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The Efficacy of Temozolomide Combined with Levetiracetam for Glioblastoma (GBM) After Surgery: a Study Protocol for a Double-Dlinded and Randomized Controlled Trial

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Abstract

Background: Temozolomide is applied as the standard chemotherapy agent in patients with glioblastoma (GBM) after surgery. However, the benefit of this treatment for patients is limited by the invasive growth of glioma and drug resistance. There are indications from fundamental experimental and retrospective studies that levetiracetam has the potential to improve the survival rate of GBM patients. However, it has yet to be ascertained whether the combination of temozolomide and levetiracetam is more effective than temozolomide chemotherapy alone. Therefore, we designed a randomized clinical trial to investigate the therapeutic effect of the new combined regime for the treatment of GBM.

Methods/design: This is a double-blind and randomized clinical trial carried out in a single center. A total of 142 patients will be recruited and screened for the inclusion and exclusion criteria. Then, eligible participants will be enrolled and randomly allocated into an Experimental group or a Control group in a 1:1 ratio. Based on the administration of radiation therapy (RT), participants in the Experimental group will be prescribed levetiracetam plus temozolomide chemotherapy for 34 weeks while participants in the Control group will be prescribed placebo tablets plus temozolomide for the same duration. All patients will be followed-up for three years after intervention. Accordingly, the primary outcome will be progression-free survival (PFS). The secondary endpoints include overall survival (OS), the Karnofsky Performance Status (KPS), the objective response rate (ORR), and the incidence of adverse events.

Discussion: The results of this trial are expected to provide high-level evidence regarding the clinical benefits of the combination of levetiracetam and temozolomide in the treatment of GBM.

Trial registration: www.ChiCTR.org.cn, ID: ChiCTR-2100049941. Registered on 14thAugust 2021.

1. Background

Glioblastoma (GBM) accounts for up to 60% of all primary malignant brain tumors in adults (1) and is also known as astrocytoma grade IV according to the amended WHO classification of 2016 (2). GBM is the most aggressive and lethal form of primary astrocytoma; this is due to the highly infiltrative and heterogeneous nature of glioma cells. Currently, the standard of care for GBM patients consists of maximal surgical resection plus adjuvant chemotherapy and radiation therapy (RT) (3). Despite multimodal treatment, the prognosis of patients with GBM is still extremely poor with a 5 -year overall survival rate no greater than 5% post-diagnosis(4); 2–3% of patients survive for up to two years (5).

Of the many chemotherapy agents that are clinically available, temozolomide (TMZ) is the only standard chemotherapy used for patients with GBM (6, 7). TMZ is an oral alkylating agent that penetrates the brain and damages DNA by inducing DNA O^6-methylguanine(8). However, the expression of the DNA repair enzyme O^6-methylguanine methyltransferase (MGMT) can abrogate the cytotoxic O^6-methylguanine DNA adduct by repairing damaged DNA and thus contribute to drug resistance (9). In addition, the overexpression of the ATP-binding cassette (ABC) efflux transporters, ABCG2 and ABCB1, provides chemoresistance by transporting drugs across the cell membrane into stem cells (10) and contributes to

the blood-brain barrier (BBB) (11). Therefore, the anti-tumor effect of TMZ monotherapy is constrained with limited clinical benefits. The majority of patients who are given TMZ monotherapy remain unable to avoid tumor recurrence after surgery or drug resistance. With the absence of a wider range of broad-spectrum and effective chemotherapy drugs, the limitations of TMZ monotherapy for patients with GBM remains a severe clinical problem that needs to be solved urgently.

Levetiracetam (LEV), as an antiepileptic drug, is mainly used for the treatment of partial seizures in adults and children over 4 years of age with epilepsy. In recent years, studies have found that levetiracetam was associated with a better survival rate when used in GBM patients (12–15). These observational studies provide a compelling background for investigating the effect of LEV on GBM. The potential antitumor activity of LEV might involve the inhibition of MGMT transcription and expression in glioblastoma cell lines, thus sensitizing glioblastoma cells to the alkylating agent TMZ (16, 17). Therefore, the combination of TMZ and LEV is expected to offer complementary strengths and thus maximize the anti-tumor effect of TMZ.

Although these fundamental experimental and retrospective studies have indicated that the combination of LEV and TMZ is emerging as an optimal approach for improving the survival of GBM patients after surgery, it remains unclear whether this new regime is effective. A prospective randomized controlled trial (RCT) is therefore needed to investigate the effects of TMZ plus LEV compared with TMZ alone. In Korea, a prospective clinical trial (*NCT02815410*) is recruiting patients to investigate the role of LEV for newly diagnosed GBM patients. However, in China, there is no correlative, randomized, and controlled trial that has been designed to investigate the effects of LEV for GBM. As a result, we decided to conduct an RCT to confirm the therapeutic effect of LEV plus TMZ for GBM, and thus provide an available therapeutic option for the treatment of GBM. The primary objective of this RCT is to determine whether the combination of TMZ and LEV is superior to TMZ alone in prolonging the progression-free survival (PFS) of GBM patients after surgery. This trial will also evaluate the efficacy of new chemotherapy regimens in improving the overall survival (OS), objective response rate (ORR), and the Karnofsky Performance status scale (KPS).

2. Methods/design

2.1 Study design

This is a prospective, single-center, randomized, double-blind, clinical trial, which will be conducted at the Second Affiliated Hospital of Chongqing Medical University in China. The study was registered at the Chinese Clinical Trial Registry on 14th August 2021 (ChiCTR-2100049941). We aim to recruit 142 eligible subjects and allocate these to the Control group (standard TMZ chemoradiotherapy) or the Experimental group (TMZ plus LEV chemoradiotherapy) at a 1:1 ratio. All participants will undergo a treatment period of 34 weeks and a follow-up period of three years. The trial flow chart is shown in Figure 1. The study protocol rigorously follows the Standard Protocol Items: Recommendations for Interventional Trials 2013 (SPIRIT 2013) checklist (See Additional File 1).

2.2Recruitment and eligibility criteria

The enrollment is expected to be completed within three years (from the beginning of recruitment to the last patient). Enrolment is projected to start in November 2021. The recruitment advertisements for the study will be placed on the WeChat public website and the hospital website. Research staff (NH, YHT and GJZ) will be responsible for screening inpatients and outpatients according to the inclusion and exclusion criteria. Then, the investigator will introduce the protocol to the participants and explain the harms and benefits of this trial in detail.

The inclusion criteria are as follows: (1) aged 18–65 years, female or male; (2) newly diagnosed GBM (WHO grade IV) patients with maximal surgical resection; (3) patients within three months of surgery; (4) KPS ≥50; (5) adequate hematological, renal, and hepatic function. All patients should meet the following criteria: (a) absolute neutrophil count (ANC)≥1.5x10 ^{9} /L, platelet count≥100x10 ^{9} /L, (b) serum creatinine ≤ 1.5 x upper limit of the normal range for each institution (ULN), (c) total bilirubin level ≤ 1.5 x ULN (except patients with Gilbert Syndrome), (d) aspartate aminotransferase (AST) ≤ 3.0 x ULN; alanine aminotransferase (ALT) ≤ 3.0 x ULN, AST/ALT < 2.5 x ULN; and (6) the patient and his/her family members were informed and provided signed and informed consent.

The exclusion criteria are as follows: (1) prior chemotherapy within the last five years; (2) planned surgery for other diseases; (3) pregnant women or those that are breastfeeding; (4) patients with a known hypersensitivity to LEV and TMZ or any of the excipients of the products; (5) concurrent illness, including unstable heart disease despite appropriate treatment, a history of myocardial infarction within 6 months, and active hepatitis (Hepatitis B Virus (HBV) or Hepatitis C Virus (HCV)); and (6) patients with serious psychological disease.

The withdrawal criteria are as follows: (1) voluntary withdrawal during the intervention; (2) alcohol and/or drug abuse; (3) patients who take part in another trial concerning glioma; (4) any other reasons considered inappropriate by the investigators.

2.3 Interventions

All patients will be allocated to the Experimental group or the Control group according to a blocked randomization sequence produced by SPSS 11 software for windows. Each group will be prescribed drugs for 34 weeks (including four weeks as an interval). The protocol interventions consist of chemotherapy and radiation therapy (RT). A chart showing the administration of interventions is shown in Table 1.

2.3.1 Co-interventions (RT)

Patients in both study arms will receive the same intensity-modulated radiation therapy (RT). The radiation dose will be 54 - 60Gy in 30 fractions (1.8 - 2.0 Gy once daily, 5 days per week, for six weeks). The particular volumes of radiation treatment will be defined by clinical target volume (CTV) using MRI data.

2.3.2 Experimental group

Concurrent chemoradiotherapy (CCRT): Patients will take TMZ one hour before meals in the per-oral form at a daily dose of 75 mg/m ^{2} continuously for 6 weeks during RT if the non-hematological toxicity ≤ grade 1 except for hair loss, nausea, and vomiting, according to the common toxicity criteria (CTC)(18). Patients in the experimental group will be given LEV tablets for the same duration. The initial treatment dose is 250 mg each time, twice a day. According to clinical effect and tolerance, the daily dose can be increased to 1500mg each time, twice a day. Dosage changes should be increased or decreased by 500 mg/time every 2–4 weeks, twice a day.

Adjuvant chemotherapy: Four weeks after the end of the CCRT, six cycles of adjuvant therapy with TMZ plus LEV will be carried out. The daily dose of TMZ in the first cycle will be 150mg/m ^{2} continuously for five days during each 28-day cycle. At the beginning of the second cycle, if the non-hematological toxicity of the first cycle CTC is ≤2 (except for alopecia, nausea, and vomiting), the ANC is ≥ 1.5×10 ^{9}/L, and platelet count is ≥ 100 ×10 ^{9} /L, then the dose of TMZ can be increased to 200 mg/m^2/day. The daily dose of LEV generally should not be less than 500mg, continuous for 6 cycles. Drugs dose adjustments will be conducted according to the liver and renal function. if the patient's creatinine clearance rate is less than 50 mL/min, the daily dose should be halved. For patients with mild and moderate liver impairment, there is no need to adjust the dosage.

2.3.3 Control group

Standard TMZ chemoradiotherapy will involve TMZ plus placebo concurrent chemoradiotherapy plus six cycles of adjuvant treatment. The dosage of TMZ will be the same as that of the experimental group; placebos for LEV (with the same dosage and appearance) will be given during treatment.

2.3.4 Concomitant care

Patients with glioma often suffer from epileptic seizures. In the clinic, antiepileptic drugs (AED) will be administered to certain patients, including levetiracetam (LEV), valproic acid (VPA), phenytoin, carbamazepine, and phenobarbital. To minimize the impact on the experiment, we will recommend these drugs except for LEV. In addition, metoclopramide tablets (10mg) will be permitted to address nausea and vomiting after taking TMZ. All of the medications used during the trial will be documented in a case report form (CRF).

2.4 Outcomes

2.4.1 Primary outcome:

The primary outcome is the PFS of patients, the time from randomization and group allocation to any recorded disease progression, and even death.

2.4.2 Secondary outcomes are as follows:

(1) overall survival (OS), the time from randomization and allocation to death for any reason,

(2) the Karnofsky Performance status scale (KPS). This scale evaluates the levels of patient activity and medical needs. On this scale, there are 11 categories; the score ranges from 100 (no evidence of disease) to 0 (dead).

(3) Objective response rate (ORR)=(CR+PR)/total number of cases × 100%. A complete response (CR) will be defined as the disappearance of all target lesions. A partial response (PR) will be defined as a minimum 30% reduction in the sum of diameters of the target lesions, taking baseline sum diameters at a reference. ORR will be assessed by MRI according to the response evaluation criteria in solid tumors (RECIST)(19).

(4) Incidence of adverse events (AEs). Adverse events (CTC-Toxicity ≥ grade3) will be recorded and analyzed based on the Common Terminology Criteria for Adverse Events (CTC-AE)(18).

2.4.3 Other measures:

Complete blood counts (CBC): ANC, platelet count; Liver and renal function: creatinine clearance rate, total bilirubin level, Aspartate Aminotransferase (AST), and Alanine Aminotransferase (ALT);

2.5 Baseline and a follow-up visit

Demographic assessment will be carried out before the interventions, including age, gender, past medical history, the molecular pathological indicators (1p/19q status, ABCG2 level, and MGMT promoter status), complete blood counts (CBC), KPS, head MRI, and hepatic and renal function. During treatment, CBC and hepatic-renal function will be monitored weekly. KPS score and head MRI will be acquired on the third and sixth cycle and then every three months over the three years. Adverse events will be monitored continuously during treatment, then every 3 months in the 3 years. A flow diagram of enrollment, interventions, and assessments for participants (participant timeline) is presented in Table 2.

2.6 Sample size

The determination of sample size was calculated by PASS 15.0 software. Based on a previous study and clinical assumptions (20), the median OS of standard care for GBM is 14.6 months while that of the experimental group (TMZ plus LEV) is 24 months. Statistical parameters are set as follows: One-sided log-rank testing with 80% power; the probability of obtaining a false positive with a statistical test at 0.05; a three years follow-up time. Considering a potential dropout rate of 10% across both groups, it is estimated that 142 patients will need to be enrolled (71 participants per group).

2.7 Randomization and blinding

Eligible subjects will be randomly divided into two parallel pairs of groups in a 1:1 ratio in line with a software-generated random sequence stratified by operation situation (have or not) (produced via SPSS software). The allocation sequence will be concealed using sealed, opaque, and stapled envelopes that will not be opened for the participants and recruiters prior to study group assignment. The

implementation of sequence generation and allocation concealment will be conducted by a researcher who will not be involved in the recruitment process. A specific investigator will be responsible for the processing of study-group assignments.

The participants and outcome assessors will be blinded to the group allocation until the end of the trial. The study data statistician will not be unaware of allocations and will not participate in the follow-up visit. Regular unblinding will be performed for the first time by the principal investigator and statistical experts to conduct statistical analysis according to the statistical plan. The second unblinding progress will be performed by researchers to determine which of the groups was the experimental group and which was the control group. To avoid unnecessary unblinding or harm, the emergency unblinding of allocation will be conducted if the patient meets the following criteria: (1) patients who severely violate the treatment plan; (2) patients have severe adverse events during intervention; (3) patients or their family members request to stop the trial, and (4) visitors lost in follow-up.

2.8 Data collection and management

A case report form (CRF) will be filled in for each participant before intervention. The collection of baseline data, along with primary and secondary outcomes, will be recorded completely in CRF. All information will be held independently as double copies in a computer and imputed into ResMan, an Internet-based Electronic Data Capture (EDC). The data files will be locked after a blind audit and confirmed to be reliable. The CRF will be owned by the principal investigator and shall not be provided to any third party in any form without the written approval of the principal who will oversee all of the final trial data. All patients will complete a registration form of follow-up to promote retention. For participants who lose from intervention, the reason for loss, survival condition, and recent outcome assessment will be collected by a researcher. Finally, all original paper files will be kept in the filing cabinet of sponsoring organization and clinical data will be saved for 5 years.

2.9 Quality control

A data monitoring committee (DMC), consisting of neurosurgery experts and statisticians, will be established; this will be independent of the sponsor and trial investigator. The DMC will periodically evaluate the progress of the clinical trials, safety data, and important efficacy data. Furthermore, the DMC will also perform an interim evaluation and advise if the trial should be modified or discontinued according to the results of the interim evaluation.

During the study, an inspector shall check the accuracy and completeness of the CRFs and compare them with the source document. The inspector must make certain that the subject’s dose changes, treatment changes, adverse events, combined medications, missed visits, and examination omissions are recorded in the CRFs. They must also verify that the withdrawal and missing visits of the selected subjects have been recorded and explained in the CRFs. In addition, the inspector will notify the researcher of the errors, omissions, or unclear handwriting in CRFs and ensure that correction, addition, or deletion is carried out by a researcher or authorized person. If necessary, the reasons for modification must be recorded in writing. After each supervision and inspection, the inspector will write to the principal in a prompt manner.

2.10 Statistical analysis

We will use SPSS 23.0 statistical software for Windows to perform statistical analysis. To ensure the reliability of our conclusions, we plan to use intention-to-treat (ITT) analysis as the main form of analysis.

2.10.1 Baseline description

Means ± standard deviation (SD) will be used to describe quantitative data that are normally distributed; medians and interquartile ranges (IQRs) will be used to describe non-normal distribution data. The constituent ratio or relative ratio will be used to describe the count data.

2.10.2 Comparison of baseline data

T-tests will be performed for quantitative data that are normally distributed. A non-parametric test will be used for quantitative data that is not normally distributed. The Chi-squared (χ 2) test will be used for counting data. A two-sided P value < 0.05 will be considered to be statically significant.

2.10.3 Comparison of therapeutic efficacy

Kaplan–Meier survival analysis with a Log-rank test will be used to compare survival data (PFS and OS) between the two arms. Confounding factors, including age, history of drug use prior to intervention, epileptic seizure, and molecular pathological indicators will be analyzed by Cox proportion hazards regression analysis. Results will be expressed as hazard ratios (HRs) and 95% confidence intervals (CIs). Furthermore, the KPS and the ORR (ranked data) of the two arms will be compared by Wilcoxon's Rank-sum Test.

2.10.4 Safety evaluation

Incidence of adverse events (CTC-Toxicity ≥ grade3) will be expressed as the number of patients (percentage) and be analyzed by the Chi-square (χ 2) test.

2.11 Reports of adverse events

Adverse events (AEs) will be evaluated mainly by abnormal variations in laboratory data (including complete blood counts (CBC), liver function tests (total bilirubin level, AST, ALT), renal function tests (creatinine clearance, blood urea nitrogen), and clinical symptoms. The time of occurrence, severity level, management strategies, the causality related to experimental agents, and the endings of all adverse events (AEs) will be recorded and preserved during clinical trials and follow-up. All severe adverse events (CTC-Toxicity ≥ grade3) will be reported to the principal investigator and the research ethics committee (REC) in a timely manner. The researchers and clinical trial institutions will ensure that the subjects are treated appropriately and truthfully informed of the relevant information. When patients are informed of adverse reactions that are related to the trial by the provisions of China's Code of Quality Management for Drug Clinical Trials, the researchers will be responsible for the cost of dealing with the adverse reactions and the compensation that the patient may receive.

3. Discussion

Historically, previous randomized trials related to adjuvant chemotherapy for GBM were performed with nitrosoureas, such as carmustine (BCNU) and lomustine (CCNU)(21, 22). However, the efficacy of these drugs is limited by the development of drug resistance and many side effects. Based on these studies, the PCV scheme (the combination of procarbazine, CCBU, and vincristine) has been used for some time. However, studies have shown that there are no significant survival benefits related to the use of PCV(23). In 2005, Stupp et al. (20) demonstrated that therapy involving concurrent and adjuvant TMZ for 6 months significantly improved the median survival rate for patients with glioblastoma (14.6 months compared to 12.1 months). To date, the Stupp protocol is the most effective chemotherapy to treat GBM.

Despite advances in chemotherapy therapy, patients with GBM who have undergone surgery are confronted by drug resistance and tumor recurrence; these factors can lead to immense physical and financial stress. If our findings confirm that the new combined chemotherapy (TMZ plus LEV) is efficient, then this RCT could provide high-level evidence and broad application prospects for use as a first-line treatment regimen for GBM. This is the first prospective, randomized, and controlled clinical trial to confirm the efficacy of TMZ combined with LEV in GBM patients after surgery in China. This new regimen is expected to maximize the role of TMZ chemotherapy by targeting multiple anti-tumor mechanisms in patients with GBM, especially in patients with TMZ drug resistance and those who are positive for MGMT. Furthermore, we will use PFS as the primary outcome indicator and will also capture several secondary outcome parameters. These relatively objective evaluation indices will be used to evaluate the efficacy of the new combined regimens.

This study has several limitations that need to be considered. First, since there is no coherent guidance that can be referenced in terms of the optimal use of LEV in patients with GBM (for example, treatment cycle, reasonable dose, and discontinuation indicators), the drug intervention protocol lacks some degree of reference. The dose of LEV to be used in the trial will be administered based on the amount of medication used during seizures. Secondly, since all patients will be recruited from one hospital, the results of the trial may not be generalized to other ethnic groups and regions.

In summary, this RCT may contribute to the development of an optimal treatment regimen to effectively prolong the survival rate of patients with GBM.

4. Trial Status

This trial has been registered at ClinicalTrials.gov, (ID: ChiCTR2100049941). Currently, the study is about to begin the process of recruiting patients, and recruitment is expected to finish in November 2024.

5. Abbreviations

GBM: glioblastoma; TMZ :temozolomide; LEV :Levetiracetam ; RCT: randomized controlled trial OS: Overall survival; PFS: Progress free survival; KPS: the Karnofsky Performance Status Scale; ORR:

Objective response rate; CR: Complete Response; PR: Partial Response; RT: radiation therapy; CCRT: Concurrent chemoradio therapy;BBB: blood-brain barrier; MGMT: O^6-methylguanine methyl transferase; ABC: ATP-binding cassette; ANC: absolute neutrophil count; ULN: upper limit of the normal range of each institution; AST: aspartate aminotransferase; ALT: alanine Aminotransferase; CTV: clinical target volume; CTC: common toxicity criteria; RECIST: respond evaluation criteria in solid tumors; SPSS: Statistical Product and Service Solutions; AED: antiepileptic drugs; VPA: valproic acid; CRF: case report form; EDC: Electronic Data Capture; IQR: interquartile range; REC: research ethics committee; AEs: adverse events; PCV: a combination of procarbazine, CCBU, and vincristine;DMC: data monitoring committee;

6. Declarations

6.1 Ethics approval and consent to participate

The clinical trial has received ethical committee approval from the Research Ethics Committee (REC) of the Second Affiliated Hospital of Chongqing Medical University (ID: LKSD-2020-214).Address: No. 76, Linjiangmen,YuzhongDistrict, Chongqing. Tel.: 026069338.Informed consent forms, describing the particular study procedures and illustrating the potential benefits and risks, will be provided to each patient. It will be voluntary for patients (or their families) to decide whether or not to participate in this study.

6.2 Consent for publication

All of the authors are willing to provide a model consent form on request.

6.3 Availability of data and materials

Not applicable

6.4 Competing interests

The authors declare that they have no competing interests to declare.

6.5 Funding

This study is supported by the Chongqing Scientific and Health Joint Medical Research Project (2020GDRC021). Contact number:0236369662The funding body will play no role in study design, collection, management, analysis, and interpretation of the data.

6.6 Authors contribution

MYS is the first author and drafted/revised the manuscript. GDL will be responsible for organizing the entire trial.NH, YHT and GJZ are responsible for recruitment and assigning participants into the two groups. ZYX and XZwill be in charge of data analysis. JNM and YCwill take lead in guiding the

packaging, numbering, and distribution, of all experimental drugs. All authors have read and approved the final manuscript.

6.7 Acknowledgments

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8. Tables

Table.1 A chart showing drug administration regimens

Groups Treatment		Experimental group	Control group
CCRT (6 weeks)	RT	1.8–2.0Gy once daily, 5 days per week	
	TMZ	A daily dose of 75 mg/m ^{2}	
	LEV	250-1500 mg, twice daily	Placebo tables
Adjuvant chemotherapy (6cycles)	TMZ	A daily dose of 150 - 200 mg/m ^{2}	
	LEV	500- 1500 mg, twice daily	Placebo tables

Abbreviations: 1cycle: 28days **RT:** radiation therapy **CCRT:** concurrent chemoradiotherapy

Table.2 A flow diagram of enrollment, interventions, and assessments for participants

	Enrollment	**Allocation**	**Intervention**							**Follow-up**
TIMEPOINT	-t1day	0	t1	t2	t3	t4	t5	t6	t7	3years
ENROLMENT										
Eligible screen	×									
Informed consent	×									
Demographic data		×								
Random allocation		×								
INTERVENTION										
RT			×							
Experience group										
Control group										
ASSESSMENT										
CBC		×	×	×	×	×	×	×	×	
Hepatic and renal function		×	×	×	×	×	×	×	×	
KPS		×				×			×	Every 3 months
Head MRI		×				×			×	Every 3 months
Adverse events			×	×	×	×	×	×	×	Every 3 months

Abbreviations: t1: 1-6w (concurrent chemoradiotherapy); **t2:** 11-14w **t3:** 15-18w **t4:** 19-22w **t5:** 23-26w **t6:** 27-30w **t7:** 31-34w 6 cycles of Adjuvant treatment**RT**radiation therapy**CBC:**complete blood counts **KPS**Karnofsky performance score**MRI:** magnetic resonance imaging;

Figures

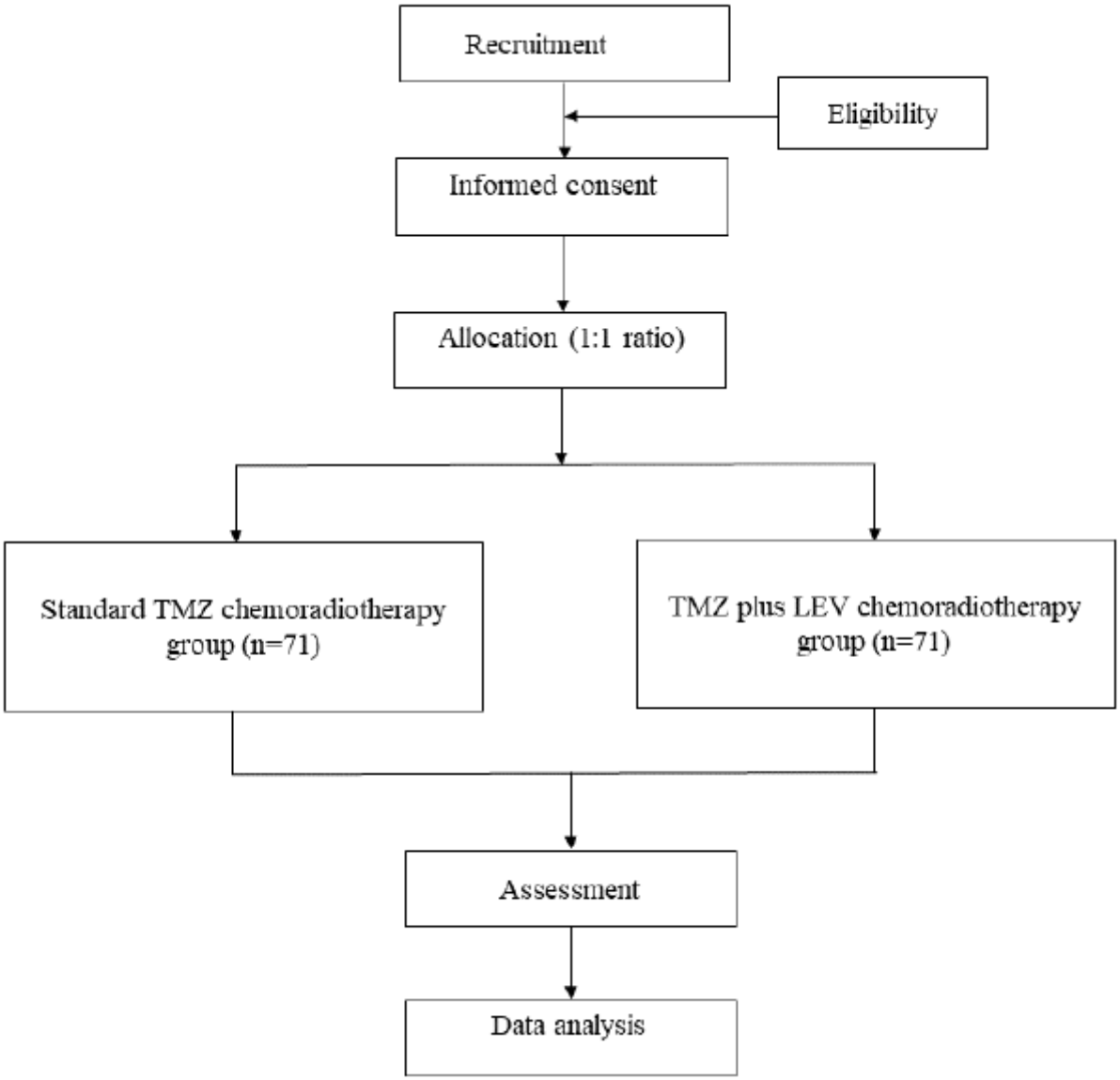

Figure 1

The trial flow chart

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- AdditionalFile1Checklist.doc