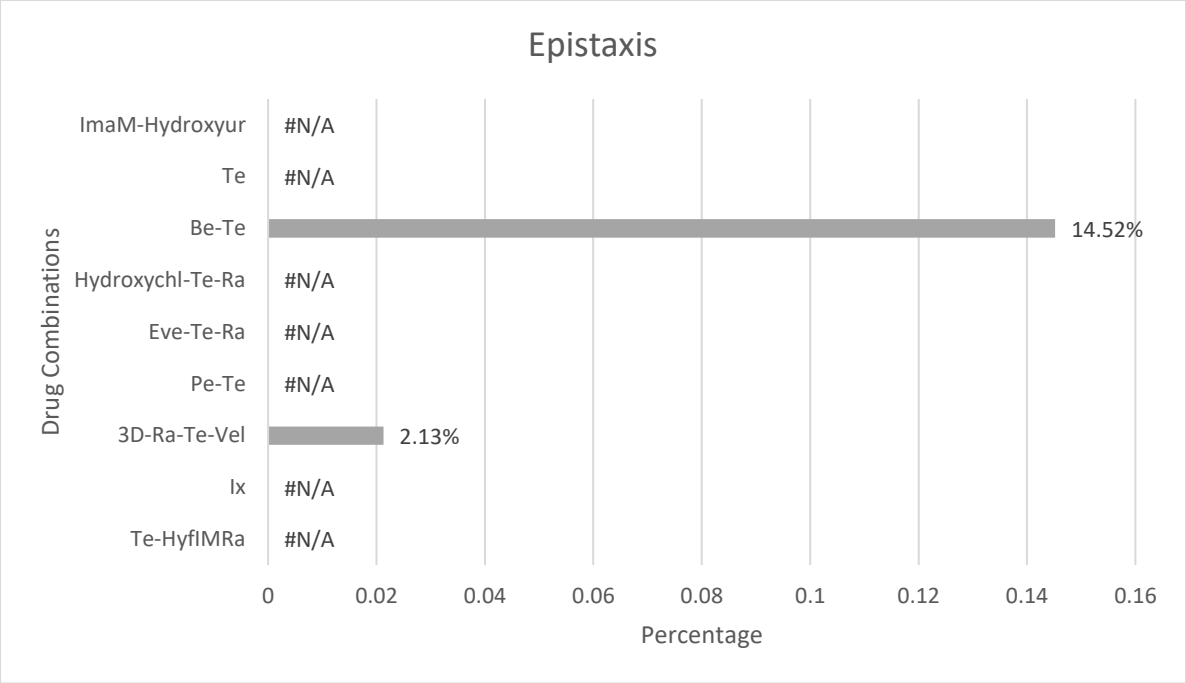


Figure 8: Percentage of Respiratory disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Respiratory disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Dyspnea observed in patients receiving chemotherapeutic drug combinations. The highest rate of dyspnea was observed 14.52% in patients receiving Bevacizumab + Temozolomide combination. (B) represents percentage of Cough observed in patients receiving chemotherapeutic drug combinations. The highest rate of cough was observed 12.90% in patients receiving

Bevacizumab + Temozolomide combination. (C) represents percentage of Epistaxis observed in patients receiving chemotherapeutic drug combinations. The highest rate of epitaxies was observed 14.52% in patients receiving Bevacizumab + Temozolomide combination.

9(A)

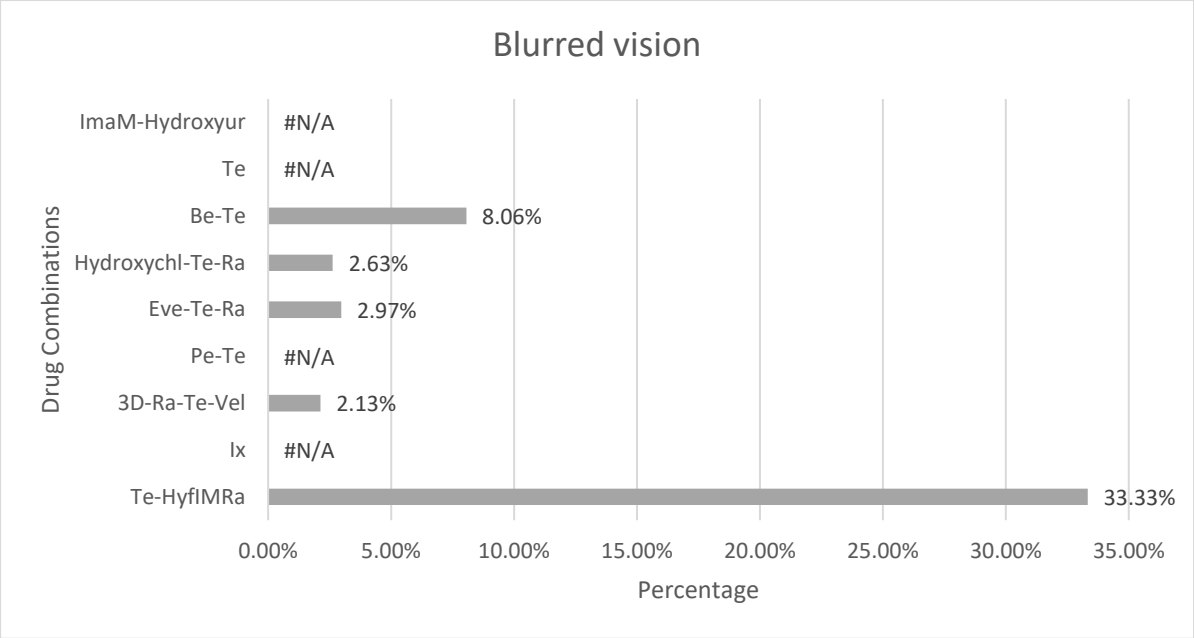
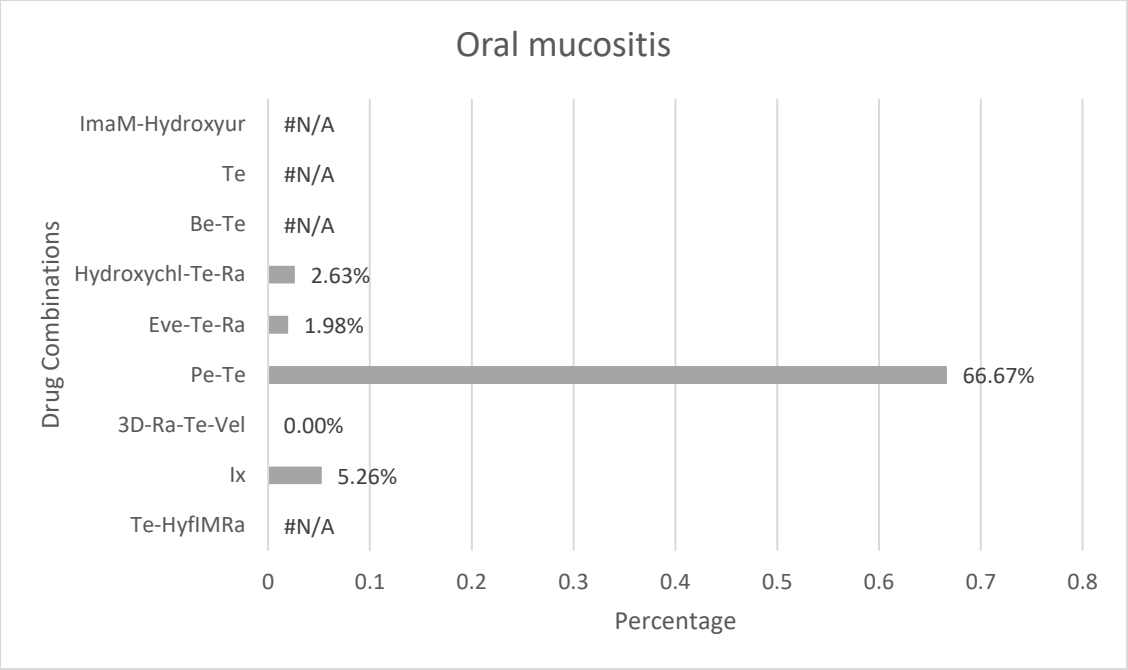


Figure 9: Percentage of Eye disorder in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Eye disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Blurred vision observed in patients receiving chemotherapeutic drug combinations. The highest rate of blurry vision was observed 33.33% in patients receiving Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy combination.

10(A):



10(B):

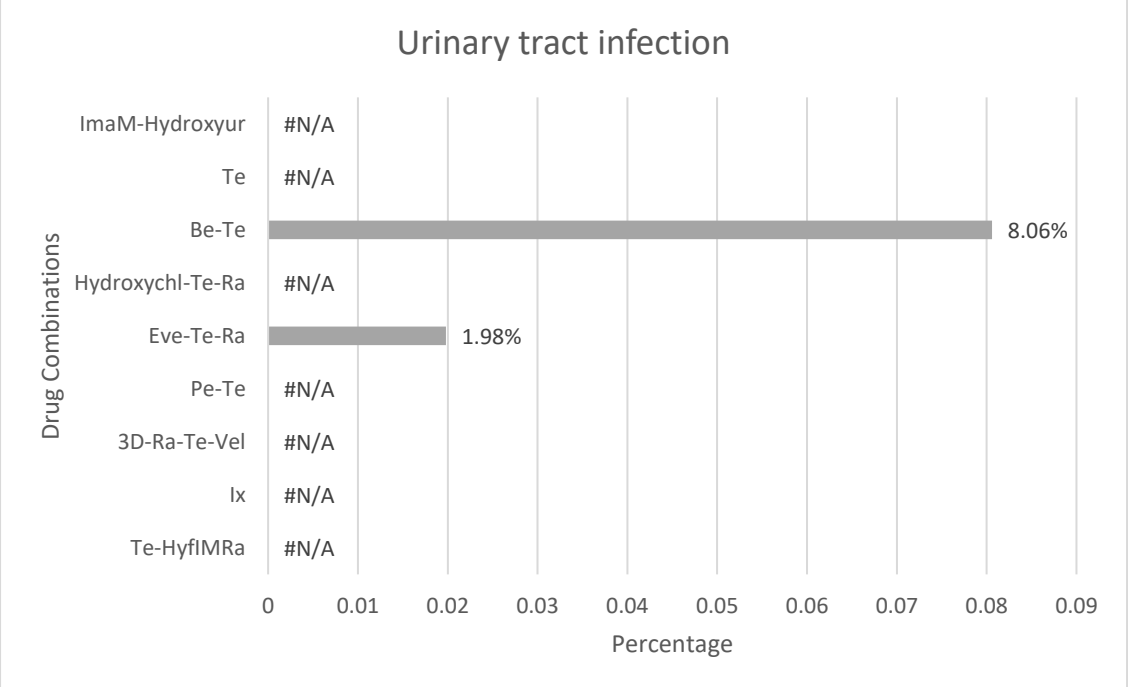
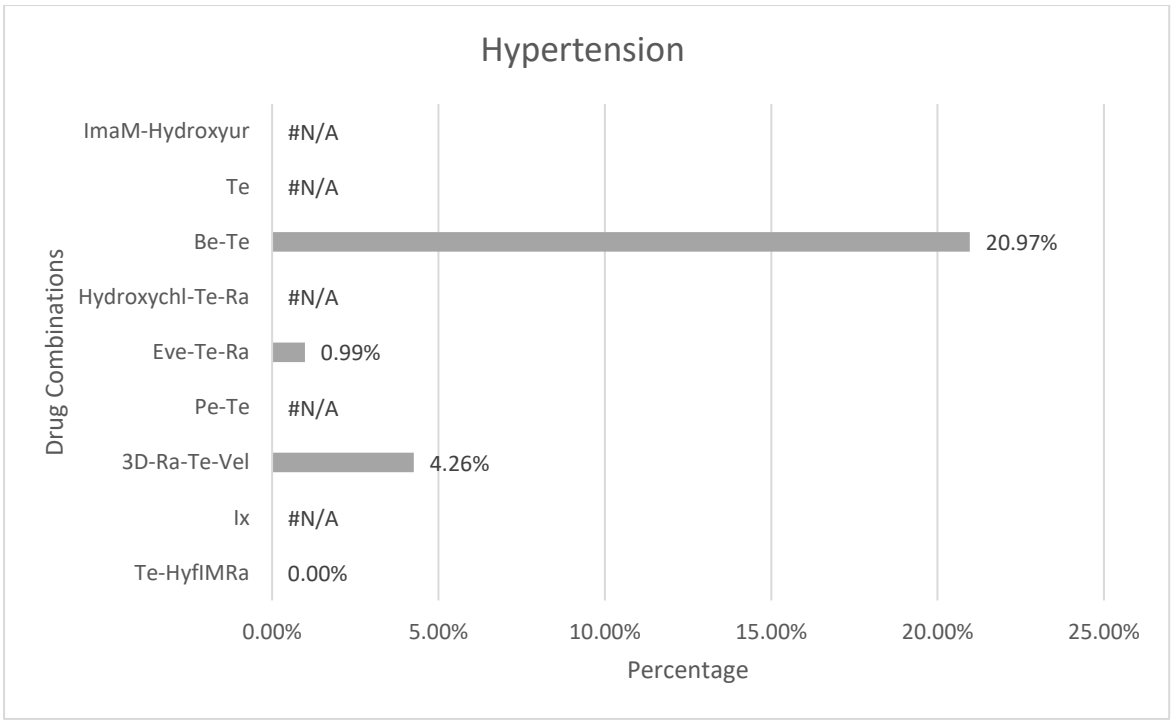


Figure 10: Percentage of Infections in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy,

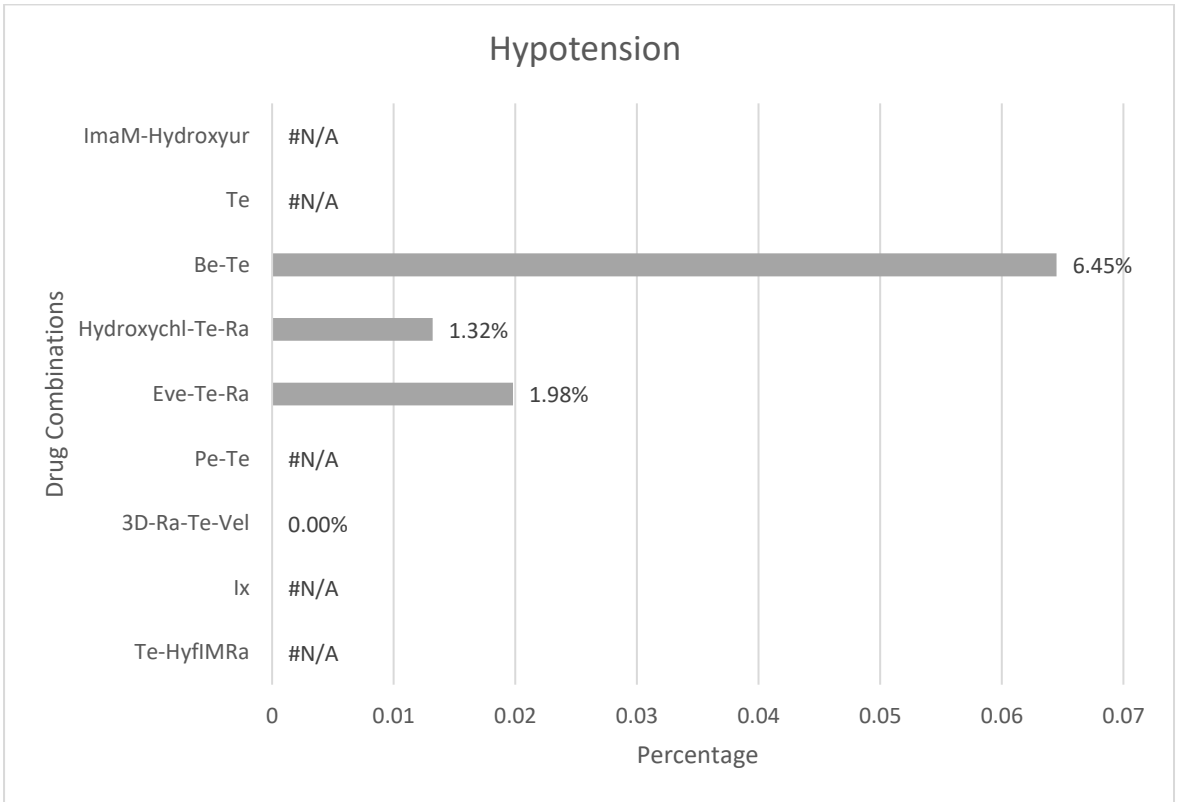
Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Infections are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Oral mucositis observed in patients receiving chemotherapeutic drug combinations. The highest rate of oral mucositis was observed 66.67% in patients receiving Perifosine + Temsirolimus combination. (B) represents percentage of Urinary tract infection observed in patients receiving chemotherapeutic drug combinations. The highest rate of urinary tract infection was observed 8.06% in patients receiving Bevacizumab + Temozolomide combination.

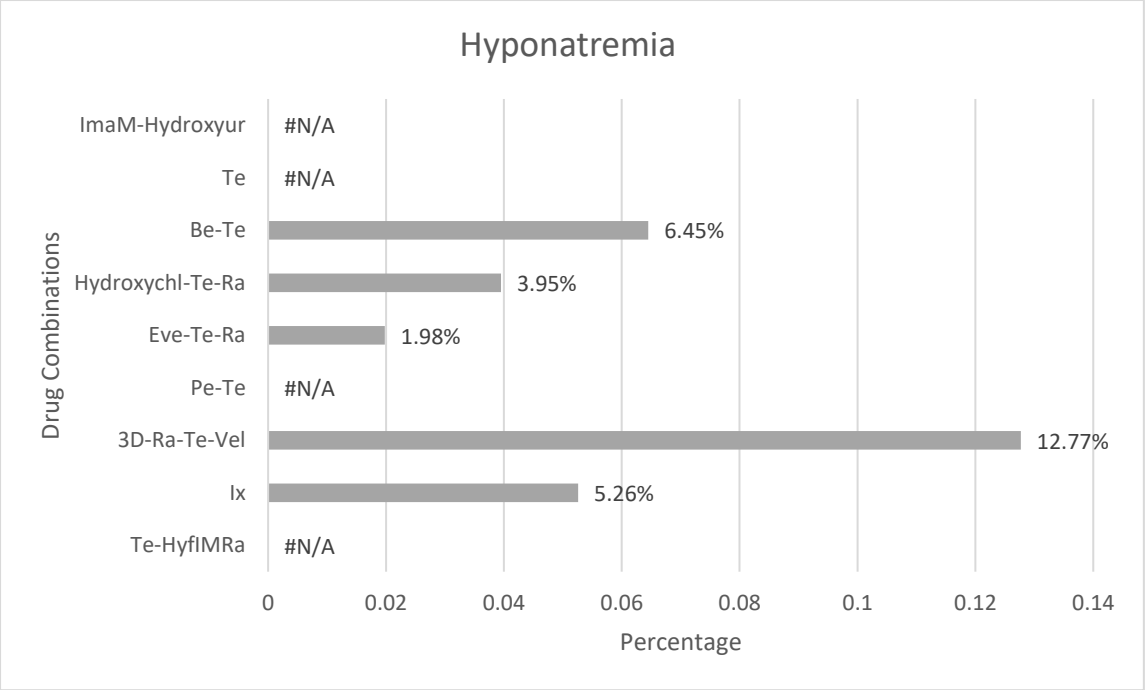
11(A):


Hypertension
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
20.97%
#N/A
0.99%
#N/A
4.26%
#N/A
0.00%
Drug Combinations
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
Percentage

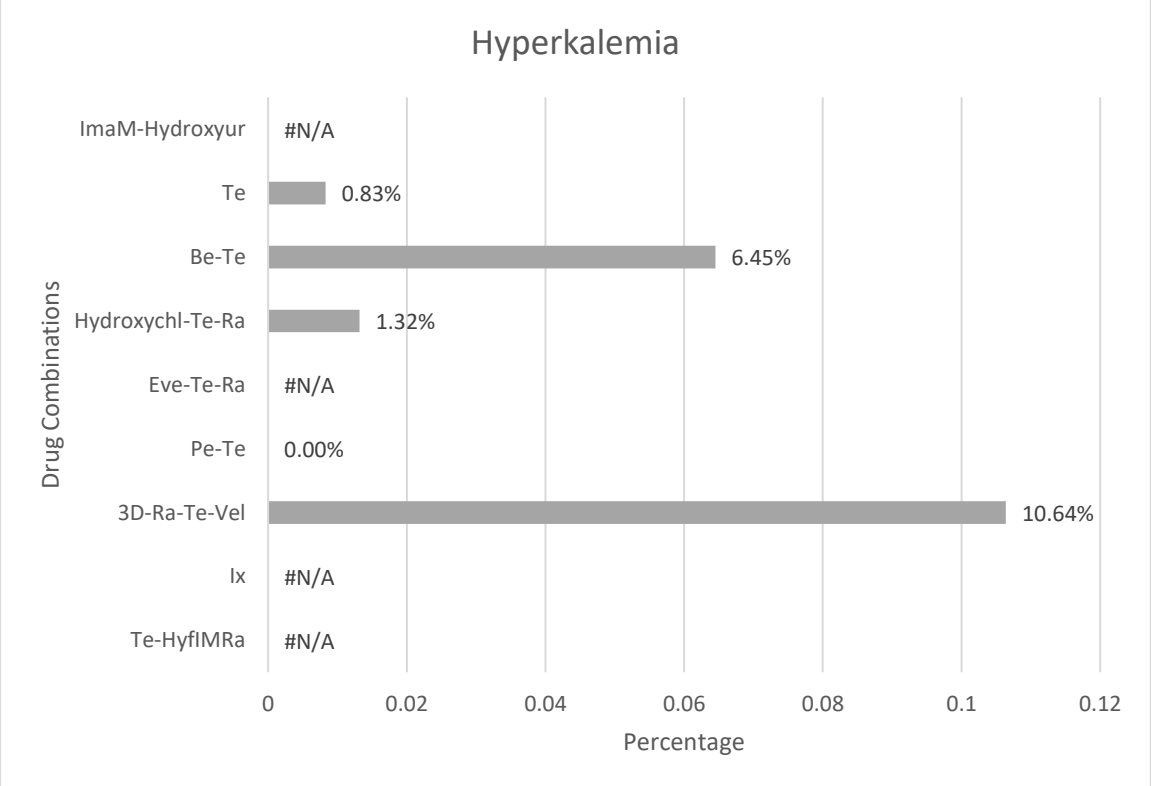
11(B):


Hypotension
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
6.45%
1.32%
1.98%
#N/A
0.00%
#N/A
#N/A
Drug Combinations
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
Percentage

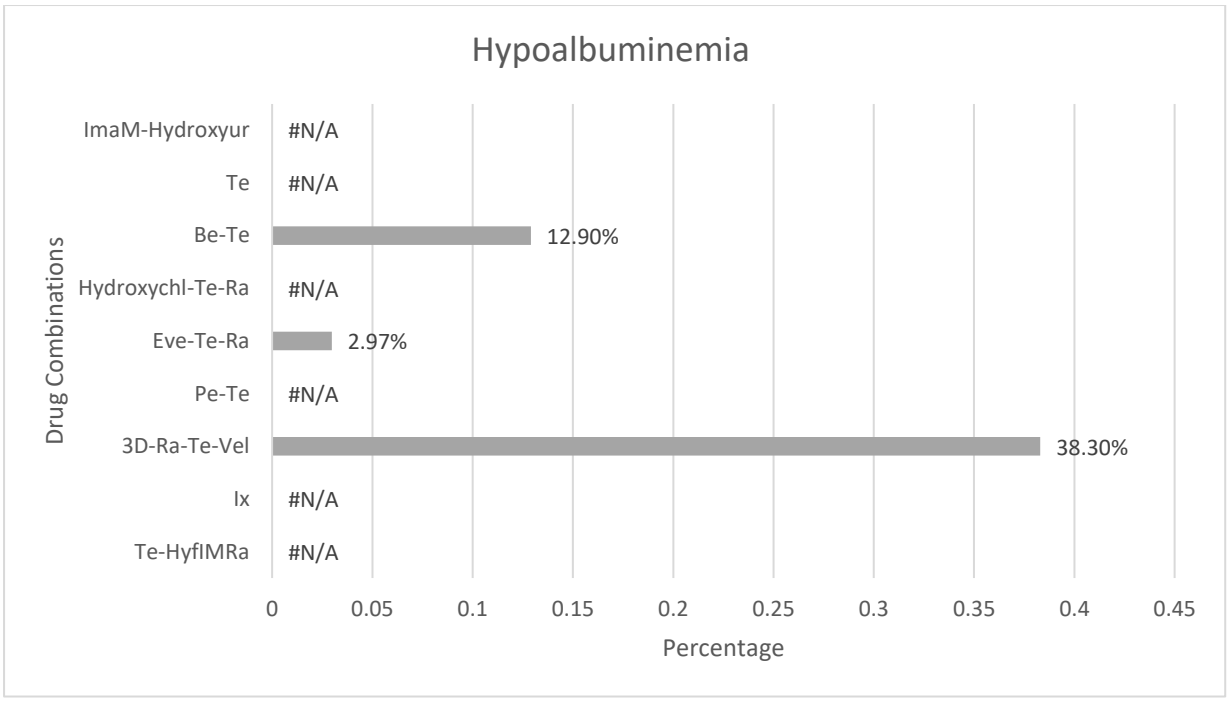
11(C):


Hyponatremia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
6.45%
3.95%
1.98%
#N/A
12.77%
5.26%
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
Percentage

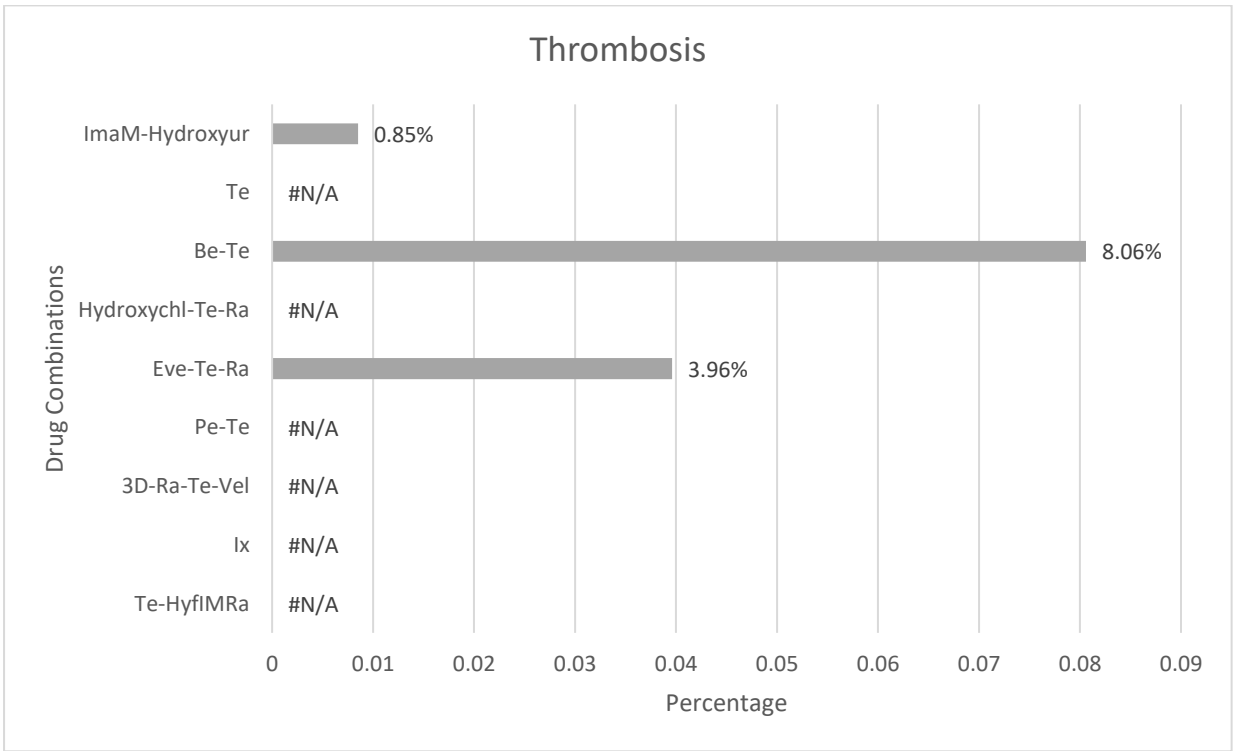
11(D):


Hyperkalemia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
0.83%
6.45%
1.32%
#N/A
0.00%
10.64%
#N/A
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
Percentage

11(E):


Hypoalbuminemia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
12.90%
#N/A
2.97%
#N/A
38.30%
#N/A
#N/A
Drug Combinations
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
Percentage

11(F):


Thrombosis
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
0.85%
#N/A
8.06%
#N/A
3.96%
#N/A
#N/A
#N/A
Drug Combinations
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
Percentage

11(G):

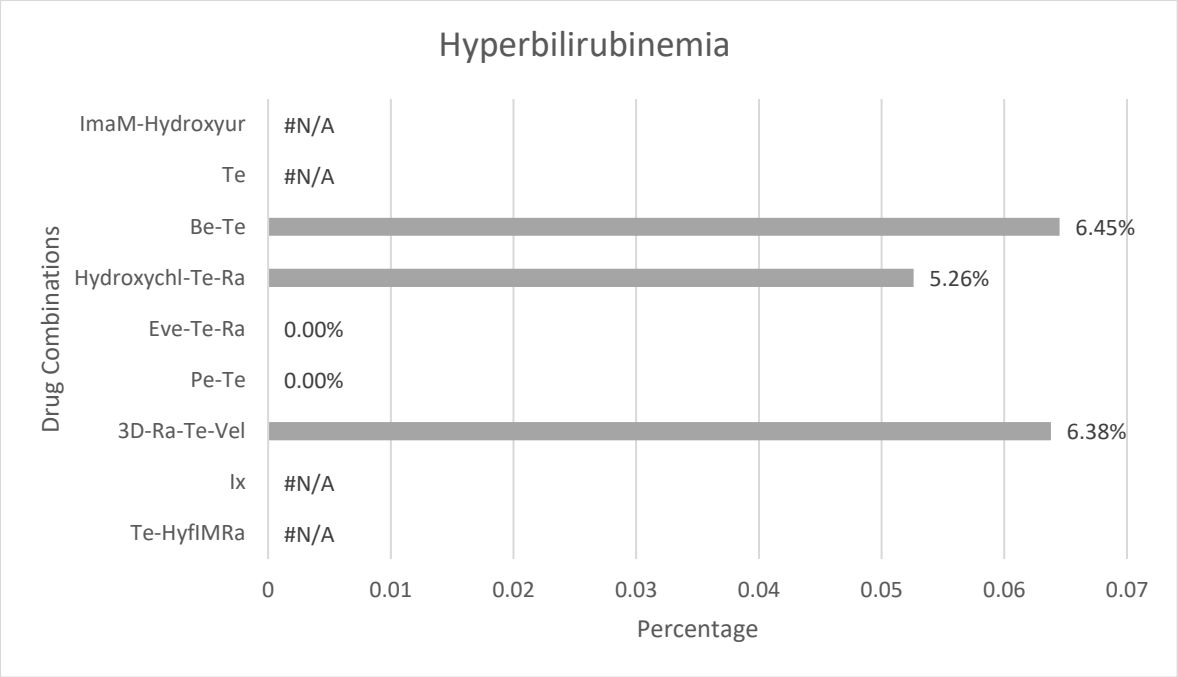
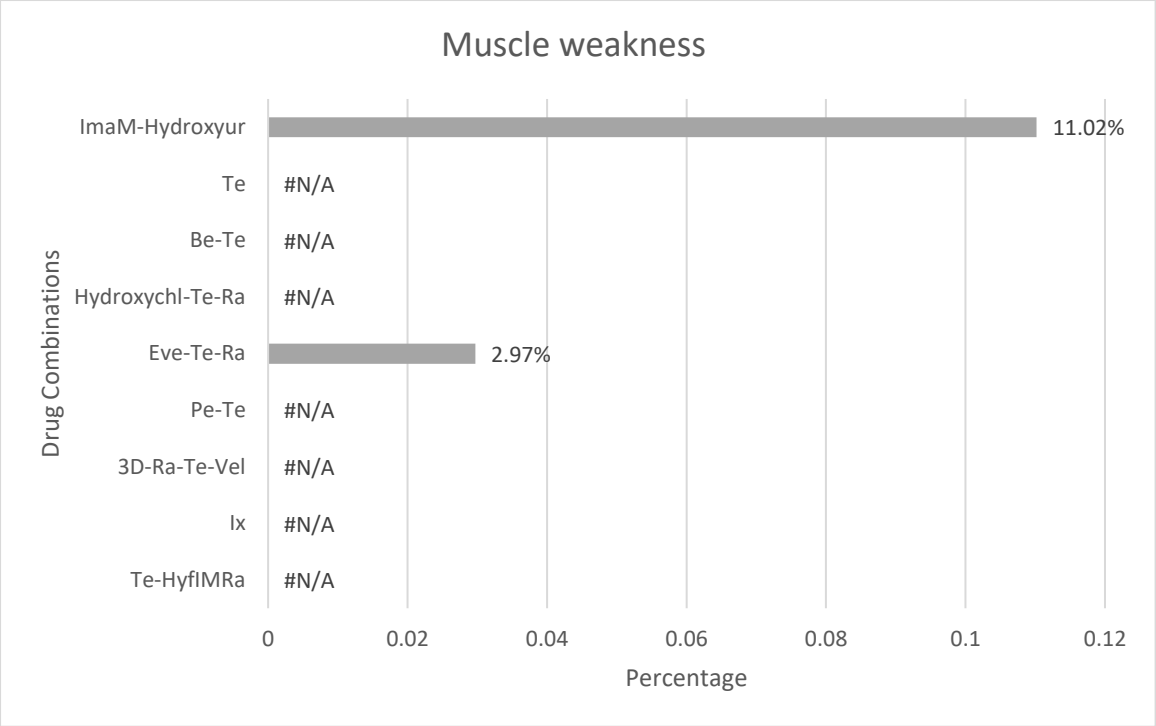


Figure 11: Percentage of Vascular disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

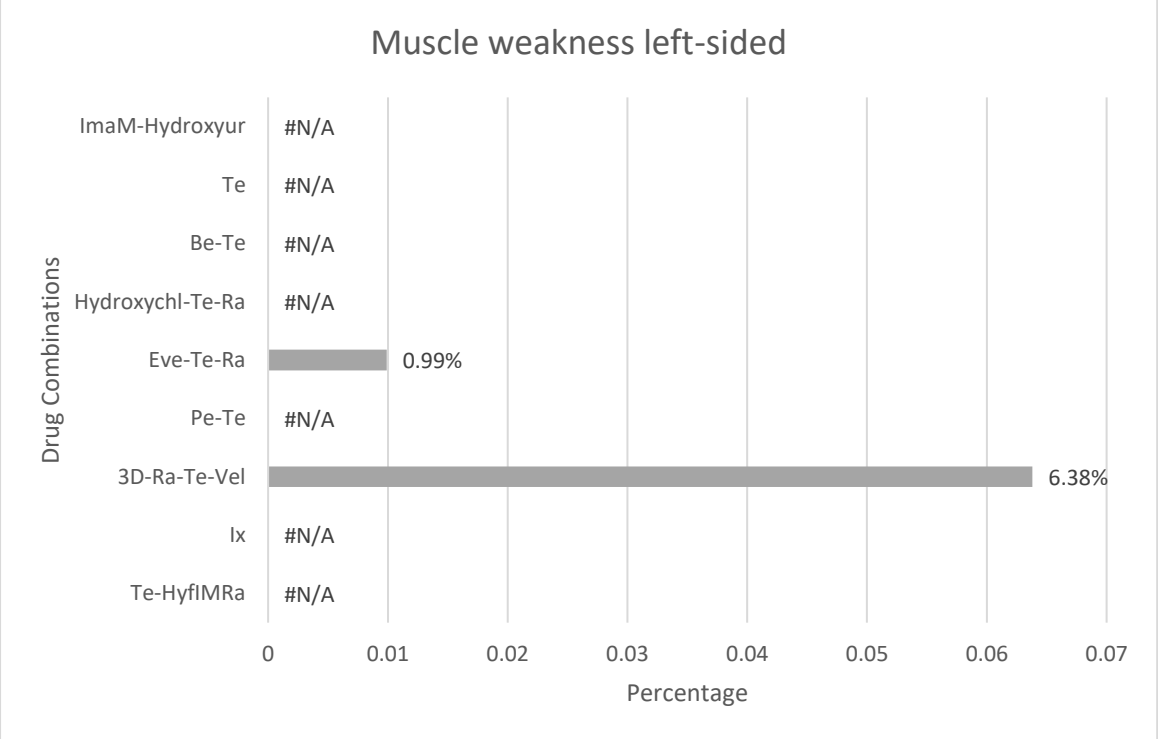
Vascular disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Hypertension observed in patients receiving chemotherapeutic drug combinations. The highest rate of hypertension was observed 20.97% in patients receiving Bevacizumab + Temozolomide combination. (B) represents percentage of Hypotension observed in patients receiving chemotherapeutic drug combinations. The highest rate of hypotension was observed 6.45% in patients receiving

Bevacizumab + Temozolomide combination. (C) represents percentage of Hyponatremia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hyponatremia was observed 12.77% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (D) represents percentage of Hyperkalemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hyperkalemia was observed 10.64% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (E) represents percentage of Hypoalbuminemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hypoalbuminemia was observed 38.30% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (F) represents percentage of Thrombosis observed in patients receiving chemotherapeutic drug combinations. The highest rate of thrombosis was observed 8.06% in patients receiving Bevacizumab + Temozolomide combination. (G) represents percentage of Hyperbilirubinemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hyperbilirubinemia was observed 6.45% in patients receiving Bevacizumab + Temozolomide combination.

12(A):


Muscle weakness
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
11.02%
#N/A
#N/A
#N/A
2.97%
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
Percentage

12(B):


Muscle weakness left-sided
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
#N/A
0.99%
#N/A
6.38%
#N/A
#N/A
Drug Combinations
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
Percentage

12(C):

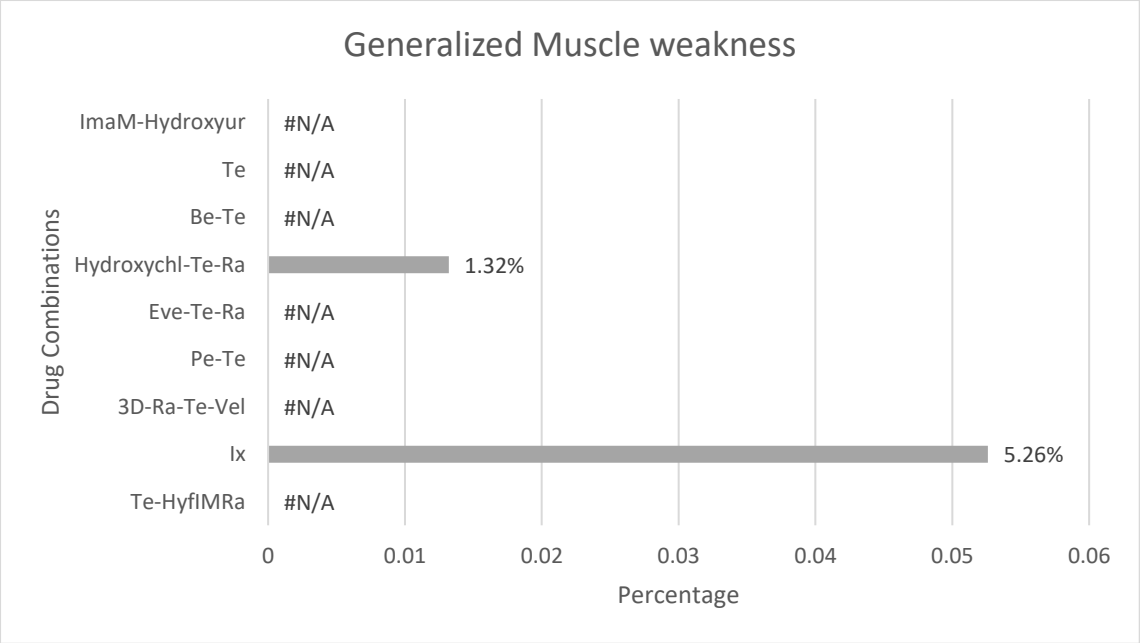
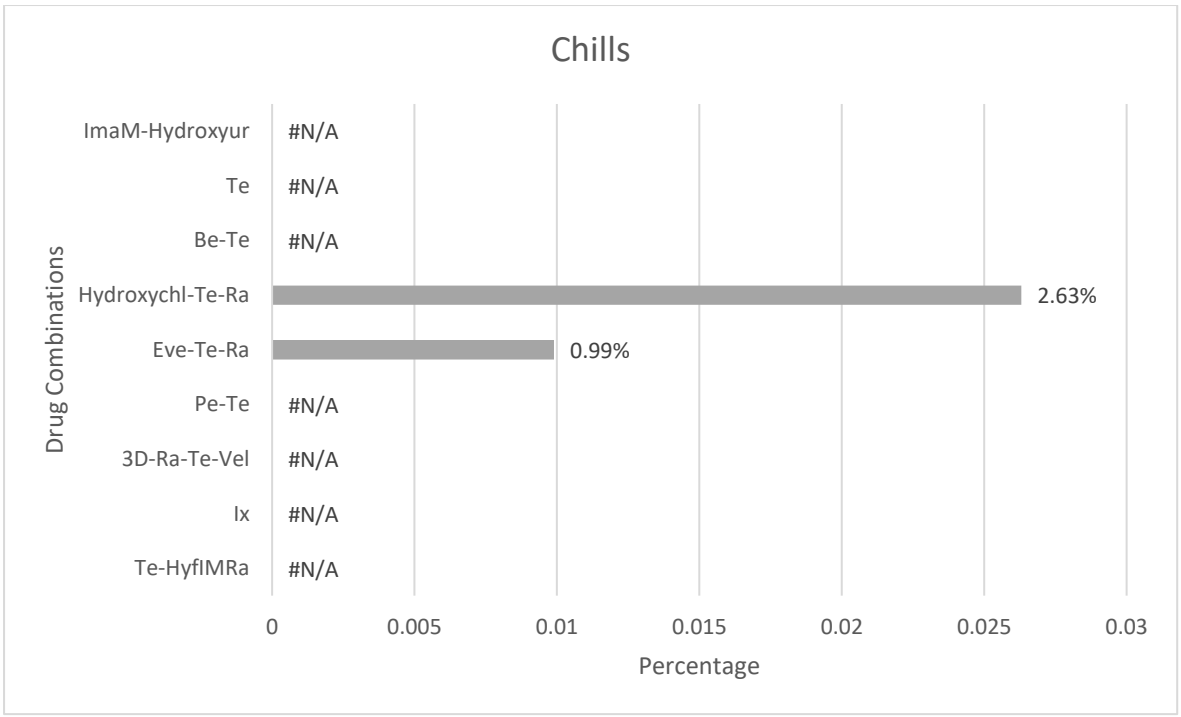


Figure 12: Percentage of Musculoskeletal disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

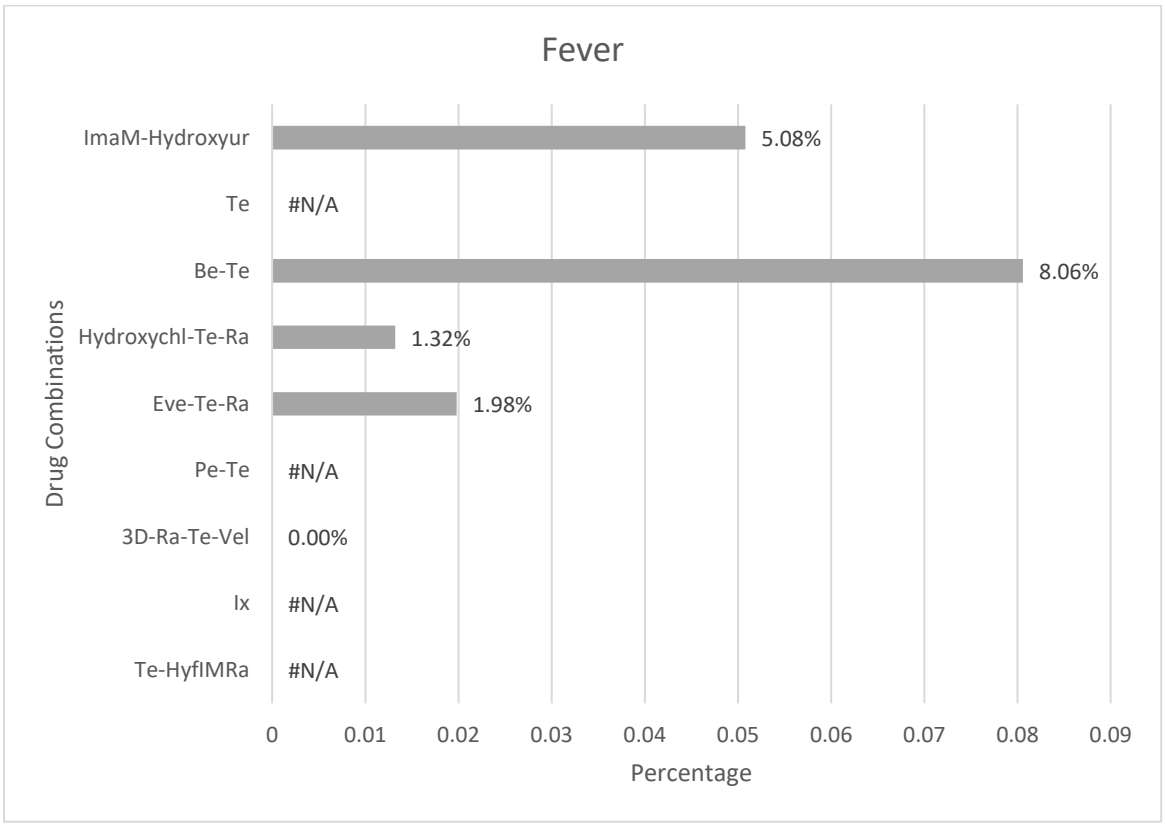
Musculoskeletal disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Muscle weakness observed in patients receiving chemotherapeutic drug combinations. The highest rate of muscle weakness was observed 11.02% in patients receiving Imatinib Mesylate + Hydroxyurea combination. (B) represents percentage of Muscle weakness left-sided observed in patients receiving chemotherapeutic drug combinations. The highest rate of left sided muscle weakness

was observed 6.38% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (C) represents percentage of Generalized Muscle weakness observed in patients receiving chemotherapeutic drug combinations. The highest rate of generalized muscle weakness was observed 5.26% in patients receiving Ixabepilone.

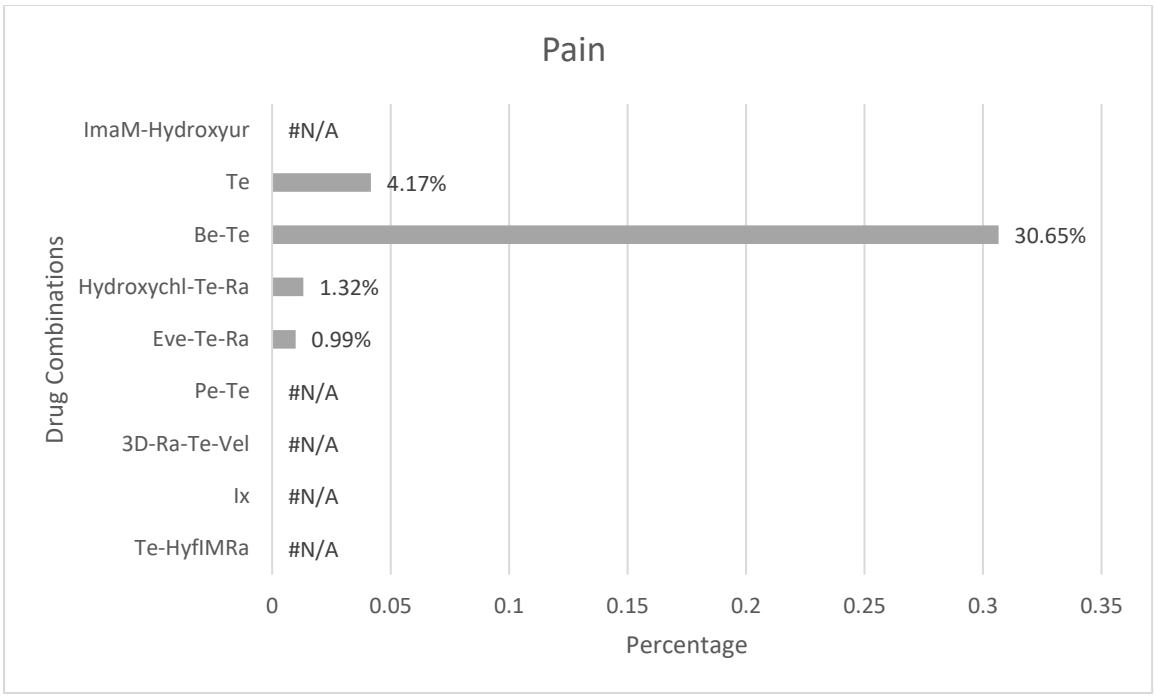
13(A):


Chills
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
2.63%
0.99%
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0
0.005
0.01
0.015
0.02
0.025
0.03
Percentage

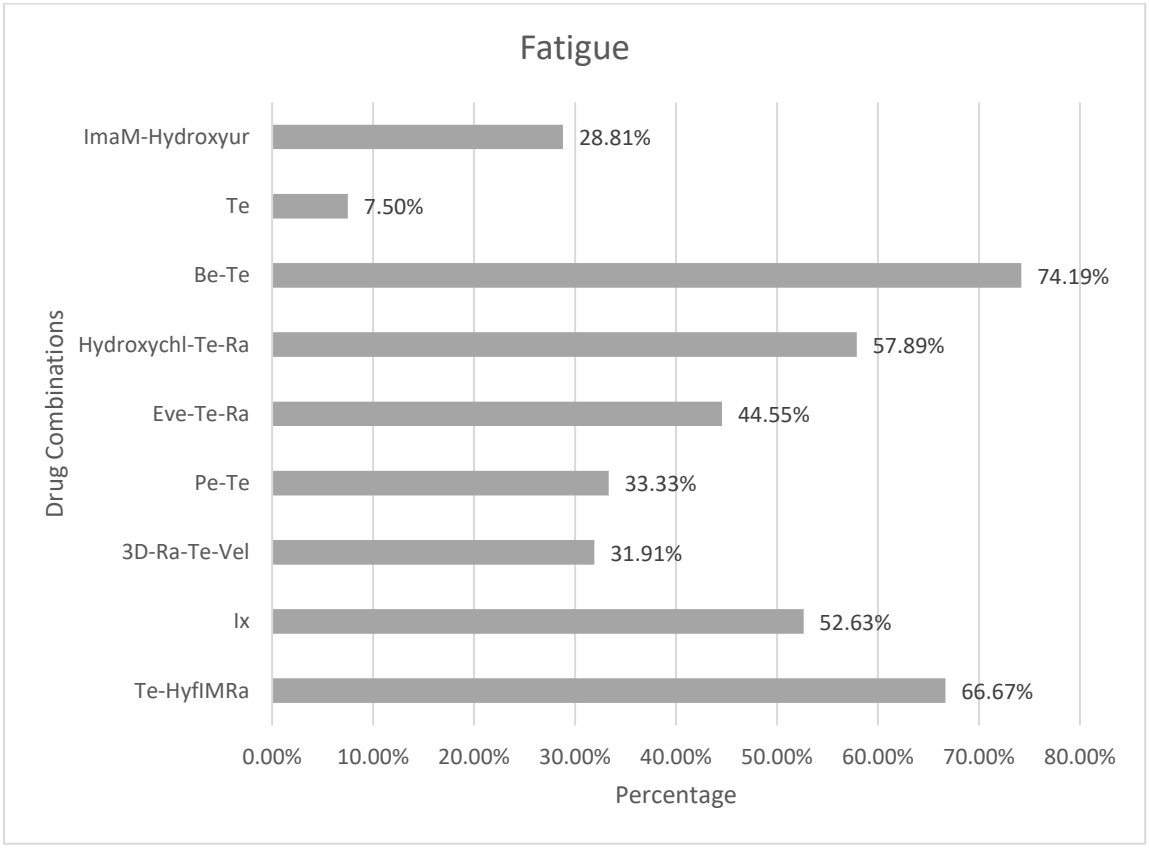
13(B):


Fever
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
5.08%
#N/A
8.06%
1.32%
1.98%
#N/A
0.00%
#N/A
#N/A
Drug Combinations
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
Percentage

13(C):


Pain
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyfIMRa
#N/A
4.17%
30.65%
1.32%
0.99%
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
Percentage

13(D):


Fatigue
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyfIMRa
28.81%
7.50%
74.19%
57.89%
44.55%
33.33%
31.91%
52.63%
66.67%
Drug Combinations
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
70.00%
80.00%
Percentage

13(E):

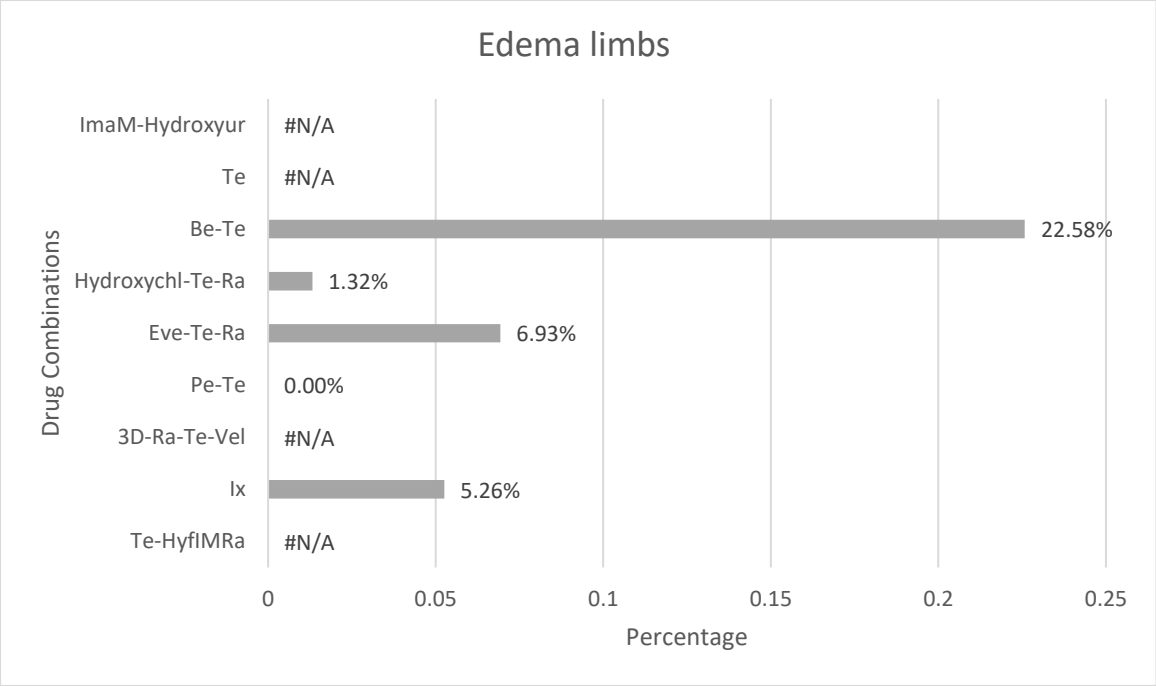
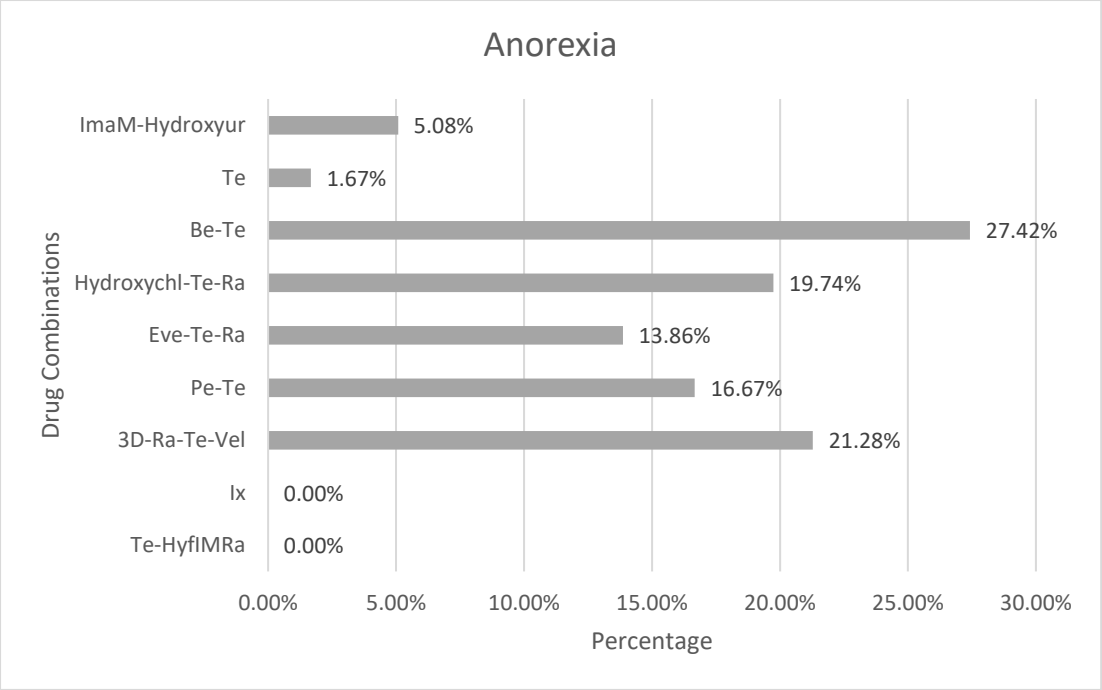


Figure 13: Percentage of General disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

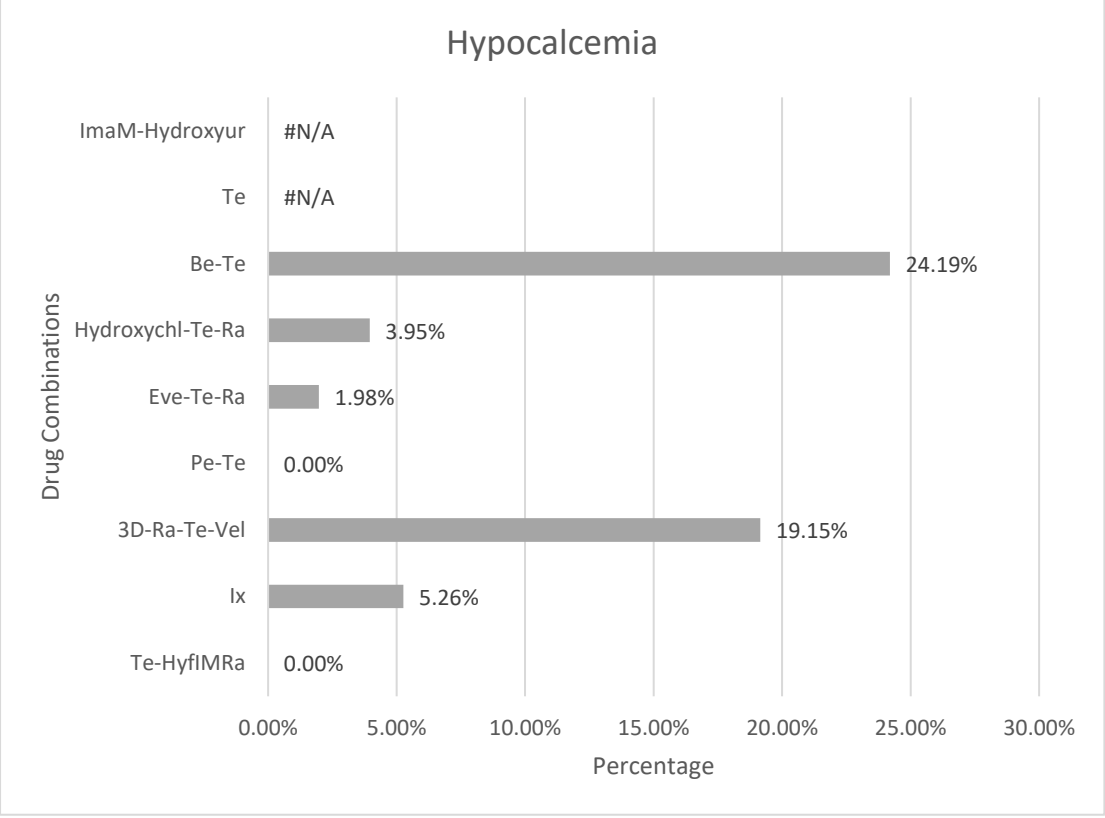
General disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Chills observed in patients receiving chemotherapeutic drug combinations. The highest rate of chills was observed 2.63% in patients receiving Hydroxychloroquine + Temozolomide + Radiotherapy combination. (B) represents percentage of Fever observed in patients receiving chemotherapeutic drug combinations. The highest rate of fever was observed 8.06% in patients receiving Bevacizumab + Temozolomide

combination. (C) represents percentage of Pain observed in patients receiving chemotherapeutic drug combinations. The highest rate of pain was observed 30.65% in patients receiving Bevacizumab + Temozolomide combination. (D) represents percentage of Fatigue observed in patients receiving chemotherapeutic drug combinations. The highest rate of fatigue was observed 74.19% in patients receiving Bevacizumab + Temozolomide combination. (E) represents percentage of Edema limbs observed in patients receiving chemotherapeutic drug combinations. The highest rate of edema limbs was observed 22.58% in patients receiving Bevacizumab + Temozolomide combination.

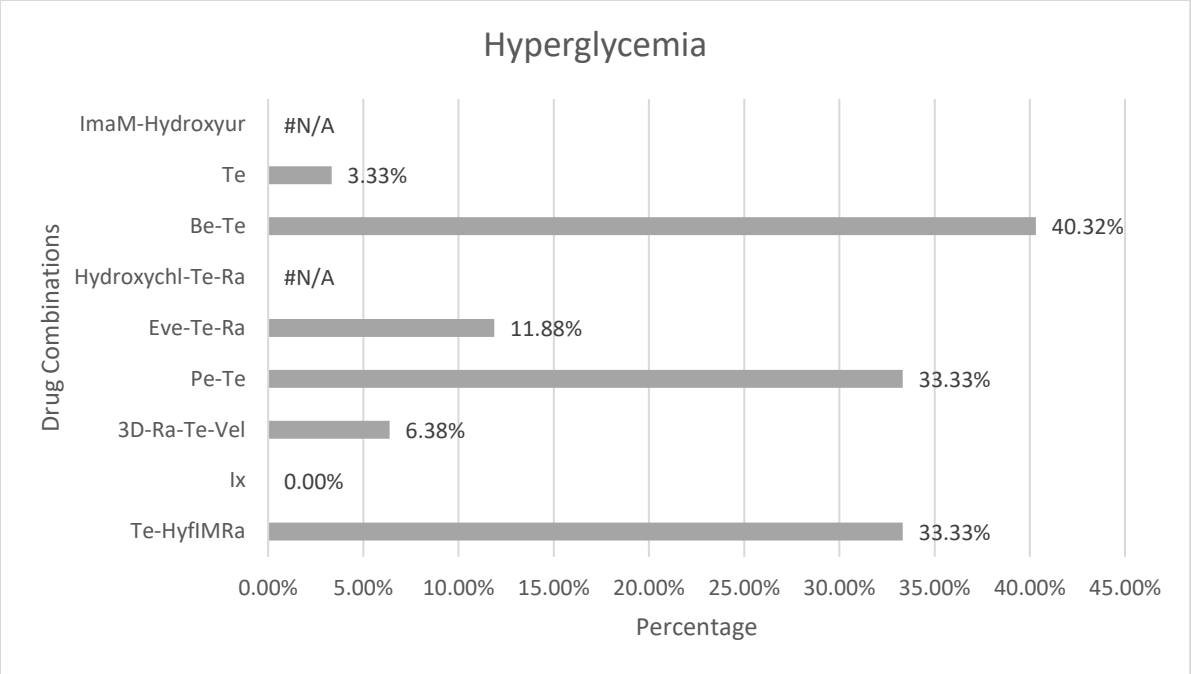
14(A):


Anorexia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
5.08%
1.67%
27.42%
19.74%
13.86%
16.67%
21.28%
0.00%
0.00%
Drug Combinations
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
Percentage

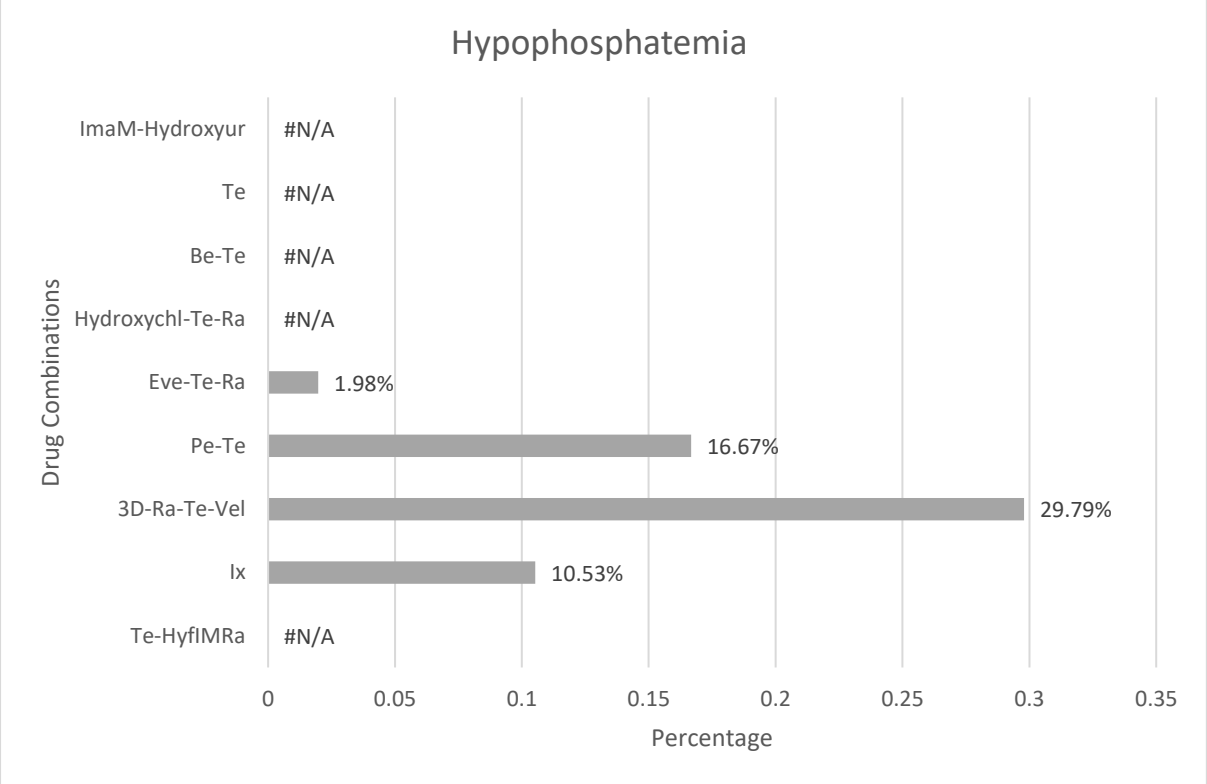
14(B):


Hypocalcemia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
24.19%
3.95%
1.98%
0.00%
19.15%
5.26%
0.00%
Drug Combinations
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
Percentage

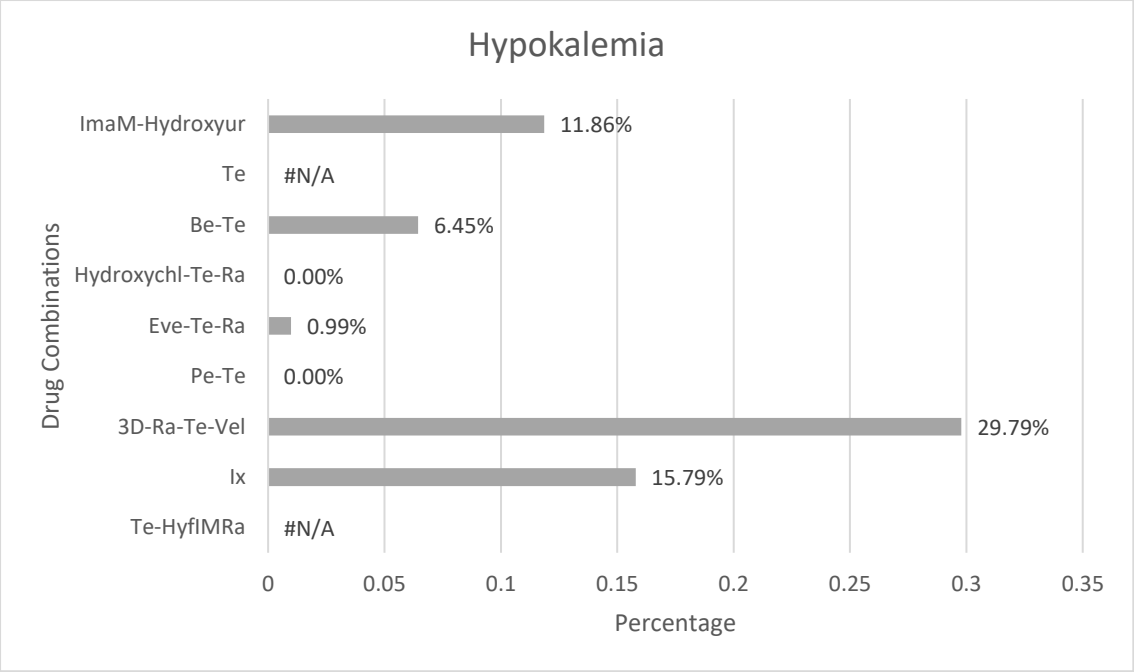
14(C):


Hyperglycemia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
3.33%
40.32%
#N/A
11.88%
33.33%
6.38%
0.00%
33.33%
Drug Combinations
0.00% 5.00% 10.00% 15.00% 20.00% 25.00% 30.00% 35.00% 40.00% 45.00%
Percentage

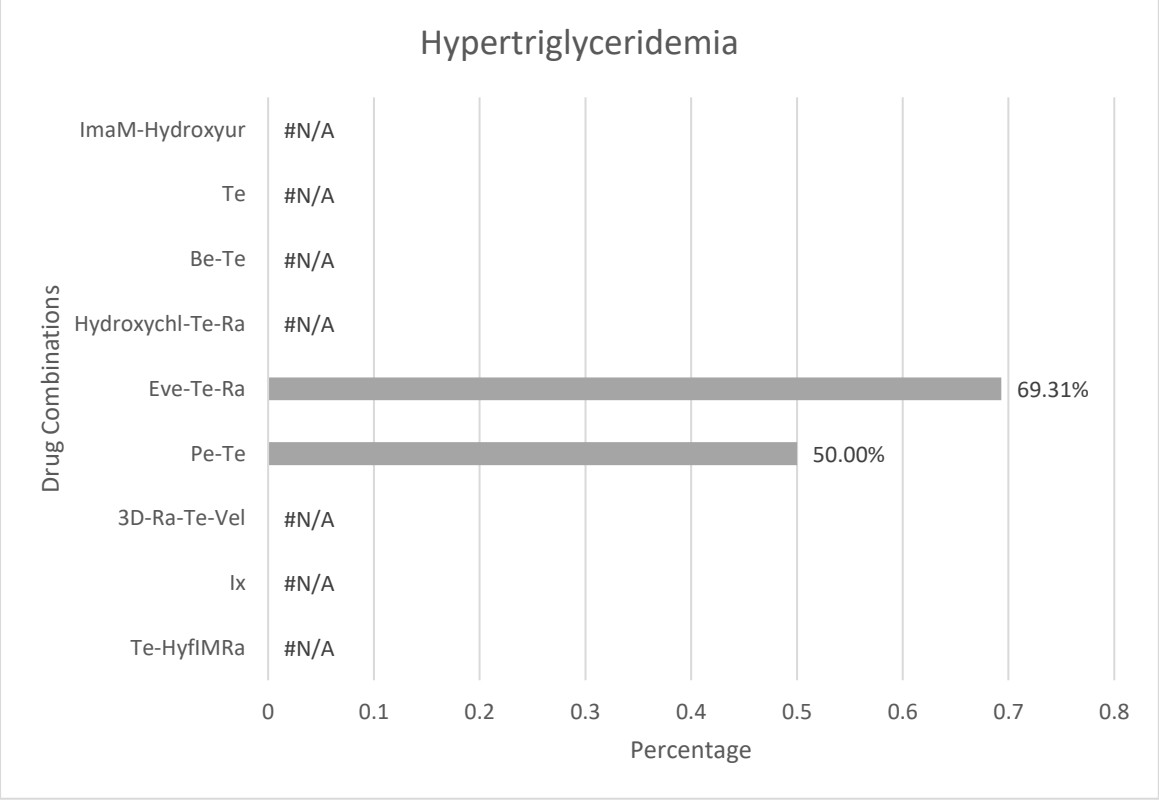
14(D):


Hypophosphatemia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
#N/A
1.98%
16.67%
29.79%
10.53%
#N/A
Drug Combinations
0 0.05 0.1 0.15 0.2 0.25 0.3 0.35
Percentage

14(E):


Hypokalemia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
11.86%
#N/A
6.45%
0.00%
0.99%
0.00%
29.79%
15.79%
#N/A
Drug Combinations
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
Percentage

14(F):


Hypertriglyceridemia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
#N/A
69.31%
50.00%
#N/A
#N/A
#N/A
Drug Combinations
0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
Percentage

14(G):

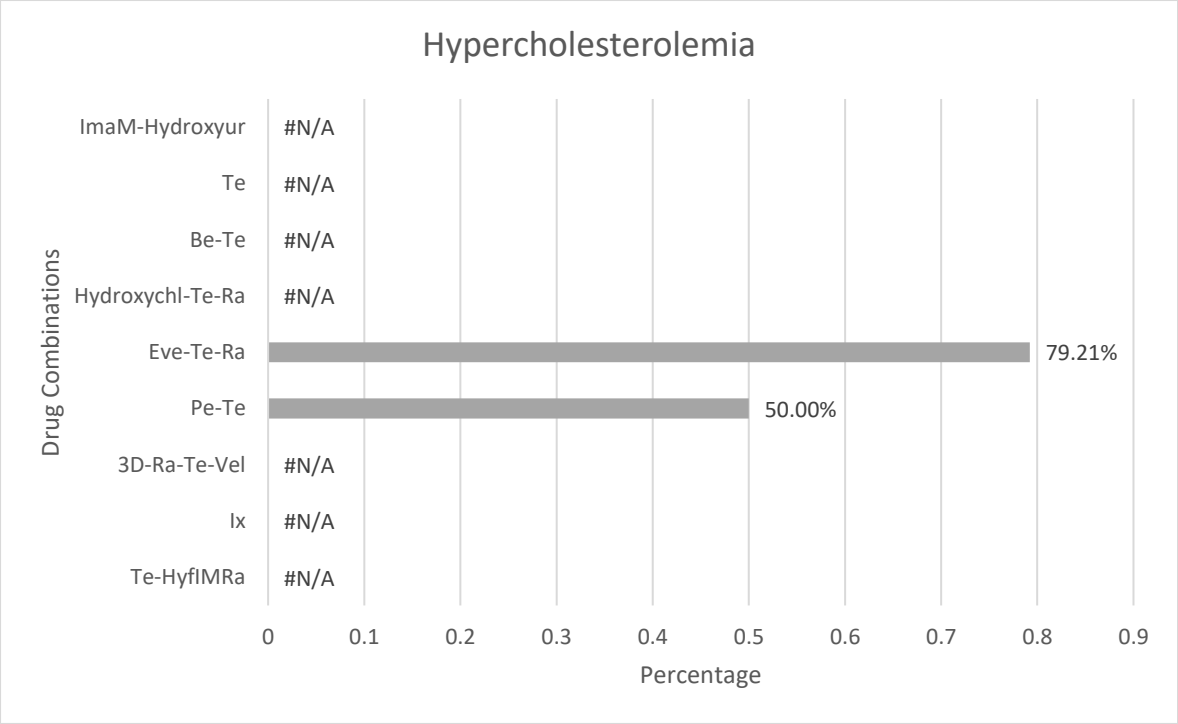
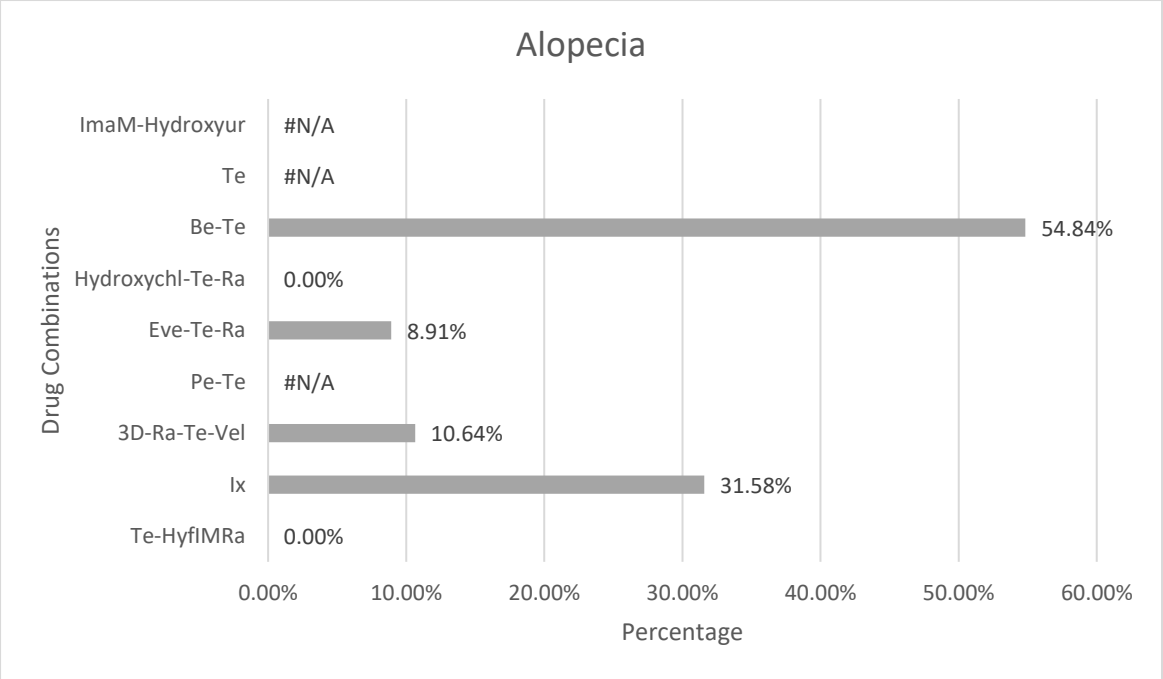


Figure 14: Percentage of Metabolism and Nutrition disorder in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

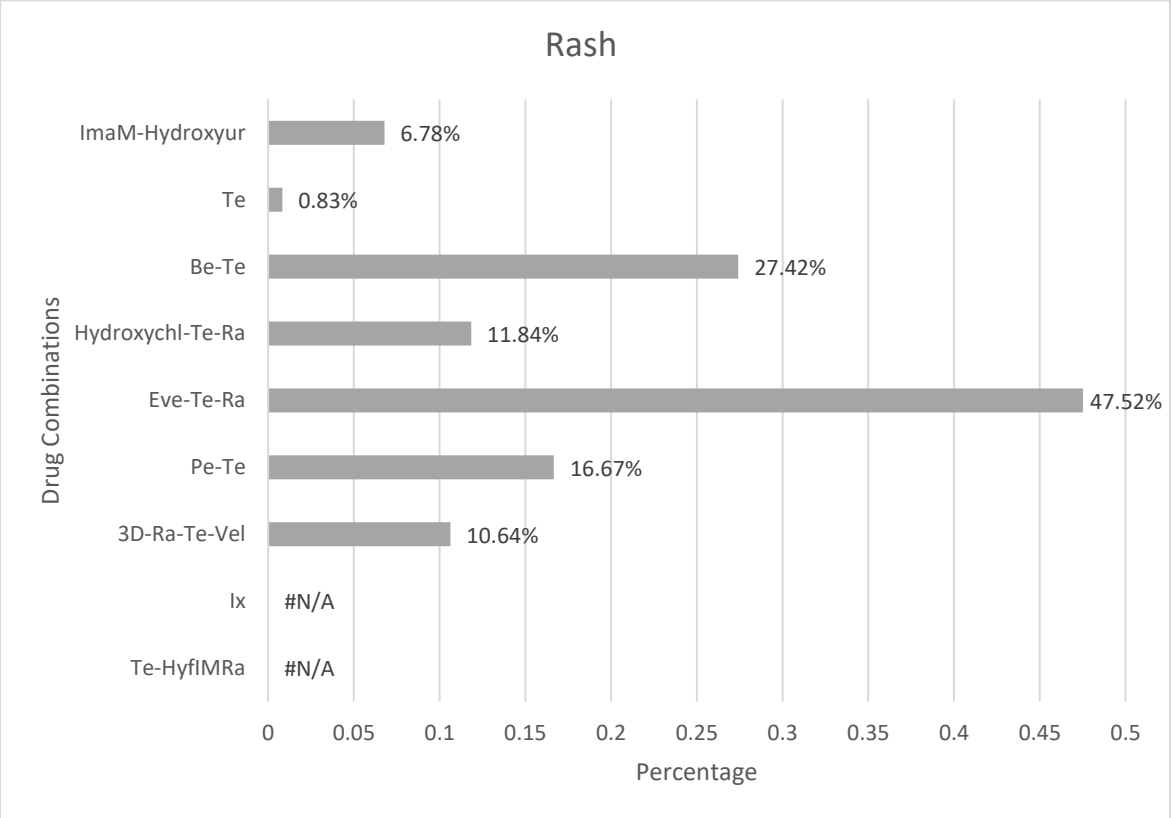
Metabolism and Nutrition disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Anorexia observed in patients receiving chemotherapeutic drug combinations. The highest rate of anorexia was observed 27.42% in patients receiving Bevacizumab + Temozolomide combination. (B) represents percentage of Hypocalcemia observed in patients receiving chemotherapeutic drug

combinations. The highest rate of hypocalcemia was observed 24.19% in patients receiving Bevacizumab + Temozolomide combination. (C) represents percentage of Hyperglycemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hyperglycemia was observed 40.32% in patients receiving Bevacizumab + Temozolomide combination. (D) represents percentage of Hypophosphatemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hypophosphatemia was observed 29.79% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (E) represents percentage of Hypokalemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hypokalemia was observed 29.79% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (F) represents percentage of Hypertriglyceridemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hypertriglyceridemia was observed 69.31% in patients receiving Everolimus + Temozolomide + Radiotherapy combination. (G) represents percentage of Hypercholesterolemia observed in patients receiving chemotherapeutic drug combinations. The highest rate of hypercholesterolemia was observed 79.21% in patients receiving Everolimus + Temozolomide + Radiotherapy combination.

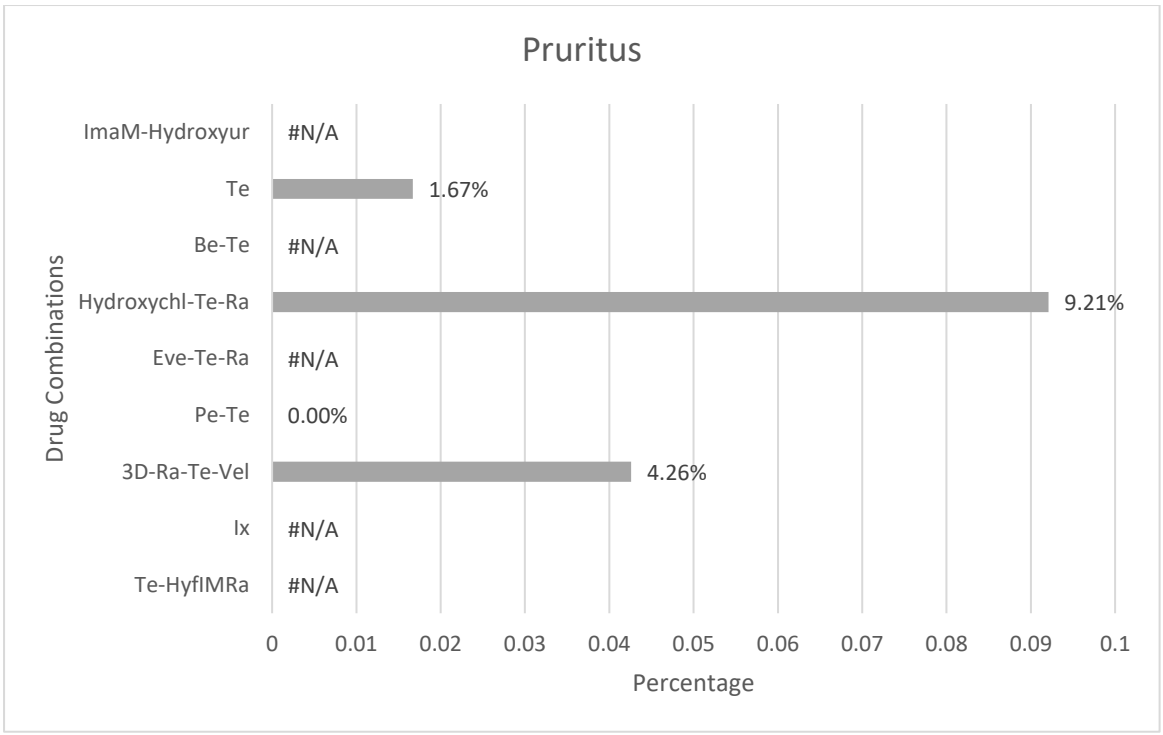
15(A):


Alopecia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
54.84%
0.00%
8.91%
#N/A
10.64%
31.58%
0.00%
Drug Combinations
0.00%
10.00%
20.00%
30.00%
40.00%
50.00%
60.00%
Percentage

15(B):


Rash
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
6.78%
0.83%
27.42%
11.84%
47.52%
16.67%
10.64%
#N/A
#N/A
Drug Combinations
0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5
Percentage

15(C):


Pruritus
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
1.67%
#N/A
9.21%
#N/A
0.00%
4.26%
#N/A
#N/A
Drug Combinations
0
0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0.1
Percentage

15(D):

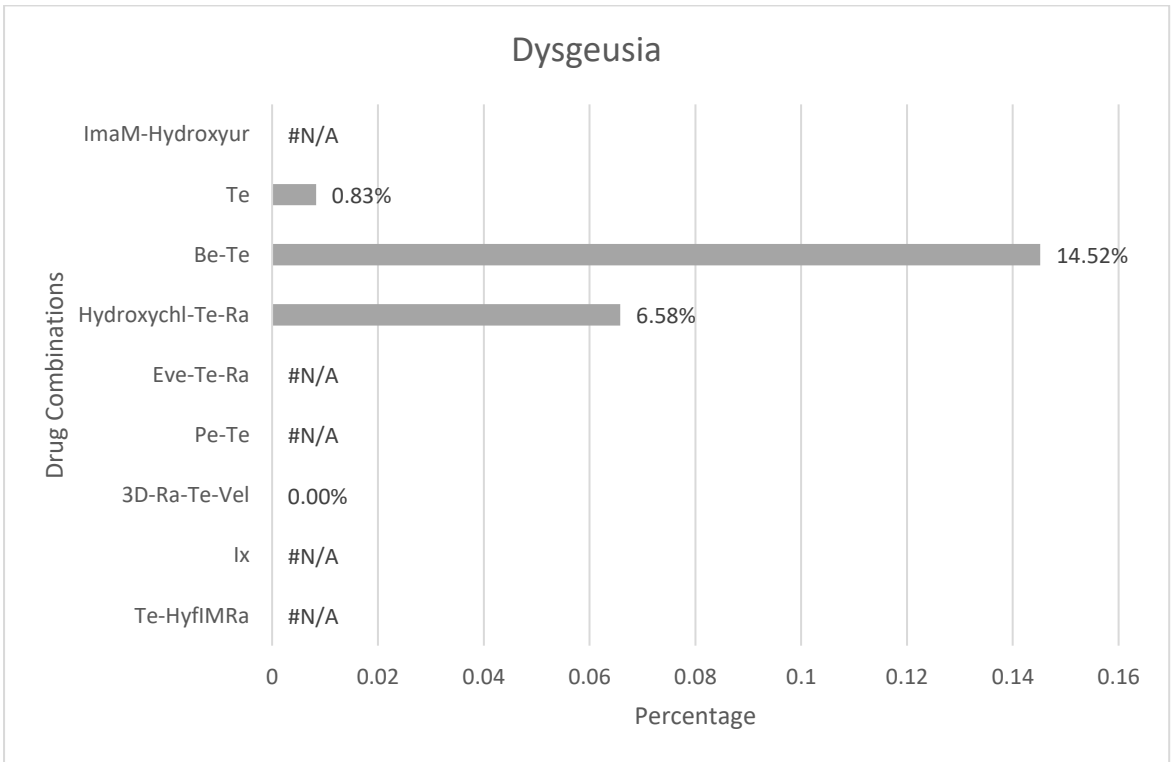
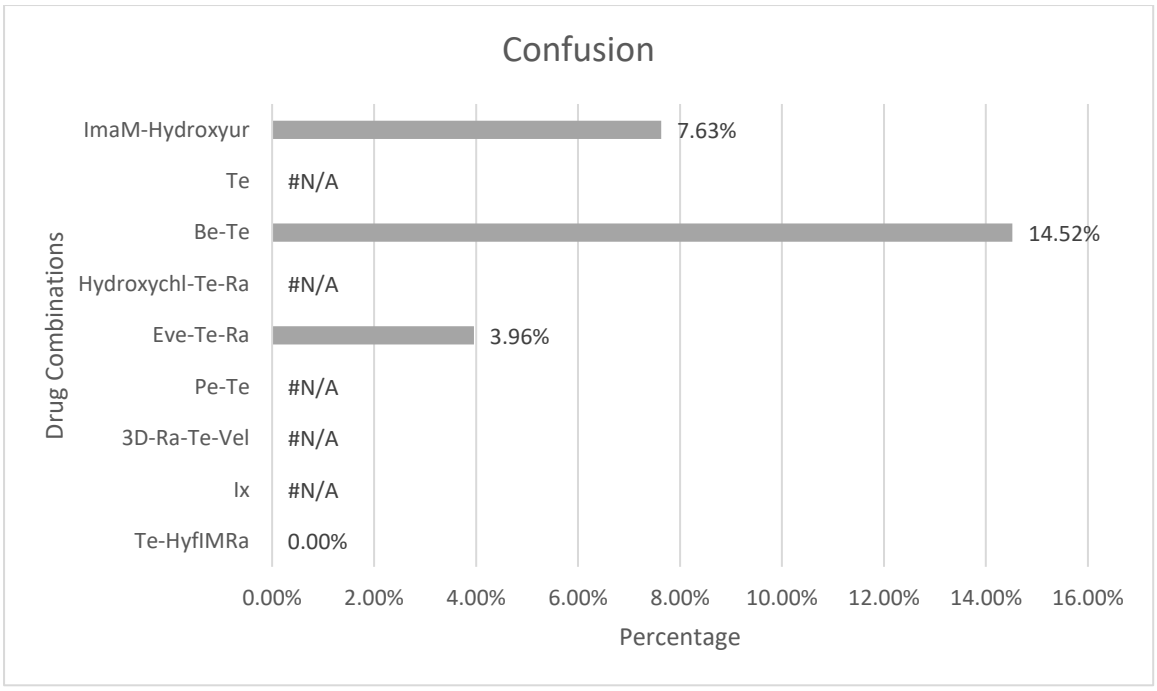

Dysgeusia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
0.83%
14.52%
6.58%
#N/A
#N/A
0.00%
#N/A
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
0.16
Percentage

Figure 15: Percentage of Skin and Subcutaneous disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Skin and Subcutaneous disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Alopecia observed in patients receiving chemotherapeutic drug combinations. The highest rate of Alopecia was observed 54.84% in patients receiving Bevacizumab + Temozolomide combination. (B) represents percentage of Rash observed in patients receiving chemotherapeutic drug combinations. The highest rate of rash was observed 47.52% in patients receiving Everolimus + Temozolomide + Radiotherapy combination. (C) represents percentage of Pruritus observed in patients receiving chemotherapeutic drug combinations. The highest rate of pruritus was observed 9.21% in patients receiving Hydroxychloroquine + Temozolomide + Radiotherapy combination. (d) represents percentage of Dysgeusia observed in patients receiving chemotherapeutic drug combinations. The highest rate of dysgeusia was observed 14.52% in patients receiving Bevacizumab + Temozolomide combination.

16(A):


Confusion
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
7.63%
#N/A
14.52%
#N/A
3.96%
#N/A
#N/A
#N/A
0.00%
Drug Combinations
0.00%
2.00%
4.00%
6.00%
8.00%
10.00%
12.00%
14.00%
16.00%
Percentage

16(B):

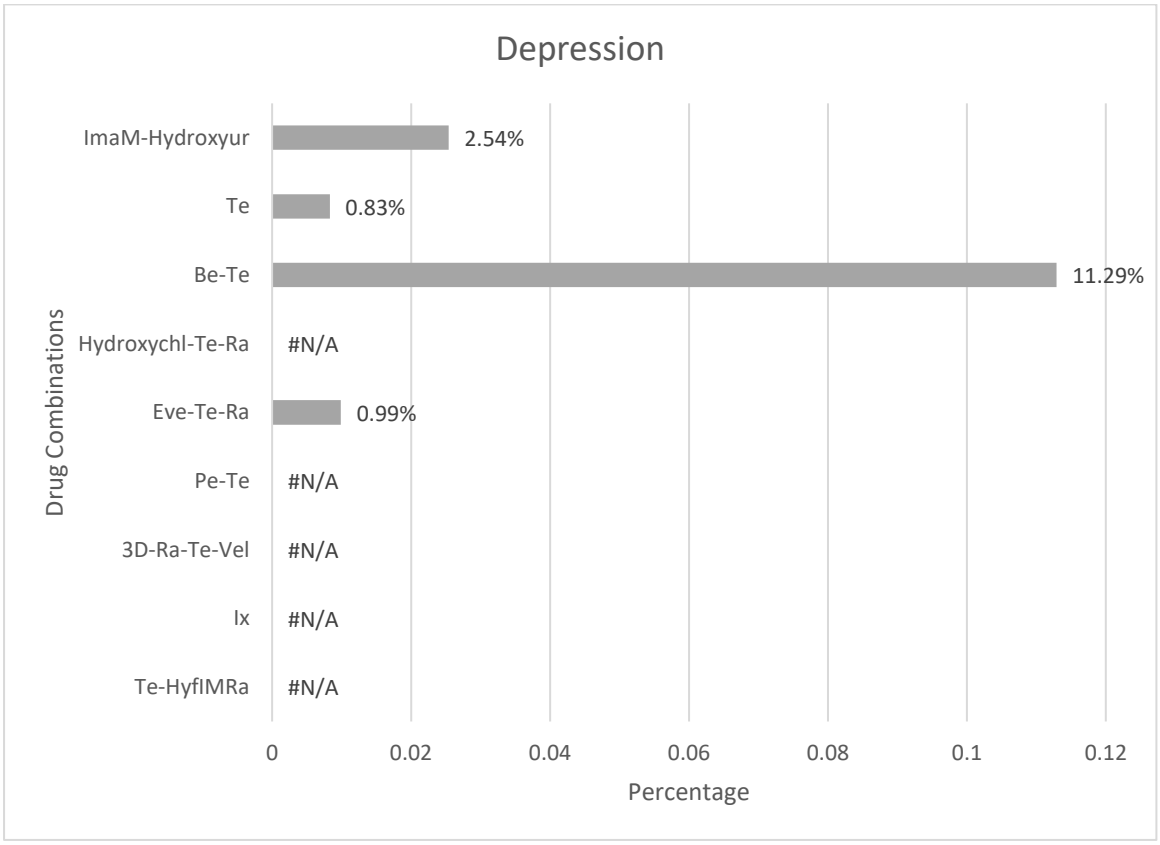
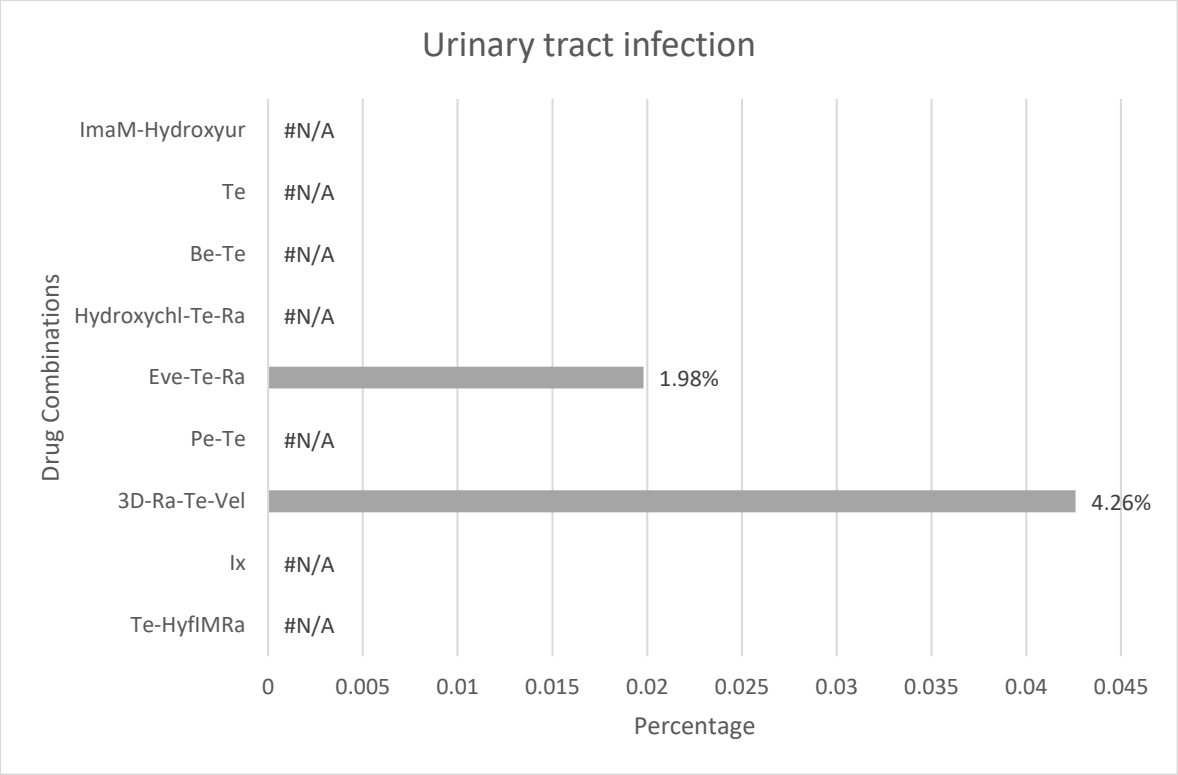

Depression
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
2.54%
0.83%
11.29%
#N/A
0.99%
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
Percentage

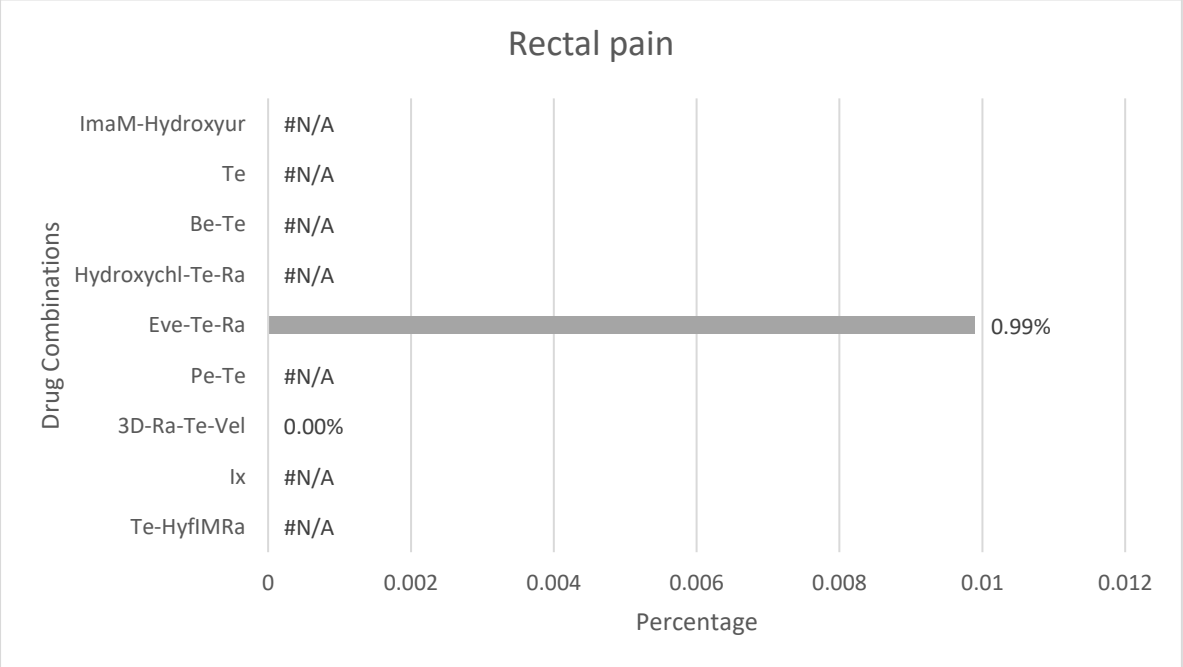
Figure 16: Percentage of Psychiatric disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Psychiatric disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Confusion observed in patients receiving chemotherapeutic drug combinations. The highest rate of confusion was observed 14.52% in patients receiving Bevacizumab + Temozolomide combination. (B) represents percentage of Depression observed in patients receiving chemotherapeutic drug combinations. The highest rate of depression was observed 11.29% in patients receiving Bevacizumab + Temozolomide combination.

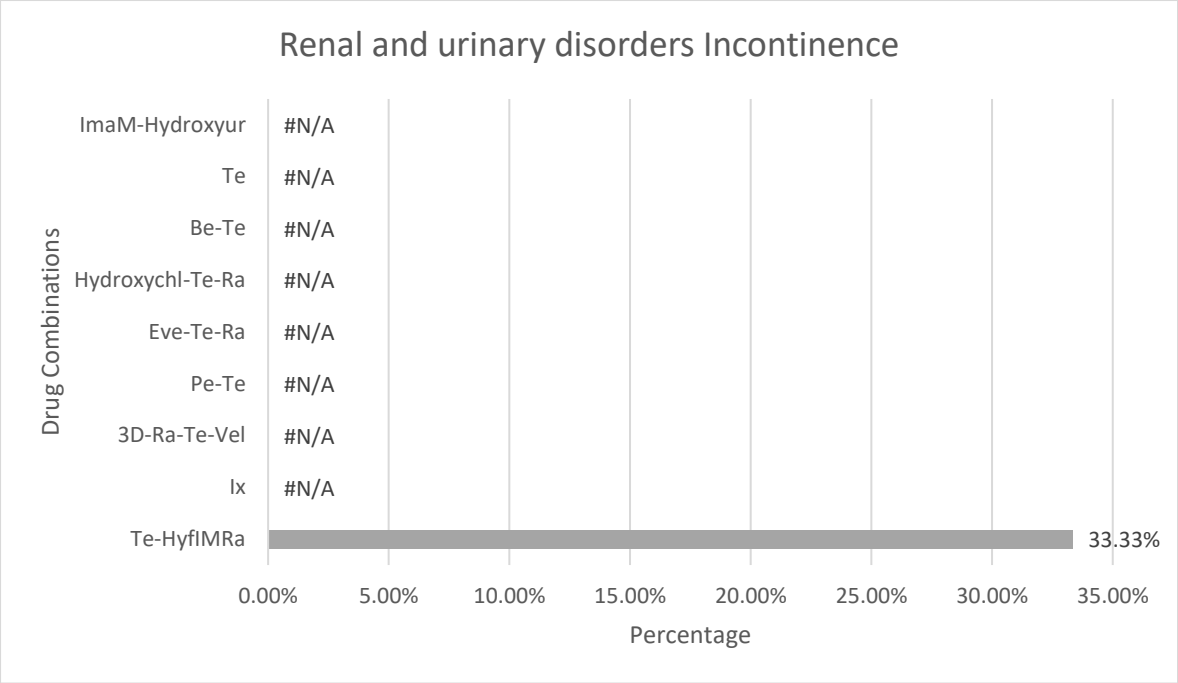
17(A):


Urinary tract infection
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
#N/A
1.98%
#N/A
4.26%
#N/A
#N/A
Drug Combinations
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04
0.045
Percentage

17(B):


Rectal pain
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
#N/A
0.99%
#N/A
0.00%
#N/A
#N/A
Drug Combinations
0
0.002
0.004
0.006
0.008
0.01
0.012
Percentage

17(C):


Renal and urinary disorders Incontinence
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
#N/A
33.33%
Drug Combinations
0.00%
5.00%
10.00%
15.00%
20.00%
25.00%
30.00%
35.00%
Percentage

17(D):

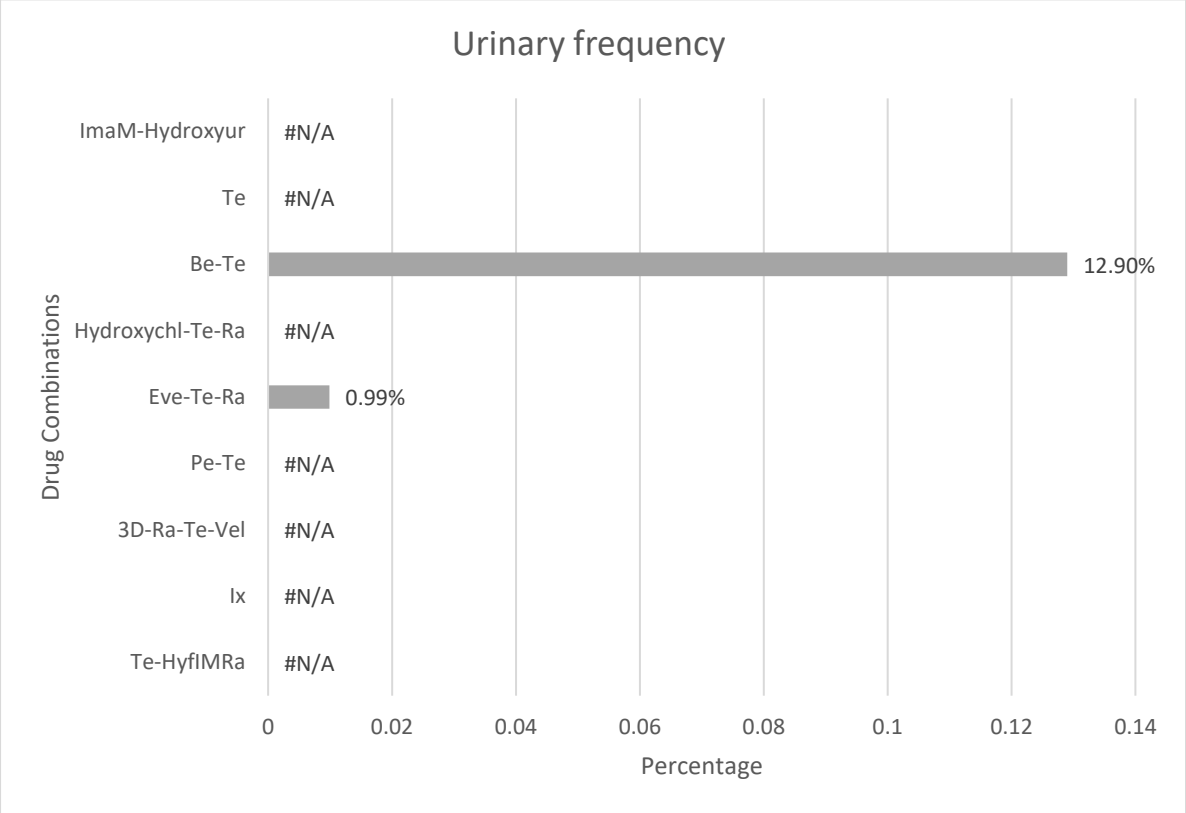
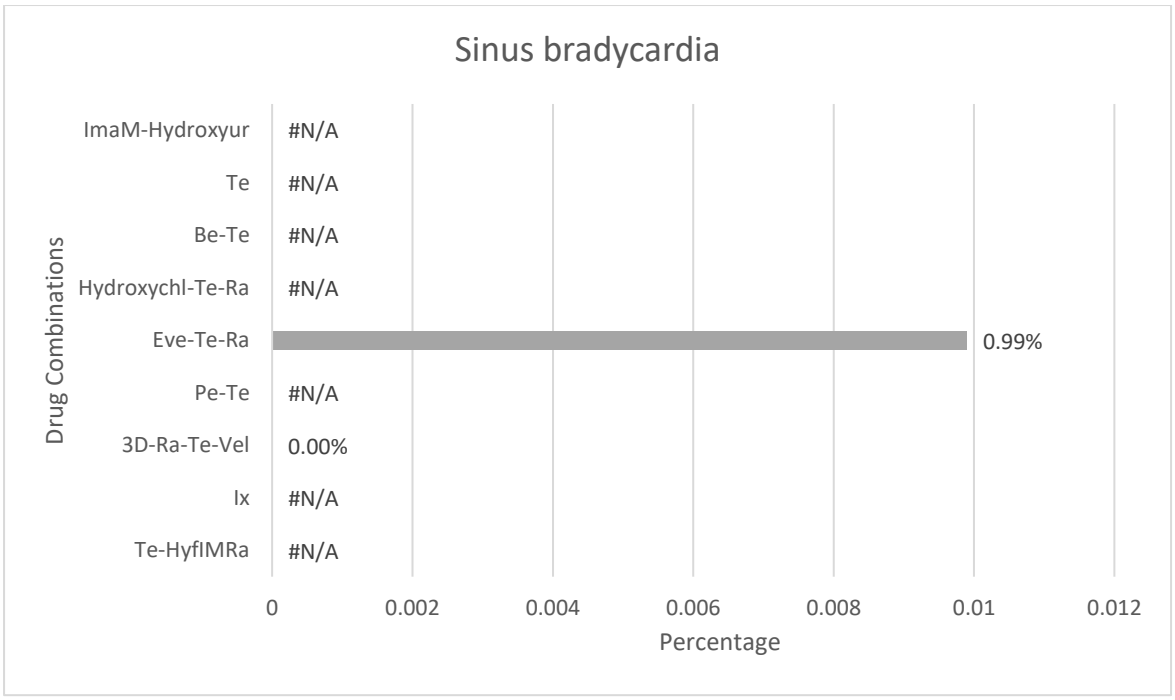

Urinary frequency
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
#N/A
#N/A
12.90%
#N/A
0.99%
#N/A
#N/A
#N/A
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
0.14
Percentage

Figure 17: Percentage of renal and urinary tract disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Renal and urinary tract disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Urinary tract infection observed in patients receiving chemotherapeutic drug combinations. The highest rate of urinary tract infection was observed 4.26% in patients receiving 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib combination. (B) represents percentage of Rectal pain observed in patients receiving chemotherapeutic drug combinations. The highest rate of rectal pain was observed 0.99% in patients receiving Everolimus + Temozolomide + Radiotherapy combination. (C) represents percentage of Renal and urinary disorders Incontinence observed in patients receiving chemotherapeutic drug combinations. The highest rate of renal and urinary disorders incontinence was observed 33.33% in patients receiving Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy combination. (d) represents percentage of Urinary frequency observed in patients receiving chemotherapeutic drug combinations. The highest rate of urinary frequency was observed 12.90% in patients receiving Bevacizumab + Temozolomide combination.

18(A):


Sinus bradycardia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyfIMRa
#N/A
#N/A
#N/A
#N/A
0.99%
#N/A
0.00%
#N/A
#N/A
Drug Combinations
0
0.002
0.004
0.006
0.008
0.01
0.012
Percentage

18(B):

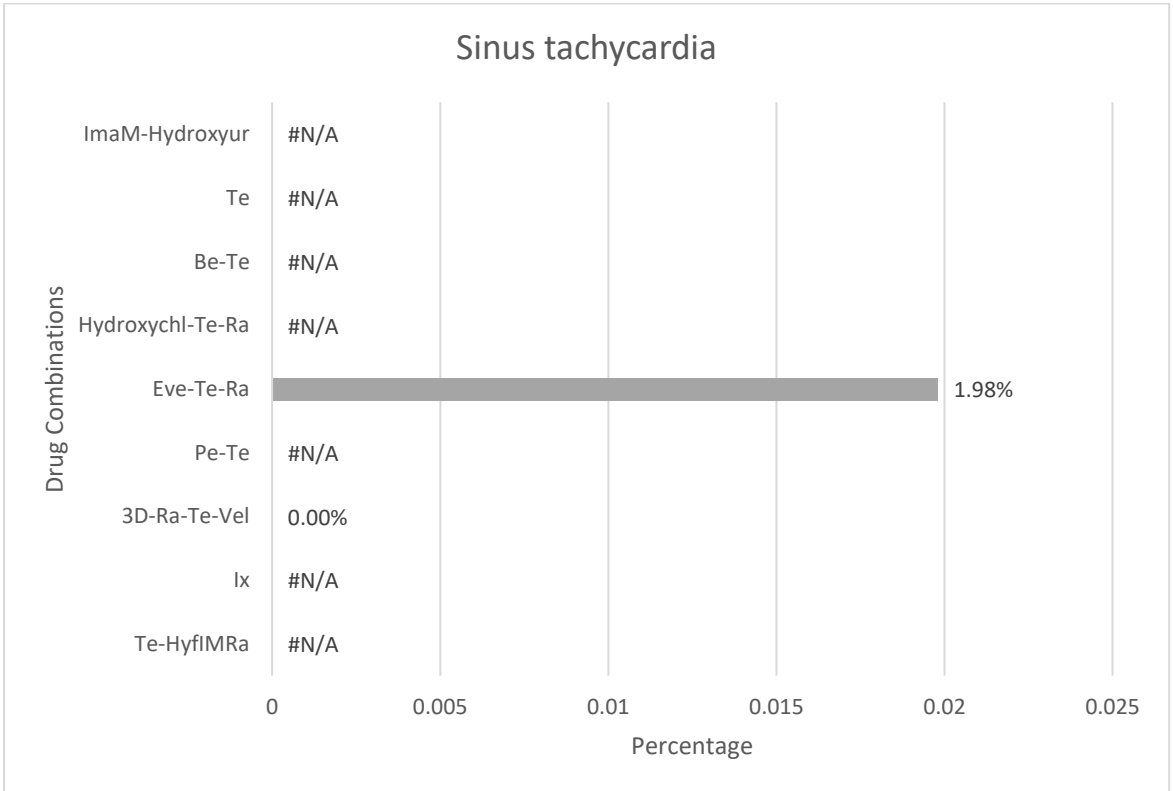
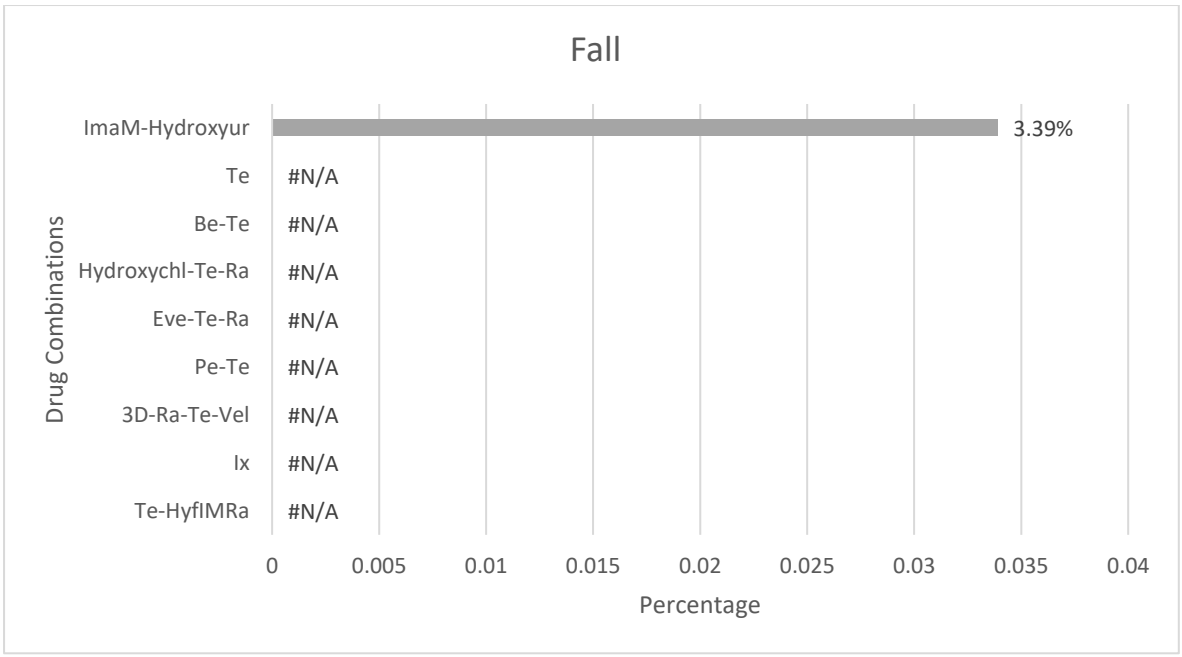

Sinus tachycardia
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyfIMRa
#N/A
#N/A
#N/A
#N/A
1.98%
#N/A
0.00%
#N/A
#N/A
Drug Combinations
0
0.005
0.01
0.015
0.02
0.025
Percentage

Figure 18: Percentage of Cardiac disorders in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Cardiac disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Sinus bradycardia observed in patients receiving chemotherapeutic drug combinations. The highest rate of sinus bradycardia was observed 0.99% in patients receiving Everolimus + Temozolomide + Radiotherapy combination. (B) represents percentage of Sinus tachycardia observed in patients receiving chemotherapeutic drug combinations. The highest rate of sinus tachycardia was observed 1.98% in patients receiving Everolimus + Temozolomide + Radiotherapy combination.

19(A):


Fall
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
3.39%
#N/A
Drug Combinations
0
0.005
0.01
0.015
0.02
0.025
0.03
0.035
0.04
Percentage

19(B):

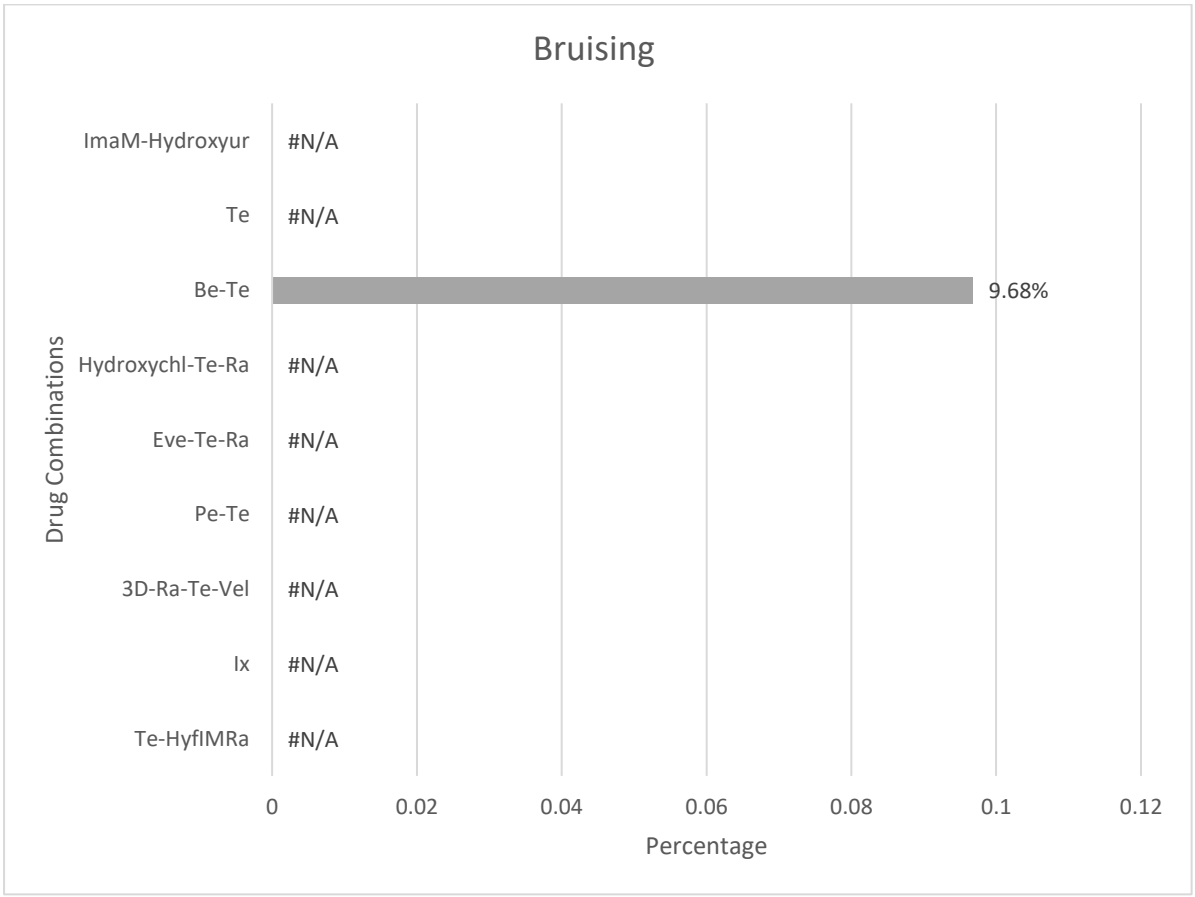

Bruising
ImaM-Hydroxyur
Te
Be-Te
Hydroxychl-Te-Ra
Eve-Te-Ra
Pe-Te
3D-Ra-Te-Vel
Ix
Te-HyflMRa
9.68%
#N/A
Drug Combinations
0
0.02
0.04
0.06
0.08
0.1
0.12
Percentage

Figure 19: Percentage of Injury, Poisoning and Procedural complications in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Injury, Poisoning and Procedural complications are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Fall observed in patients receiving chemotherapeutic drug combinations. The highest rate of fall was observed 3.39% in patients receiving Imatinib Mesylate + Hydroxyurea combination. (B) represents percentage of Bruising observed in patients receiving chemotherapeutic drug combinations. The highest rate of bruising was observed 9.68% in patients receiving Bevacizumab + Temozolomide combination.

20(A):

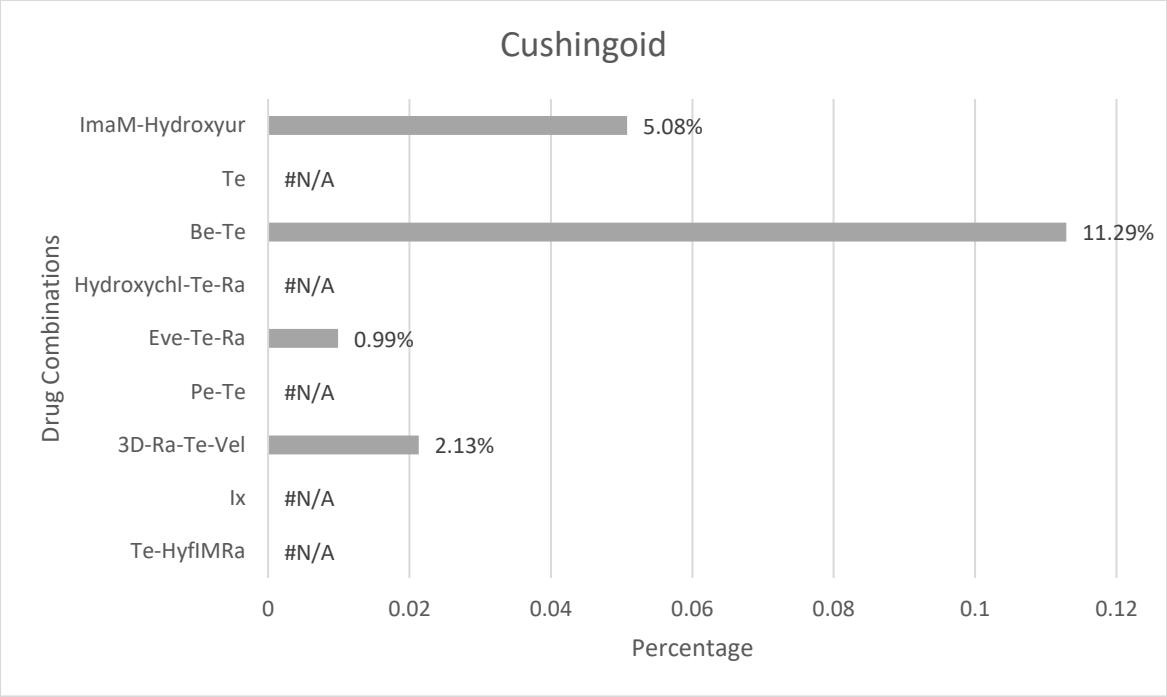


Figure 16: Percentage of Endocrine disorder in patients receiving chemotherapeutic drug in combination and alone for the treatment of astrocytoma. The different combinations that were observed are: Temozolomide + Hypo fractionated Intensity Modulated Radiotherapy, Ixabepilone, 3-Dimensional Conformal Radiation therapy + Temozolomide + Veliparib, Perifosine + Temsirolimus, Everolimus + Temozolomide + Radiotherapy, Hydroxychloroquine + Temozolomide + Radiotherapy, Bevacizumab + Temozolomide, Temozolomide, Imatinib Mesylate + Hydroxyurea. The values are presented as percentages in the graphs.

Endocrine disorders are common adverse effects observed in patients receiving chemotherapeutic drug combinations. (A) represents percentage of Cushingoid observed in patients receiving chemotherapeutic drug combinations. The highest rate of cushingoid was observed 11.29% in patients receiving Bevacizumab + Temozolomide combination.

Chapter 5:

Discussion:

Different drug combinations show different progression free survival, overall survival and adverse effects in patients with Astrocytoma. However, these survival rate and adverse effects vary when those chemotherapeutic drugs are used alone rather than used as combinations. In this study, 9 different types of chemo therapy drug combinations are evaluated based on the outcome or efficacy of the treatment, including response to the treatment, such as OS, PFS, time on treatment, and treatment-related adverse events and death rate.

Combination of hypo fractionated intensity-modulated conformal stereotactic radiotherapy and Temozolomide is used for newly diagnosed glioblastoma multiforme or anaplastic astrocytoma, a typical dose escalation period of 3+3 phase I study was conducted. In phase I, patients were administered with TMZ for 5 weeks with the dose HIMRT at 52.5 Gy in 15 portions at 75 mg/m2 per day which enables delivery to just a large target tumor volume without developing RN. Following 45 minutes of radioactivity, the intra - operative addition to HIMRT activates the DNA and causes twofold breaking. After a week of pre-RT TMZ, the radio sensitivity would be enhanced, allowing for more cell killing with RT. During the treatment period, there was no evidence of irreversible grade 3 or non-hematologic damage. Moreover, the combination was well tolerated and can shorten treatment times for these patients in the phase I trial. Despite the fact that a participant experienced temporary stage III lethargy and drowsiness. Due to a scalp infection, one patient's post-RT TMZ had to be interrupted thus the adjuvant TMZ was subsequently resumed as planned. As the condition progresses, one of the patients suffered from a stage III tremor accompanied by left sensory dysfunction. One patient experienced a stage III serious thrombus that dispirited from the medication. Despite taking nine adjuvant TMZ regimens, two more patients developed grade

4 persistent late thrombocytopenia. These two patients were not given any more adjuvant cycles. Most common acute grade 1 and 2 toxicities were fatigue (66.67%), constipation (66.67%), vision changes (33.33%), memory deficits (33.33%), high alt (66.67%), anemia (33.33%), nausea (100.00%), headache (33.33%). The employment of pre-RT TMZ has shown PFS of 3.9 months (95% confidence interval [CI]: 0.9–7.4; range, 0.9–9.9 months) and OS of 12.7 months(95% CI: 2.5–17.6; range, 2.5–20.7 months) and the average time on treatment was 10 months (range, 1–15) in patients GBM-derived cells with and without O6-methylguanine DNA-methyl transferase (MGMT) activity (Ammirati et al., 2014).

In the treatment of advanced astrocytoma, the stage I/II study of Ixabepilone(BMS-247550) included 57 participants who also received radiotherapy but not over two cytotoxic treatments. This non-randomized treatment based therapy categorized into three groups in this combination therapy: anticonvulsants/+EIAED (group A), non-anticonvulsants/-EIAED (group B), and MTD (group C). To assess the optimum therapeutic dosage (MTD) and bioavailability of the drug, all phase I patents underwent ixabepilone as a 1-hour intravenous transfusion daily for 5 days, with repetition for every 21 days. Additional phase II patients were given ixabepilone at the MTD (6.8 mg/m2 for -EIAEDs and 9.6 mg/m2 for +EIAED) and the response rate were 5.8 (95% CI, 5.0–8.6) months(OS) and 1.5 (95% CI, 0–22%) months(PFS). In this trial, the most serious toxicity was hematological, including neutropenia and thrombocytopenia. According to the study, Ixabepilone has shown serious adverse effect rate of 5.26% with no mortality rate. Despite the fact that this medication indeed a poor ligand for p-glycoprotein but also has strong effect upon taxane tumor tissues, throughout the investigation treating persistent GBM patients, this drug had no anticancer activity. Although ixabepilone may be ineffective in this condition due to therapeutic concentrations of the drug may not have been established in the tumor. Intertumoral drug concentrations should be evaluated in future investigations of

this or comparable medicines to see if therapeutic levels may be attained after intravenous injection (Peereboom et al., 2010).

In the treatment with the combination of Veliparib (ABT-888) with radiotherapy and Temozolomide, patients were given veliparib at 25 mg/m2 b.i.d. and TMZ 135 mg/m2 respectively every day for 5 days and 28 days followed by the recommended phase II dose (RP2D) method. Due to high alanine aminotransferase (48.94%), one phase II patient was declared unable to begin treatment. During veliparib and radiation therapy, four patients in the phase I arm developed DLTs. A grade 2 intracranial hemorrhage occurred in one of six people diagnosed at dosage grade 1 (50 mg/m2/dose), and three patients taken at dosage grade 3 (85 mg/m2/dose) developed DLTs (2 maculopapular rashes (10.64%) and 1 worsening of neurologic symptoms). Lymphopenia (93.62%) and neutropenia (40.43%) were the most common side effects of veliparib and radiation. Two out of five patients at 175 mg/m2 and two out of three patients at 200 mg/m2 exhibited toxicities above the predetermined threshold while receiving interpatient dosage escalation of TMZ during maintenance, and hence interpatient dose escalation was suspended for the continuation of the study. Blood related toxic effect was the most common class 3 or higher toxicity throughout maintenance. Despite the fact that the innovative combination medication was generally well tolerated, it did not improve survival when compared to a current PBTC historical series. PFS was not discovered, however OS was discovered to be 24 months, with 6.3 month overall treatment interval. Common adverse effects were anemia (57.45Aspartate aminotransferase (AST, SGOT) increased (25.53%), High Creatinine (4.26%), Weight gain (6.38%), Vomiting (44.68%). These findings show that clinical responses to PARP inhibition are likely to be varied, and that resistance is expected to occur in a large percentage of patients; yet, these findings may help to guide sensible combination therapy development in the future. GBMs with methylated O6-methylguanineDNA methyl transferase promoters are predicted to respond to veliparib and

radiation therapy but not to veliparib or TMZ. This shows that a combination of veliparib and a histone deacetylase inhibitor or a cyclin dependent kinase inhibitor, after veliparib and radiation treatment, is likely to be more successful than veliparib plus TMZ. Although a combination of veliparib, radiation, and TMZ failed to improve survival in children with DIPG, drug entry and biological efficacy may differ between brainstem and non-brainstem high-grade gliomas, and a current Children's Oncology Group trial is evaluating such a strategy for pediatric high-grade gliomas without H3K27M mutations. (Baxter et al., 2020).

Incorporation of Perifosine with temsirolimus to help patients with reoccurring or developing benign cancer, which were combined to suppress various processes in the protein kinase signaling pathways. Despite the fact that each medicine had only minor clinical efficacy in GBM when used alone, preclinical studies showed that combining them had a synergistic effect. However, no previous trial had paired these agents. At the highest dose (temsirolimus 115 milligrams each week with perifosine loaded at 600 mg on day 1 (in 4 divided doses) accompanied by everyday 100 mg) levels, toxicity was severe, among many people suffering from typical hematopoietic as well as mild physiological side effects (i.e., hypophosphatemia, hypertriglyceridemia, hypercholesterolemia). Three individuals had intraventricular bleed, most of which had stage 1 and 2. Additionally , 5 people were infected with pneumocystis (jiroveci) pneumonia, three of which were fatal(PJP). Lymphoma could have increased the incidence of PJP, but all three patients were taking corticosteroids at the same time. The MTD dose was more than four times that FDA-approved temsirolimus single dose against hepatocellular carcinoma (25 milligram every week). It seems to be unexplained why greater temsirolimus concentrations, especially when paired with another drug, were tolerated in this research. Others have discovered that temsirolimus 170 milligram or 250 milligram per week was tolerated like a monotherapy among individuals who do not take or even using EIAEDs. The unavailability of pharmacokinetic data further constrained the capacity in establishing

significant decisions about its regimen's effectiveness. Therefore , PSF6 was 2.7 months and OS were 10.4 months throughout this combination. As both outcomes suggests that, combining a mTOR blocker temsirolimus only with AKT blocker perifosine is acceptable with recurrent MGs who have been previously medicated (Kaley et al., 2020).

Another combination drug Everolimus (RAD001), Radiation, and Temozolomide (TMZ) was used for the treatment of grade IV astrocytoma. This was a phase II study with a single initial screening for effectiveness. The ultimate outcome with this study was 12-month overall survival (OS12), with secondary outcomes including time to progression (TTP), overall survival (OS), progression-free survival (PFS), and adverse events. The use of 70 mg everolimus once a week during and after conventional chemo radiotherapy involved mean follow-up of 17.5 months, average OS of 15.8 months (95% CI: 13.0, 20.3), and a maximum PFS of 6.4 months (95% CI: 5.4, 9.0). In recently diagnosed glioblastoma, adding weekly everolimus to conventional chemo radiation is unlikely to be beneficial. The difficulties of evaluating progression- free survival together in broad, cross experiment with different referral sites is demonstrated in this study. When compared to historical controls, the combining everolimus during conventional RT/TMZ caused considerable morbidity and did not enhance OS. According to the Clinical Trial Identifier (NCT00553150), the serious adverse effect rate for this combination was 31.68% including Leukopenia (15.84%), Febrile Neutropenia (1.98%), Fever (1.98%), Fatigue (44.55%), Urinary tract infection (1.98%), Hyperglycemia (11.88%), Hypercholesterolemia (79.21%) (Ma et al., 2015).

Throughout the combination with hydroxychloroquine (HCQ), Temozolomide(TMZ) and radiotherapy, patients received oral TMZ (75 mg/m2) 1 h before every RT cycle, rather than no RT. A 6-week RT and TMZ (chemo radiation) initiation cycle was followed by a 4-week rest interval. Following an initial session, maintenance cycles included TMZ at such a dosage of 150 mg/m2/d over 5 days per month for six months (increased to 200 mg/m2 in future cycles

if sensitivity was not present). According to the treatment plan, HCQ administration proceeded on the first day of chemo radiation and continued every day, including during the 4-week recovery period, with no planned disruptions. After completing 6 maintenance cycles of TMZ + HCQ, patients were switched to daily HCQ alone in monthly cycles with no limit on the number of cycles. Hematological and no hematological toxicities were taken into consideration after overcoming the situation, the doses of HCQ levels included 200 mg, 400 mg (administered two times a day), as well as 800 mg. Once sensitivity has been discovered with 800 mg per day, this procedure has been changed to a 600 mg HCQ per day cohort. For each dose level, three patients were treated. Most participants within that specific group underwent their 10-week induction phase before moving on with the next dose level, allowing toxicities to be monitored (DLT phase). As a result, there was no plan to increase the dose beyond 800 mg/d. However, HCQ-related DLT was categorized as non-grade 3 and 4 toxicities. Also, hematological toxicities were considered to be aggravated by HCQ. This dose being maintained till 3rd grade HCQ-related adverse event (AE) (dizziness, sickness, dysentery, acne, or visual acuity impairment) improved to 1st grade or zero. Unless the adverse events resolved, therapy was resumed at 200 milligrams once daily and up to three dose increments was permitted for further sensitivity. Temozolomide dose has been reduced to 50 percent during maintenance cycles. To rate possible risks and fatalities, researchers utilized the Common Terminology Criteria for Adverse Events, version 3.0. These findings indicate that many people may not achieve significant autophagy inhibition with HCQ 600 mg/d in combination with TMZ as well as RT, and that the part II study's success, as evaluated by prolonged OS, could be limited by inconsistent autophagy inhibition by HCQ. Considering the safety of relatively high HCQ concentrations throughout the combined effect of occasional temozolomide, more consistent and stronger autophagy in this patient population could certainly be achieved if the HCQ intake

was kept at 600 mg/d for the first six weeks of chemo radiation and afterwards dosing frequency scaled up during adjuvant temozolomide (Taylor et al., 2014).

Incorporation of Avastin(Bevacizumab) and Temozolomide, patients were given BV (10 mg/kg) and TMZ (75 mg/m2) intravenously as well as orally during RT (60.0 Gy) cycles. However, the study schedule was tolerable in general. The addition of BV to the radiation phase did not appear to cause any significant or unexpected toxicity. Four wound infections developed at the craniotomy site; three occurred during RT, two of which were linked with CSF leak, and one occurred three months after RT was completed. According to this review, adding BV to RT/TMZ as a first-line chemotherapy was shown to be tolerated with no unexpected side effects. Furthermore, this combination has improved PFS (13.6 months) but lack of benefit in OS (19.6 months) rate (Lai et al., 2011).

In the treatment of low grade glioblastomas(LGGs), this single arm stage II experiment of Temozolomide(TMZ) was conducted on 120 patients. The patients were given 200 mg/m2 for 5 days then every 28 days for up to 12 rounds or until disease progression. The primary goal was to observe radiographic response rate and secondary goal was to evaluate PFS and OS. During therapy with TMZ, 7 patients (6%), had objective responses, and 86% had stable or improved condition. The average rate of survival was 9.7%, with a 4.2-year progression-free survival rate. Anova analysis further revealed that oligodendroglioma cytology ($p = 0.02$), complete excision ($p = 0.009$), as well as the absence of cancer reaching the baseline (p 0.001) have all been associated with a higher overall survival rate. Moreover, in this analysis, Temozolomide has shown the highest PFS (50 months) and OS (115 months). In addition, according to clinical trial identifier TMZ has shown serious adverse event rate only 14.17%. as a result, it can be depicted that, the treatment was well tolerated, with only minor side effects including neutrophils (5.00%), thrombocytopenia (4.17%), vomiting(4.17%), seizure(5.83%) (Wahl et al., 2017).

In the combined regimen of Imatinib mesylate and Hydroxyurea while imatinib has been identified to suppress the signal transduction of PDGFRa, PDGFRb, and c-KIT receptors and Hydroxyurea (HU) has been thought to improve drug absorption throughout the blood-brain barrier and trigger the deletion of enlarged gene mutations, such as the Epidermal growth factor receptor. Although overexpression of PDGFR, c-KIT, and EGFR has been linked to GBM and HU can promote the penetration of blood tissues , integrating aforementioned medications has been thought to be the promising therapy strategy. Thus, 240 patients were randomized for receiving 1,500 mg dosage with HU daily (500 mg three times every day) or imatinib 600 mg per day through additional 1,000 mg of HU per day (500 mg twice daily). But comparing this combination to HU monotherapy together in randomized controlled phase III trial, GBM patients being in an initial episode, this combination should be avoided. Because there were no statistically significant differences between the two groups in terms of the primary and secondary end goals, this research suggests that imatinib + HU combination therapy was not superior to HU alone in the current glioblastoma setting. Furthermore, this combination did not present significant PFS or OS rather the adverse events were expected as the disease consequence (Dresemann et al., 2010).

Chapter 6:

Conclusion:

Astrocytoma, the most common and aggressive brain glioma in children and adults but it is difficult to diagnose. Various chemotherapies are available for the treatment of astrocytoma and they are different from each other due to their access on BBB, average survival rate, mortality rate and side effects. Although Temozolomide based chemotherapeutic treatments are known as first line treatments of astrocytoma brain cancer and they are used widely alone or with combination but other combinations are also available and contribute a significant part in the development of poor-grade gliomas. Depending to the mechanism of action, adverse effects, toxicities, efficiency, effectiveness, time on treatment or follow up time, and other factors, each combination is incompatible with the others. Addition of bevacizumab to temozolomide and radiation did not improve PFS and OS but has shown moderate adverse effects. On the other hand, temozolomide alone did improve PFS and OS but possessed serious adverse events. It would be predicted that combination therapy might improve treatment outcomes. In this review, clinical trials of different chemotherapeutic combinations were considered and analyzed for developing a prominent outcome by assessing their efficacy. According to all available data, it would be stated that patient receiving temozolomide alone and the combination of bevacizumab, temozolomide and radiation improved response rate than other combinations. However, this outcome is still an argumentative, hence, there is still lacking of relevant and sufficient information and data, therefore, further research on the combined medication regimens is required to evaluate more beneficial outcomes and to overcome the challenges of the treatments. Although these drug combinations are practiced widely in the treatment of astrocytoma. As a result, bevacizumab and temozolomide based treatments are known as first line treatment for high grade and low grade glioma. This treatment

works against VEGF activity, inhibits angiogenesis, and so limits tumor progression by limiting the proliferation of malignant cells and production of DNA.

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