Review Paper:

Safety and Efficacy of Temozolomide Combinations in Glioblastoma Patients; A Meta-Analysis

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Abstract

Globally, glioblastoma is the fetal brain tumor with the highest incidence. Patients with glioblastoma who have received a clinical diagnosis need combination therapy, which combines radiation and chemotherapy drugs that have shown promising benefits. The treatment of choice for glioblastoma, both alone and in combination, is temozolomide. Studies have shown that temozolomide combined with other medications and radiotherapy in the management of glioblastoma is effective in reducing tumor size, preventing recurrence and limiting tumor progression. The study also emphasizes the safety profile of temozolomide combinations and pathophysiology of tumor, size, growth and reoccurrence.

For the meta-analysis, a detailed search of scientific literature was conducted utilizing the most relevant scientific studies published to date on the intervention of temozolomide combinations to manage Glioblastoma. A search was conducted across a number of databases including Scielo, Cochrane Central Register of Controlled Trials and PubMed. The MedCalC tool was used to do a meta-analysis in accordance with Prisma standards for odds ratio between studies, risk factor analysis and relative risk. The Cochrane Central Register of Controlled Trials, Scielo and other databases were used to retrieve a total of 1635 studies for the current analysis. The meta-analysis with three distinct parameters odds ratio, risk difference and relative risk was significant with p value <0.001 (for TMZ with other chemotherapeutic agents) and p value <0.003 (for TMZ with radiation therapy). The 95% Cl for TMZ with other chemotherapeutic agents was higher for odds ratio (2.539 to 3.466), risk difference (1.345 to 1.669) and relative risk (0.192 to 0.280) over TMZ with radiation therapy (Odds ratio 1.051 to 1.327; Risk difference 0.0116 to 0.0623 and Relative risk 1.016 to 1.100). When treating GBM, TMZ in combination with other chemotherapeutic drugs has been found to be more successful than TMZ alone. Clinical trials based on TMZ offer GBM patients with freshly diagnosed solid tumors a better survival rate.

Keywords: Glioblastoma, Temozolomide, Meta-analysis, Odds ratio, Risk factor analysis, Relative risk.

Introduction

Glioblastoma is one of the brain-associated tumors having an incident rate of 10 per 100,000 people worldwide.[1, 2] The global report shows that age-standardized incidence rates of CNS cancer increased from the year 1990 to 2016.[3] Compared with other cancers such as lung, breast, prostate and colon cancer, glioblastoma is having low incidence rate, the life span is too short.[4,5] GBM has a low likelihood of recovery and up to this point, no specific carcinogenetic substances or risk factors have been linked to the disease's origin. According to research, ionizing radiation exposure at high doses is the main factor contributing to the development of GBM.[6-8.] Salvati et al[43] reported almost 116 cases of GBM from 1960 due to exposure to ionizing radiations. Epidermal growth factor receptor is linked to the disease's pathogenesis, which accelerates the development of GBM.[10]

In general, phenotypic changes occur due to over expression, amplification, or mutation in the EGFR gene.[11] Sidransky et al[47] also demonstrated in their study the significant correlation between mutations of p53 which involved the progression of low-grade astrocytoma to the high-grade glioblastoma.

In this progression, the PTEN, p53 and iso-citrate dehydrogenase (IDH-1) mutations were considered potential players.[13] In supratentorial brain areas such the frontal, temporal, parietal and occipital lobes, glioblastoma formation predominates, while the cerebellum, brain stem and spinal cord of the CNS hardly ever experience it.[14] Astrocytes and oligodendrocytes are involved in the development of GBM tumors as primary glioblastoma or from lower-grade astrocytomas which further progress as secondary glioblastomas.[15] Moreover, the recurrent relapse of GBM in patients is very frequent from the initial tumor site; glioblastomas gained primary importance in the oncology field due to a lack of prognosis and treatment of the disease.[16]

Glioblastoma is a serious public health issue with a dismal prognosis because it is always associated with a survival rate of 14–15 months following diagnosis in primary malignant brain tumors, even in the present era with highly precise brain surgery and irradiation.[17] Diagnosis of GBM is through MR and GBM-specific biomarkers such as microvesicles.

Microvesicles are small membrane-enclosed particles that enclose mRNA, miRNA and proteins from cells.[18] The GBM-derived vesicles are tumor-specific which promotes the microenvironment for tumor growth.**[19]** For instance, the GBM driver mutant form of the EGF receptor EGFRvIII can promote neighbor cells to transform into GBM-like phenotypes.[20]

GBM is a highly diffusive, invasive and vascularized tumor and is not curable with the surgical intervention.[21] FDA-approved known monoclonal antibody against VEGF is Avastin or bevacizumab. During GBM tumor progression, high amount of VEGF was released from cancer cells for neoangiogenesis. Systemic injections of Avastin block neovascularization inside the tumor and consequently decrease its size.[22] Inhibition of VEGF signaling causes deep vein thrombosis.[23] Once, the tumor cells were destroyed, the patients underwent antiviral therapy.[24] Inhibition role of SEN461 is a potential small molecule that targets on WNT pathway proven in *in vivo* and *in vitro*.[25]

TMZ is a small (194 Da) lipophilic molecule used as a drug that is administered orally and is available as mono-functional DNA alkylating agent of the imidazotetrazine class of drugs. TMZ is a DNA alkylating agent with considerable antitumor activity and potential effects on the central nervous system.[26] TMZ acts as a pro drug that is stable at acidic pH values, but labile above pH 7, with a plasma half-life of 1.8 hours at pH 7.4.[27] The molecular mechanism of the drug begins with the addition of methyl group O^6- methylguanine to DNA which activates DNA mismatch repair. The bonding of O^6-methylguanine is permanent on guanines residue in DNA resulting in DNA double-strand breaks and cellular apoptosis.[28] The antagonist to O^6-methylguanine to DNA is via DNA methyltransferase enzyme which is a suicide enzyme itself.[29] Hence, high MGMT expression levels in cells induce resistance to TMZ drugs.[30]

European Organization for Research and Treatment of Cancer 26981-22981/National Cancer Institute of Canada Clinical Trials Group CE3 intergroup trial compared radiotherapy alone with concomitant and adjuvant TMZ to improve median survival and 2-year survival relative to postoperative radiotherapy alone.[31] TMZ readily diffuses the blood-brain barrier and effective concentrations are achieved in the CNS with the plasma-CSF ratio 30% to 40%.[32,33] In surgery and radiotherapy, addition of TMZ is clinically and statistically significant in survival with the least toxicity. In large randomized phase II trial with patients with recurrent GBM, the 6-month progression-free survival rate was 21% for patients treated with TMZ, compared with only 8% for patients treated with pro-carbazine drug.[35] Comparative analysis of alkylating drugs showed that TMZ has more advantages over other drugs in the clinical treatment of GBM.[36,37]

Meta-Analysis

The PRISMA statement is followed when conducting meta-analysis. The Cochrane Central Register of Controlled Trials, Scielo and PubMed databases were all examined. The most pertinent scientific papers that relate to the use of Temozolomide both alone and in combination for the treatment of GBM were thoroughly examined. To research the most pertinent studies, namely RTCs, meta-analyses and expert opinions, several databases and resources were utilized.

Procedure: The studies associated with RCTs and meta-analysis are incorporated here. Different keywords were used in search of the most relevant studies. The keywords used here in search of the most relevant studies included "Glioblastoma", ''therapeutics for Glioblastoma'', ''Temozolomide and Glioblastoma", "safety and efficacy of Temozolomide", "Temozolomide and combination therapeutics", "Temozolomide adverse effects and complications". In search of the most relevant studies, keywords were used as alone and/or in combination. Full-length studies fulfilling inclusion and exclusion criteria were selected for the study as in table 1.

The inclusion and exclusion criteria applied to the present study are summarized in table. The study strictly includes RCTs explicitly in the synthesis of the hypothesis for the involvement of Temozolomide in Glioblastoma

Table 1
Inclusion and Exclusion Criteria

Inclusion and Exclusion Criteria	
Inclusion Criteria	
Outline	RCTs; Studies that provide interventional details of oral antispasticity drug in non-progressive neurological diseases.
Patients	Non-progressive neurological diseases patients opted oral antispasticity drugs.
Intervention	Oral antispasticity drugs and placebo
Language	English
Exclusion Criteria	
Outline	Poorly explained and/or incomprehensible methodology
Publication Method	Abstract only

The scientific data that was gathered was used to evaluate and interpret the effectiveness and results of Temozolomide intervention in Glioblastoma. In this study, safety and efficacy of therapies for patients with glioblastoma were both examined. RCT studies were the topic of a recent study that sought to build a sound scientific argument. The analysis also took the inclusion and exclusion criteria into account. Prisma criteria were used to interpret the findings. The study also highlights the difficulties in finding relevant scientific data and how they affect the investigation. The present study's focus was to highlight findings either not discussed before or poorly addressed in previous studies. Meta-analysis concludes and highlights recommendations. A meta-analysis of selected studies was carried out using the MedCalC tool (https://www.medcalc.org/).

Data Extraction and Bias assessment: Data from the majority of eligible studies was retrieved and bias assessment was carried out in accordance with the PRISMA statement. The absence of symptoms following intervention and the follow-up period in each trial are the basis for the outcome and efficacy statistics.

Here, in the present study, a total of 1635 studies were selected and retrieved from predefined databases including PubMed, Cochrane Central Register of Controlled Trials and Scielo databases. Among these, 1620 were originally collected from listed databases and the other 15 studies were from non-defined databases. Further, out of 1620 studies from predefined databases, 970 were associated with the intervention of TMZ with other therapeutics while 650 were associated with the intervention of TMZ with radiation therapy (Figure 1).

Similarly, in 15 studies collected from non-defined databases, 9 were associated with TMZ interventions with other therapeutics while 6 studies were associated with TMZ interventions with radiation therapy. Predefined inclusion and exclusion criteria were applied to pool studies and 1140 were excluded.

Further screening involves the exclusion of 35 as duplicate and 439 as non-relevant clinical studies. Complete screening based on inclusion and exclusion criteria results in a total of 21 eligible studies for meta-analysis where 11 were associated with the intervention of TMZ with other therapeutics and 10 were associated with the intervention of TMZ and radiation therapy.

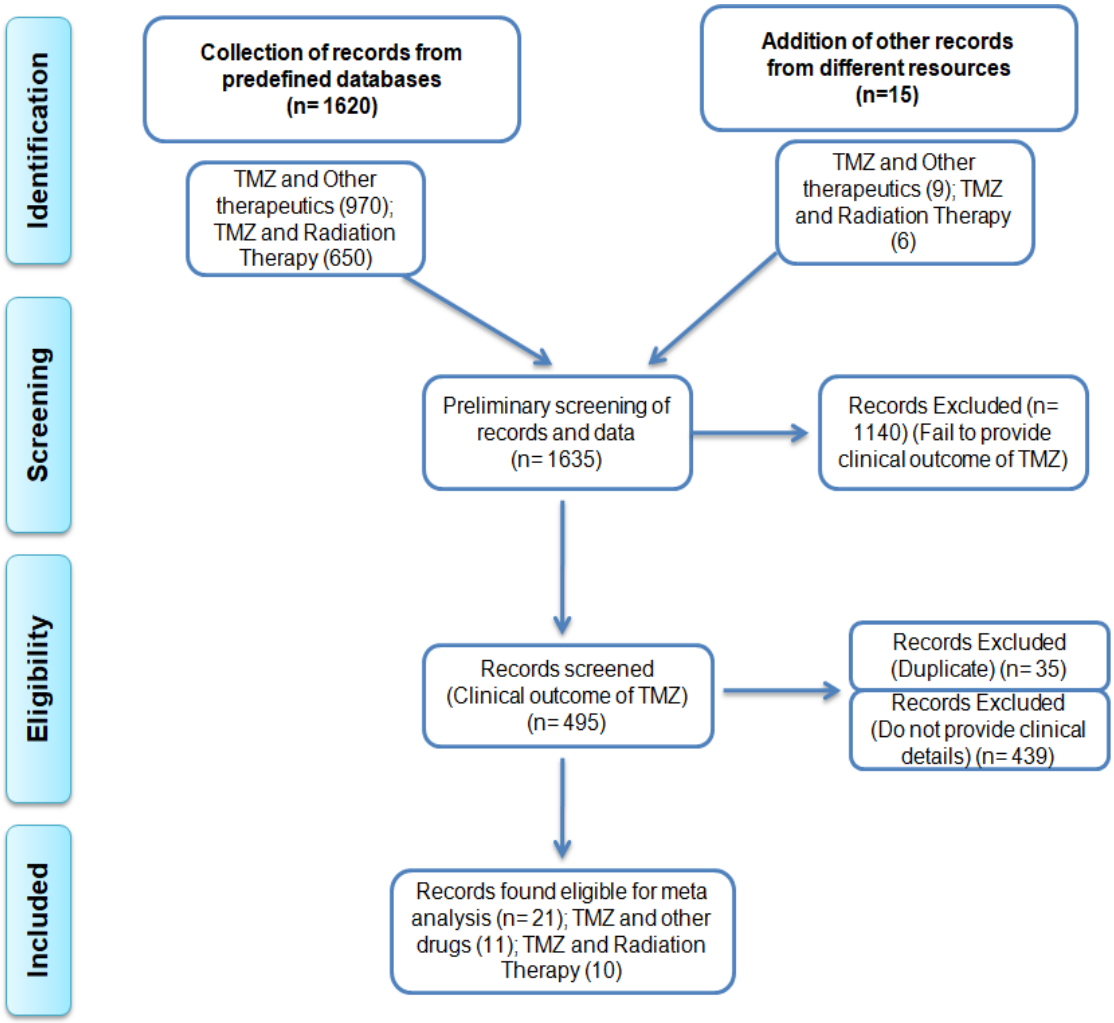


Figure 1: PRISMA flow diagram demonstrates search strategy and study selection (http://prisma-statement.org/).

TMZ Intervention with Radiation Therapy: Meta-analysis was carried out in two aspects: one using those clinical studies where TMZ interventions were involved with other therapeutics while second one where TMZ intervention were involved with radiation therapy. In the present study, meta-analysis was carried out using three parameters including odds ratio analysis, risk difference analysis and relative risk analysis. As shown in figure 2, the efficacy of TMZ with other therapeutics was evaluated. The odds ratio random effect was reported at 2.967 (Suppl. Table 2) while the total effect was 2.831. The odds ratio analysis demonstrated that 95%Cl reported 2.537-3.466 (random effect) and 2.537-3.158 (total effect). Odds ratio analysis was significant as a p-value was reported ($p<0.001$). Odds ratio analysis demonstrated a higher weight % for fixed and random both 100%.

In the test for heterogeneity, I^2 value (inconsistency) was reported as 35.08% where 95%Cl for I^2 was 0.00-68.10. Significance level reported p= 0.118. Q and DF values were reported at 15.40 and 10 respectively. Further, publication bias analysis was carried out where intercept in Egger test reported 1.4230 and 95%Cl and the significance level was determined -0.1928-3.0387. Additionally, the Begg`s Test analysis demonstrated a significance level of p = 0.2429. Compared to odds ratio analysis, risk difference analysis data summarized in suppl. table 2 and figure 2 demonstrated random and total effects 95%Cl 1.92-0.280 and 1.89-0.231 respectively.

The risk difference analysis was reported significant ($p<0.001$) with a higher weight % i.e. 100%. Additionally, test for heterogeneity demonstrated significance level p=0.0004 (Q= 32.2899 and DF= 10). Inconsistent I^2 was reported at 69.03% and 95%Cl I^2 42.15-83.42. Publication bias in risk difference analysis was reported significant (p=0.0223) with intercept 2.266 and 95%Cl 0.4062-4.1253.

The study also compared the clinical findings for relative risk analysis and reported total and random relative risk among the studies 1.375 and 1.498. The 95%Cl values in relative risk analysis reported 1.35-1.669 and 1.329-1.422 for random and total effect (Suppl. Table 3 and figure 2). In the present study, results reported significant ($p<0.0001$) using three distinct parameters odds ratio, relative risk and risk difference where TMZ intervention was done with other therapeutics.

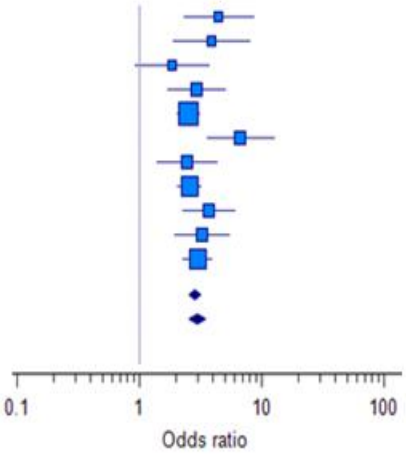
TMZ Intervention with Radiation Therapy: In another set of meta-analysis, in clinical studies were associated with the TMZ intervention with radiation therapy. As per the results shown suppl. table 4 and figure 3, the efficacy of TMZ intervention with radiation therapy was summarized where odds ratio analysis demonstrated total and random effect as 1.177 and 1.181 respectively. The odds ratio analysis was significant (p=0.005) where 95%Cl for total and random effect reported 1.055-1.312 and 1.051-1.37 respectively. The odds ratio weight % was high as reported at 100% for both total and random effects. Heterogeneity test shows insignificant where inconsistency I^2 reported 7.54% and 95%Cl for I^2 was 0.00-65.39 (Q= 9.7334; DF= 9).

Further, publication bias analysis demonstrates a p-value of 0.2079 for the Egger Test and 0.1284 for the Begg Test. Risk difference analysis for TMZ with radiation intervention group was shown in suppl. table 5 and figure 3. For odds ratio, total risk difference for TMZ with the radiation intervention group was reported as 0.0369 and 0.358 respectively. The risk difference was significant where p = 0.003 with higher weight % (100%). The 95%Cl value for risk difference in TMZ with radiation intervention group was reported as 0.0116-0.0623 and 0.0118-0.0597 for random and fixed effect. In comparison to the odds ratio, the risk difference heterogeneity test was insignificant (p=0.3752) where inconsistency I^2 reported 7.23% and I^2 for 95%Cl was 0.00-65.27.

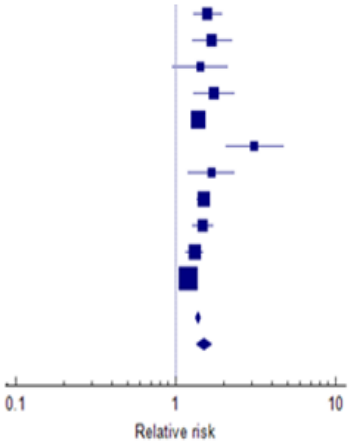
Table 2
Data Table demonstrates clinical uses of TMZ for the treatment of newly diagnosed Glioblastoma (GBM). Table also summarizes outcome of clinical interventions of TMZ and combination precisely with other therapeutics.

Study	Patients	Drug Interventions (TMZ Combination)		Duration of treatment
		TMZ	Other drug	
Khasraw et al	102	TMZ; 150-200 mg/m2/day	Nivolumab; 240-480 mg/m2/day	28 Days
Yang et al	71	TMZ; 150-200 mg/m2/day	Dexamethasone; 2.5 mg/m2/day	28 Days
Rayes-Botero et al	66	TMZ 130–150 mg/m^2/ day	Bevacizumab; 100–150 mg/m^2/ day	28 Days
Lee et al	114	TMZ; 150-200 mg/m2/day	Vandetanib; 100 mg/m2/day	28 Days
Gilbert et al[19]	833	TMZ; 150-200 mg/m2/day	TMZ; 75 mg/m2/day	28 Days
Bower et al[5]	103	TMZ; 150-200 mg/m2/day	Placebo	28 Days
Balana et al[2]	102	TMZ; 85 mg/m2/day	Bevacizumab; 10mg/kg/day	28 Days
Weller et al	745	TMZ; 150-200 mg/m2/day	Rindopepimut (500 µg/day)	28 Days
Schafer et al	170	TMZ; 150-200 mg/m2/day	Bevacizumab 10 mg/kg/day; Irinotecan 125 mg/m^2/Day	28 Days
Herrlinger et al	182	TMZ; 150-200 mg/m2/day	Bevacizumab 10 mg/kg/day; Irinotecan 125 mg/m^2/Day	28 Days
Saran et al	911	TMZ; 150-200 mg/m2/day	Bevacizumab 10 mg/kg/day	28 Days

Study	Intervention	Controls	Odds ratio	95% CI
Khasraw et al., 2018	85/102	54/102	4.444	2.320 to 8.513
Yang et al., 2018	54/71	32/71	3.871	1.888 to 7.938
Rayes-Botero et al., 2018	34/66	24/66	1.859	0.927 to 3.730
Lee et al., 2015	71/114	41/114	2.940	1.716 to 5.036
Gilbert et al., 2013	622/833	451/833	2.497	2.029 to 3.072
Bower et al., 1997	65/103	21/103	6.679	3.577 to 12.472
Balana et al, 2016	55/102	33/102	2.447	1.385 to 4.322
Weller et al., 2017	511/745	344/745	2.546	2.061 to 3.145
Schafer et al., 2018	140/170	95/170	3.684	2.241 to 6.057
Herrlinger et al., 2016	157/182	120/182	3.245	1.926 to 5.467
Saran et al., 2016	822/911	688/911	2.994	2.295 to 3.905
Total (fixed effects)	2616/3399	1903/3399	2.831	2.537 to 3.158
Total (random effects)	2616/3399	1903/3399	2.967	2.539 to 3.466



Study	Intervention	Controls	Relative risk	95% CI
Khasraw et al., 2018	85/102	54/102	1.574	1.286 to 1.927
Yang et al., 2018	54/71	32/71	1.687	1.265 to 2.251
Rayes-Botero et al., 2018	34/66	24/66	1.417	0.954 to 2.105
Lee et al., 2015	71/114	41/114	1.732	1.304 to 2.299
Gilbert et al., 2013	622/833	451/833	1.379	1.281 to 1.485
Bower et al., 1997	65/103	21/103	3.095	2.056 to 4.660
Balana et al, 2016	55/102	33/102	1.667	1.195 to 2.325
Weller et al., 2017	511/745	344/745	1.485	1.356 to 1.628
Schafer et al., 2018	140/170	95/170	1.474	1.268 to 1.713
Herrlinger et al., 2016	157/182	120/182	1.308	1.161 to 1.474
Saran et al., 2016	822/911	688/911	1.195	1.145 to 1.247
Total (fixed effects)	2616/3399	1903/3399	1.375	1.329 to 1.422
Total (random effects)	2616/3399	1903/3399	1.498	1.345 to 1.669



Study	Intervention	Controls	Risk Difference	95% CI
Khasraw et al., 2018	85/102	54/102	0.304	0.183 to 0.425
Yang et al., 2018	54/71	32/71	0.310	0.157 to 0.462
Rayes-Botero et al., 2018	34/66	24/66	0.152	-0.0158 to 0.319
Lee et al., 2015	71/114	41/114	0.263	0.138 to 0.388
Gilbert et al., 2013	622/833	451/833	0.205	0.160 to 0.250
Bower et al., 1997	65/103	21/103	0.427	0.306 to 0.549
Balana et al, 2016	55/102	33/102	0.216	0.0830 to 0.348
Weller et al., 2017	511/745	344/745	0.224	0.175 to 0.273
Schafer et al., 2018	140/170	95/170	0.265	0.171 to 0.359
Herrlinger et al., 2016	157/182	120/182	0.203	0.118 to 0.288
Saran et al., 2016	822/911	688/911	0.147	0.113 to 0.181
Total (fixed effects)	2616/3399	1903/3399	0.210	0.189 to 0.231
Total (random effects)	2616/3399	1903/3399	0.236	0.192 to 0.280

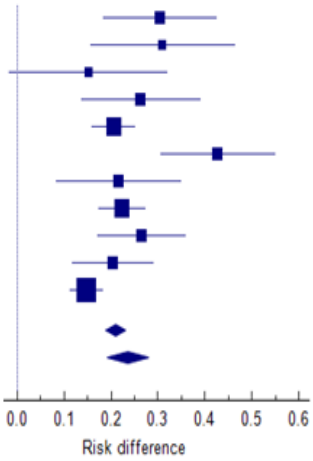
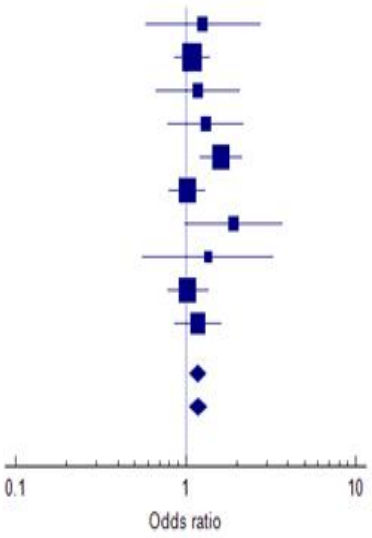


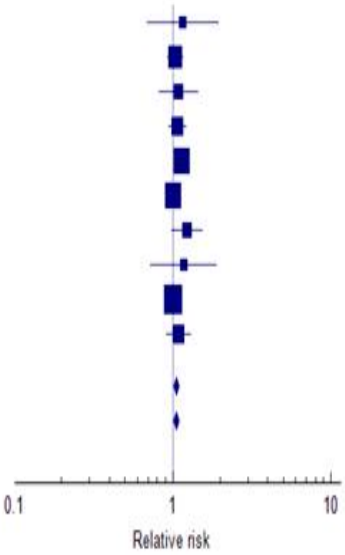
Figure 2: Figure demonstrates Odds ratio, relative risk and Risk Difference analysis among intervention (TMZ) and control group (other therapeutics).

On the contrary, publication bias analysis for risk difference in TMZ intervention with radiation therapy group was significant (p=0.0397) for the Begg`s test while insignificant p=0.2418 for the Egger test. Further, relative risk analysis was summarized in suppl. table 6 and figure 3. The relative risk analysis for TMZ with the radiation intervention group was significant p= 0.006. The relative risk for TMZ with the radiation intervention group was reported at 1.058 and 1.057 for a total and random effect. The study also demonstrated that 95% Cl for TMZ with radiation intervention group was 1.016-1.100 and 1.019-1.099 (random and fixed effect). The test for heterogeneity in TMZ intervention with radiation therapy group was found insignificant with inconsistency I^2 8.03% and 95%Cl I^2 0.00-65.57 (Q=9.7863; DF= 9). Publication bias analysis also demonstrated insignificant relative risk for TMZ intervention with a radiation therapy group for both Egger (p=0.1909) and Begg Test (p=0.1284).

Study	Intervention	Controls	Odds ratio	95% CI
Szczepanek et al., 2013	21/58	18/58	1.261	0.583 to 2.730
Stupp et al., 2005	322/573	310/573	1.088	0.862 to 1.374
Mao et al., 2015	51/99	47/99	1.176	0.673 to 2.053
Combs et al., 2008	124/160	116/160	1.307	0.786 to 2.171
Stupp et al., 2015	355/466	310/466	1.609	1.208 to 2.145
Cohen et al., 2005	387/573	385/573	1.016	0.794 to 1.301
Clark et al., 2009	63/85	51/85	1.909	0.996 to 3.661
Bhandari et al., 2017	20/40	17/40	1.353	0.560 to 3.267
Perry et al., 2017	421/562	418/562	1.029	0.786 to 1.346
Wick et al., 2009	154/318	141/318	1.179	0.863 to 1.610
Total (fixed effects)	1918/2934	1813/2934	1.177	1.055 to 1.312
Total (random effects)	1918/2934	1813/2934	1.181	1.051 to 1.327



Study	Intervention	Controls	Relative risk	95% CI
Szczepanek et al., 2013	21/58	18/58	1.167	0.698 to 1.950
Stupp et al., 2005	322/573	310/573	1.039	0.936 to 1.153
Mao et al., 2015	51/99	47/99	1.085	0.819 to 1.438
Combs et al., 2008	124/160	116/160	1.069	0.942 to 1.213
Stupp et al., 2015	355/466	310/466	1.145	1.055 to 1.243
Cohen et al., 2005	387/573	385/573	1.005	0.927 to 1.090
Clark et al., 2009	63/85	51/85	1.235	0.997 to 1.530
Bhandari et al., 2017	20/40	17/40	1.176	0.731 to 1.892
Perry et al., 2017	421/562	418/562	1.007	0.941 to 1.078
Wick et al., 2009	154/318	141/318	1.092	0.924 to 1.291
Total (fixed effects)	1918/2934	1813/2934	1.058	1.019 to 1.099
Total (random effects)	1918/2934	1813/2934	1.057	1.016 to 1.100



Study	Intervention	Controls	Risk Difference	95% CI
Szczepanek et al., 2013	21/58	18/58	0.0517	-0.120 to 0.223
Stupp et al., 2005	322/573	310/573	0.0209	-0.0366 to 0.0785
Mao et al., 2015	51/99	47/99	0.0404	-0.0988 to 0.180
Combs et al., 2008	124/160	116/160	0.0500	-0.0447 to 0.145
Stupp et al., 2015	355/466	310/466	0.0966	0.0388 to 0.154
Cohen et al., 2005	387/573	385/573	0.00349	-0.0508 to 0.0578
Clark et al., 2009	63/85	51/85	0.141	0.00147 to 0.281
Bhandari et al., 2017	20/40	17/40	0.0750	-0.143 to 0.293
Perry et al., 2017	421/562	418/562	0.00534	-0.0455 to 0.0562
Wick et al., 2009	154/318	141/318	0.0409	-0.0366 to 0.118
Total (fixed effects)	1918/2934	1813/2934	0.0358	0.0118 to 0.0597
Total (random effects)	1918/2934	1813/2934	0.0369	0.0116 to 0.0623

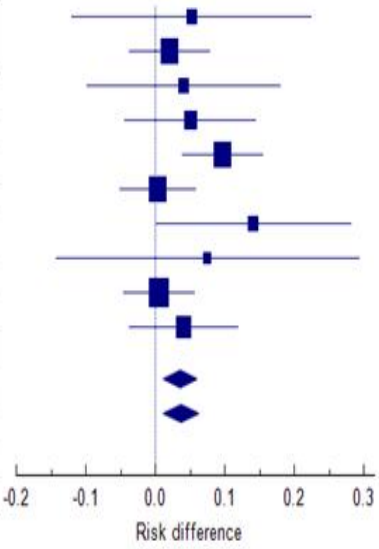


Figure 3: Figure demonstrates Odds ratio, relative risk and Risk difference analysis intervention (TMZ) and control group (Radiation).

Table 3
Data Table demonstrates clinical uses of TMZ for the treatment of newly diagnosed Glioblastoma (GBM). Table also summarizes outcome of clinical interventions of TMZ and radiation Therapy.

Study	Patients	Drug Interventions (TMZ Combination)		Duration of treatment
		TMZ	Radiation Therapy	
Szczepanek et al	58	TMZ; 150-200 mg/m²/day	Radiation Therapy	28 Days
Stupp et al	573	TMZ; 150-200 mg/m2/d	Radiation Therapy	28 Days
Mao et al	99	TMZ; 200 mg/m^2/ day	Radiation Therapy	28 Days
Combs et al[10]	160	TMZ; 50-75 mg/m2/day	Radiation Therapy	28 Days
Stupp et al	466	TMZ plus TTF 150-200 mg/m2/d	TMZ alone 150-200 mg/m2/d	28 Days
Cohen et al[9]	573	TMZ; 150 or 200 mg/m2 daily	Radiation Therapy	28 Days
Clark et al[7]	85	TMZ; 150 or mg/m2 daily	Radiation Therapy	28 Days
Bhandari et al[3]	40	TMZ; 150-200 mg/m2/d	Radiation Therapy	28 Days
Perry et al	562	TMZ; 150-200 mg/m2/d	Radiation Therapy	28 Days
Wick et al	318	TMZ, procarbazine, lomustine and vincristine; 10-200 mg/m2/day	Radiation Therapy	28 Days

Suppl. Table 1
Table summarizes Odds ratio data and analysis among intervention (TMZ) and control group (other therapeutics).

Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
Khasraw et al	85/102	54/102	4.444	2.320 to 8.513			2.85	4.81
Yang et al	54/71	32/71	3.871	1.888 to 7.938			2.34	4.06
Rayes-Botero et al	34/66	24/66	1.859	0.927 to 3.730			2.49	4.28
Lee et al	71/114	41/114	2.940	1.716 to 5.036			4.16	6.53
Gilbert et al[19]	622/833	451/833	2.497	2.029 to 3.072			28.04	19.60
Bower et al[5]	65/103	21/103	6.679	3.577 to 12.472			3.09	5.14
Balana et al[2]	55/102	33/102	2.447	1.385 to 4.322			3.72	5.99
Weller et al	511/745	344/745	2.546	2.061 to 3.145			26.96	19.33
Schafer et al	140/170	95/170	3.684	2.241 to 6.057			4.87	7.38
Herrlinger et al	157/182	120/182	3.245	1.926 to 5.467			4.43	6.86
Saran et al	822/911	688/911	2.994	2.295 to 3.905			17.05	16.01
Total (fixed effects)	2616/3399	1903/3399	2.831	2.537 to 3.158	18.645	<0.001	100.00	100.00
Total (random effects)	2616/3399	1903/3399	2.967	2.539 to 3.466	13.705	<0.001	100.00	100.00

Suppl. Table 2
Table summarizes Risk Difference data and analysis among intervention (TMZ) and control group (other therapeutics).

Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Khasraw et al	85/102	54/102	1.574	1.286 to 1.927			2.36	9.25
Yang et al	54/71	32/71	1.687	1.265 to 2.251			1.16	6.93
Rayes-Botero et al	34/66	24/66	1.417	0.954 to 2.105			0.62	4.81
Lee et al	71/114	41/114	1.732	1.304 to 2.299			1.20	7.04
Gilbert et al[19]	622/833	451/833	1.379	1.281 to 1.485			17.66	12.90
Bower et al[5]	65/103	21/103	3.095	2.056 to 4.660			0.58	4.61
Balana et al[2]	55/102	33/102	1.667	1.195 to 2.325			0.87	5.94
Weller et al	511/745	344/745	1.485	1.356 to 1.628			11.54	12.50
Schafer et al	140/170	95/170	1.474	1.268 to 1.713			4.26	10.83
Herrlinger et al	157/182	120/182	1.308	1.161 to 1.474			6.77	11.75
Saran et al	822/911	688/911	1.195	1.145 to 1.247			52.98	13.45
Total (fixed effects)	2616/3399	1903/3399	1.375	1.329 to 1.422	18.382	<0.001	100.00	100.00
Total (random effects)	2616/3399	1903/3399	1.498	1.345 to 1.669	7.360	<0.001	100.00	100.00

Suppl. Table 3
Table summarizes a Risk Difference analysis among intervention (TMZ) and control group (other therapeutics).

Study	Intervention	Controls	Risk Difference	95% CI	z	P	Weight (%)	
							Fixed	Random
Khasraw et al	85/102	54/102	0.304	0.183 to 0.425			2.89	7.30
Yang et al	54/71	32/71	0.310	0.157 to 0.462			1.82	5.51
Rayes-Botero et al	34/66	24/66	0.152	-0.0158 to 0.319			1.51	4.86
Lee et al	71/114	41/114	0.263	0.138 to 0.388			2.69	7.02
Gilbert et al[19]	622/833	451/833	0.205	0.160 to 0.250			20.93	13.84
Bower et al[5]	65/103	21/103	0.427	0.306 to 0.549			2.86	7.27
Balana et al[2]	55/102	33/102	0.216	0.0830 to 0.348			2.40	6.56
Weller et al	511/745	344/745	0.224	0.175 to 0.273			17.64	13.48
Schafer et al	140/170	95/170	0.265	0.171 to 0.359			4.77	9.31
Herrlinger et al	157/182	120/182	0.203	0.118 to 0.288			5.83	10.09
Saran et al	822/911	688/911	0.147	0.113 to 0.181			36.67	14.75
Total (fixed effects)	2616/3399	1903/3399	0.210	0.189 to 0.231	19.543	<0.001	100.00	100.00
Total (random effects)	2616/3399	1903/3399	0.236	0.192 to 0.280	10.477	<0.001	100.00	100.00

Suppl. Table 4
Table summarizes Odds ratio data and analysis among intervention (TMZ) and control group (Radiation Therapy).

Study	Intervention	Controls	Odds ratio	95% CI	z	P	Weight (%)	
							Fixed	Random
Szczepanek et al	21/58	18/58	1.261	0.583 to 2.730			2.01	2.24
Stupp et al	322/573	310/573	1.088	0.862 to 1.374			22.08	20.99
Mao et al	51/99	47/99	1.176	0.673 to 2.053			3.85	4.22
Combs et al[10]	124/160	116/160	1.307	0.786 to 2.171			4.64	5.05
Stupp et al	355/466	310/466	1.609	1.208 to 2.145			14.53	14.62
Cohen et al[9]	387/573	385/573	1.016	0.794 to 1.301			19.64	19.01
Clark et al[7]	63/85	51/85	1.909	0.996 to 3.661			2.83	3.12
Bhandari et al[3]	20/40	17/40	1.353	0.560 to 3.267			1.54	1.72
Perry et al	421/562	418/562	1.029	0.786 to 1.346			16.58	16.42
Wick et al	154/318	141/318	1.179	0.863 to 1.610			12.31	12.60
Total (fixed effects)	1918/2934	1813/2934	1.177	1.055 to 1.312	2.920	0.003	100.00	100.00
Total (random effects)	1918/2934	1813/2934	1.181	1.051 to 1.327	2.804	0.005	100.00	100.00

Suppl. Table 5
Table summarizes Risk Difference data and analysis among intervention (TMZ) and control group (Radiation Therapy).

Study	Intervention	Controls	Risk Difference	95% CI	z	P	Weight (%)	
							Fixed	Random
Szczepanek et al	21/58	18/58	0.0517	-0.120 to 0.223			1.92	2.14
Stupp et al	322/573	310/573	0.0209	-0.0366 to 0.0785			17.10	16.91
Mao et al	51/99	47/99	0.0404	-0.0988 to 0.180			2.93	3.23
Combs et al[10]	124/160	116/160	0.0500	-0.0447 to 0.145			6.32	6.78
Stupp et al	355/466	310/466	0.0966	0.0388 to 0.154			17.02	16.84
Cohen et al[9]	387/573	385/573	0.00349	-0.0508 to 0.0578			19.24	18.73
Clark et al[7]	63/85	51/85	0.141	0.00147 to 0.281			2.91	3.20
Bhandari et al[3]	20/40	17/40	0.0750	-0.143 to 0.293			1.19	1.34
Perry et al	421/562	418/562	0.00534	-0.0455 to 0.0562			21.92	20.93
Wick et al	154/318	141/318	0.0409	-0.0366 to 0.118			9.45	9.90
Total (fixed effects)	1918/2934	1813/2934	0.0358	0.0118 to 0.0597	2.928	0.003	100.00	100.00
Total (random effects)	1918/2934	1813/2934	0.0369	0.0116 to 0.0623	2.861	0.004	100.00	100.00

Suppl. Table 6
Table summarizes Relative Risk data and analysis among intervention (TMZ) and control group (Radiation Therapy).

Study	Intervention	Controls	Relative risk	95% CI	z	P	Weight (%)	
							Fixed	Random
Szczepanek et al	21/58	18/58	1.167	0.698 to 1.950			0.51	0.59
Stupp et al	322/573	310/573	1.039	0.936 to 1.153			12.22	12.86
Mao et al[31]	51/99	47/99	1.085	0.819 to 1.438			1.68	1.94
Combs et al[10]	124/160	116/160	1.069	0.942 to 1.213			8.29	9.04
Stupp et al	355/466	310/466	1.145	1.055 to 1.243			19.82	19.58
Cohen et al[9]	387/573	385/573	1.005	0.927 to 1.090			20.52	20.16
Clark et al[7]	63/85	51/85	1.235	0.997 to 1.530			2.90	3.33
Bhandari et al[3]	20/40	17/40	1.176	0.731 to 1.892			0.59	0.69
Perry et al	421/562	418/562	1.007	0.941 to 1.078			28.71	26.45
Wick et al	154/318	141/318	1.092	0.924 to 1.291			4.76	5.35
Total (fixed effects)	1918/2934	1813/2934	1.058	1.019 to 1.099	2.919	0.004	100.00	100.00
Total (random effects)	1918/2934	1813/2934	1.057	1.016 to 1.100	2.758	0.006	100.00	100.00

Discussion

The research and clinical evidence demonstrated that GBM is the most common and aggressive malignant brain tumor worldwide. The diagnosis and treatment of GBM remains complex where functional MRI and DTI, ultrasound, CT scans and MRI are available options. The therapy approved for the treatment of GBM including multimodal and includes surgical resection, radiation and chemotherapy.[38] Innovative treatments such as TT Fields and immunotherapy, gave hope for enhanced survival. TMZ, an oral alkylating pro-drug which delivers a methyl group to purine bases of DNA, is frequently used together with radiotherapy as part of the first-line treatment of high-grade gliomas.[39]

TMZ is a lipophilic alkylating agent that showed an advantage as a chemotherapeutic agent for GBM over other therapeutics.[40] TMZ offers a high bioavailability in cerebrospinal fluid with higher diffusion through the BBB. TMZ is effective not only in newly GBM tumors but also in solid GBM tumors. Higher outcomes and survival rates of GBM patients with the intervention of TMZ were reported with a combination of therapeutic approaches, radiation and other chemotherapeutic agents.[41]

NUTMEG comparative efficacy of TMZ alone and with nivolumab demonstrated that TMZ in combination with nivolumab is more effective in offering a higher survival rate over TMZ alone.[42] TMZ intervention via oral route was reported effective with nilustine. Earlier studies also demonstrated higher doses of TMZ as effective in newly diagnosed GBM patients.[43] Radiation therapies are often used along with chemotherapy for a higher survival rate in GBM patients. TMZ with and without radiation therapy is effective for new and solid GBM tumors.[44] TMZ intervention with other chemotherapeutic agents is much more effective than TMZ along with radiation therapy.[45,46]

TMZ has been used as a maintenance dose as well where different treatment tumor treating fields provide an extended therapeutic window and higher survival rate.[47] TMZ was reported significant when administered to newly diagnosed GBM patients where TMZ and Rindopepimut were used[48]. There are numerous clinical findings where TMZ was used with other chemotherapeutic agents for the treatment of GBM with a higher survival rate.[49-51] Combination of TMZ with Bevacizumab is effective not only in newly diagnosed GBM cases but also in old cases as well.[52]

TMZ alone is an effective chemotherapeutic agent widely used for the management of GBM including both newly diagnosed and solid tumors. However, combination therapeutics showed higher efficacy than other therapeutics and radiations are frequently used clinically. Survival efficacy in GBM, TMZ and radiation therapy was investigated extensively in the past.[53-55] In a multi-center, randomized open-label Phase II clinical trial demonstrated the efficacy of TMZ with radiation therapy in newly diagnosed GBM patients.[56] In radiation therapy, TMZ is generally used as adjuvant in both new and solid GBM tumors.[57] Randomized phase II trial demonstrated a higher dose of TMZ with radiation and reported a higher survival rate in newly diagnosed GBM patients.[58] FDA approved TMZ and radiation therapy for newly diagnosed GBM patients.[59]

Multiple clinical trials are underway where radiation therapy and TMZ are used for the treatment of both newly diagnosed and solid tumors of GBM.[42] In GBM, glioblastoma multiforme is the most critical case where a higher rate of mortality was reported. A comparative study showed the use of TMZ as an adjuvant for six to twelve cycles for the management of glioblastoma multiforme with radiation therapy.[60]

In radiation therapy, TMZ is not the chemotherapeutic agent but several others are also used clinically such as procarbazine, lomustine and vincristine or temozolomid.[61-63] In this meta-analysis based on Odds ratio, risk difference and relative risk TMZ with other chemotherapeutic agents were

reported more effective over TMZ with radiation therapy for the management of GBM.

Conclusion

In the management of GBM, both freshly diagnosed and solid tumors, the meta-analysis shows that TMZ combined with other chemotherapeutic drugs is significantly more successful than TMZ combined with radiation. However, TMZ is utilized as an adjuvant in single and multiple doses for several cycles. TMZ is one of the most potent chemotherapeutic drugs now available for clinical usage in the treatment of GBM. When used as an adjuvant to improve the efficacy of radiation therapy, TMZ has demonstrated effectiveness. With a greater survival rate for GBM patients, TT fields have gained popularity in addition to TMZ and other treatments and TMZ with radiation therapy. TT Fields are especially safe and do not have any extra systemic effects as compared to TMZ.

In the current meta-analysis, the effectiveness of TMZ with other chemotherapeutic agents was compared to TMZ with radiation therapy and shown to be more successful with a greater survival rate in patients with GBM, including those with freshly diagnosed tumors and those with solid tumors. The most common and lethal form of tumor to neural tissue is called GMB and it is also the most aggressive. The survival rate for GBM is quite low, necessitating the use of various therapies in conjunction with or in addition to radiation therapy. According to TMZ, radiation treatment and other chemotherapeutic drugs work best in combination with TMZ to treat GMB as shown in various studies.

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