ORIGINAL ARTICLE

Radiotherapy alone with concurrent chemoradiotherapy plus temozolamide in locally advanced soft tissue sarcoma at Mayo Hospital Lahore: A randomized controlled trial

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Abstract

Objective: To evaluate the efficacy of combining an oral chemotherapeutic agent temozolamide with radiotherapy in the management of the un-resectable non-metastatic soft tissue sarcomas compared with radiotherapy alone.

Methods: The randomised controlled phase 3, double-arm study was conducted at King Edward Medical University / Mayo Hospital, Lahore, Pakistan, from December 2012 to July 2017. Patients with all sub-types of locally advanced un-resectable soft tissue sarcomas were randomised into two groups. Group-A received radiotherapy alone while Group-B received concomitant chemoradiotherapy with temozolamide after receiving two cycles of standard chemotherapy. Response was evaluated according to response evaluation criteria in solid tumours through computed tomography scan or magnetic resonance imaging after 6 weeks following completion of radiotherapy. SPSS 21 was used for data analysis.

Results: Of the 64 patients, 32(50%) were assigned to each group. The mean age of Group-A was 36.25±20.31 and of Group-B 37.84±15.79 years .There were 18(56.3%) males in Group-A and 20(62.5%) in Group-B. Improvement in trends of overall response rate was observed in Group-B 24(75%) compared to 18(56.3%) in Group-A (p=0.12).

Conclusion: Though not statistically significant, there was improvement in response rate with the addition of temozolamide to standard radiation therapy.

Keywords: Temozolamide, Radiotherapy, Soft tissue sarcomas. (JPMA 70: 572; 2020) **https://doi.org/10.5455/JPMA.293442**

Introduction

Soft tissue Sarcomas (STS) accounts for 1-2% of all malignant tumours. The incidence rate analysed by the United States (USA) in 2002 using World Health Organisation (WHO) criteria reported 26,758 STS cases regardless of primary sites, excluding tumours arising from bones and joints.[1] Localised sarcomas are treated surgically, and the surgery with wide local excision to achieve tumour-free margins remains the mainstay of treatment. The recurrence rate is 30%. Post-operative local radiation revealed no benefit in negative resection margins (<5cm) and low-grade tumours, but it certainly has a role in larger and high-grade STS lesions that have recurrence rates of up to 30% in the absence of adjuvant therapies.[2]

The major drawback is poor wound healing after surgery.[3] There is limited data available for using preoperative chemo-radiation for STS. Intravenous (IV) doxorubicin, ifosfamide, dacarbazine (DTIC) and other similar agents have improved the response and survival rates, but have been found to have higher toxicities compared to radiation alone. Therefore, no optimal chemotherapeutic drug has been devised for STS to be used in concurrent setting with radiotherapy (RT).[4] Temozolamide(TMZ) is an oral form of alkylating agent which methylates the guanine residues of tumour cell deoxyribonucleic acid (DNA), creating a mismatch that an enzyme repair system cannot fix.[5]

In a review of TMZ, the tolerance of radio-sensitizer with modest side effects was found and it may be useful in sarcoma radio-sensitisation for primary control as well as metastatic disease with the recommended dose.[6] TMZ has proven radio-sensitising effects in other tumours, like glioblastoma, and it has shown promise in vitro as well as in a few small trials for STS management.[7] With the added convenience of oral administration and already known safety profile, patients with locally advanced and unresectable STS can be studied for radio-sensitising effects of TMZ in neoadjuvant setting.

The current study was planned to evaluate the efficacy of combining TMZ, an oral chemotherapeutic agent, with RT in the management of the un-resectable non-metastatic STS compared with RT alone.

Patients and Methods

The randomised controlled phase 3, double-arm study was conducted at the Department of Oncology and

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Radiotherapy and Orthopaedic Surgery, King Edward Medical University / Mayo Hospital, Lahore, Pakistan, from December 2012 to July 2017.

The sample was raised using probability random sampling technique. Those included were patients of either gender aged 18 years and above with locally advanced un-resectable stage IIA, IIB and IIISTS determined with local magnetic resonance imaging (MRI) or computed tomography (CT) scan according to the 7th edition tumour, lymph node and metastasis (TNM) classification,[8] with either high or low grade STS on histopathology and immunohistochemistry (IHC). Tumour had to be located on the upper extremity, including shoulder, lower extremity, including hip, or trunk involving trunk and extremities. Patients had good performance status in line with Eastern Cooperative Oncology Group (ECOG 0-2) criterion.[9]

Those excluded had locally recurrent disease with previous history of RT established through history and medical records, and those with evidence of overt metastasis established with CT scan of chest and abdomen, and with bone scan. Also excluded were patients with left ventricular ejection fraction (LVEF) <50%, having history of second malignancy, those who could not take oral medications, pregnant or nursing mothers, patients who underwent surgical procedures affecting absorption or had active peptic ulcer disease, any psychiatric illness or had any social situation that would preclude study compliance. After advanced study research board approval, patients who presented in the out-patients and fulfilled the above criteria were counselled and explained the details of the study. Written informed consent and detailed history was taken from each patient. The final sample was randomly divided into two equal groups, Group-A and Group-B, by computer allocation method.

After informed consent from the patients, baseline investigation were carried out that included complete blood count (CBC), comprehensive chemistry profile, electrocardiography, urine analysis and chest radiographs that were taken regularly before and during the trial to ensure safety of the patients. Fertile patients were instructed for strict compliance with the use of two effective methods of contraception for four weeks before, during and for at least four weeks after the study. Documentations of disease parameters included record of histopathology, stage and measurable disease according to Response Evaluation Criteria in Solid Tumours (RECIST).[10] TMZ capsules 75mg/m^2/day were taken per oral one hour before the meal. Patients were started on oral TMZ therapy three days before RT to the tumour site and took TMZ till the completion of 60-70 GyRT to the tumour site. Involved-field radiation therapy (IFRT) was given with Co-60 photon beams. Total dose of 60-70 Gy was delivered with daily dose of 2 Gy per fraction per day, 5 days per week (within 6-7 weeks) to the tumour volume as defined by clinical examination and investigations.

Primary objective measured was response rate according to the RECIST system,[10] based on CT and MRI scans. Eligible patients were given two cycles of chemotherapy, including ifosfamide, mesna and doxorubicin according to the institutional practice in both groups. Group-A received RT alone, while Group-B, as the intervention arm, received concomitant chemoradiotherapy with TMZ. Secondary objectives measured was safety of concurrent RT-TMZ therapy according to the National Cancer Institute Common Toxicity Criteria version 3.0,[11] and determination of the number of patients becoming eligible for resection at the end of the treatment as well as the margin status of patients actually undergoing resection at the end of the treatment.

Data was analysed using SPSS 21. Quantitative variables, like age, were presented as mean ± standard deviation (SD). Qualitative variables, like gender, were presented as frequencies and percentages. Comparison between the two groups were done using independent sample t test. $P \leq 0.05$ was taken as significant.

Results

Of the 106 patients assessed, 64(60.3%) formed the final

Table-1: Frequency distribution of various Patients characteristics.

Variables	Group-A (n=32)	Group-B (n=32)	P Value
Gender of the patient			
Male	18(56.3%)	20(62.5%)	0.798
Female	14(43.8%)	12(37.5%)	
Age (years) (Mean±SD)	36.25±18.318	37.84±15.791	0.363
Co-morbid conditions			
No co-morbid condition	29 (90.6%)	28 (87.5%)	0.334
Diabetes mellitus	02 (6.3%)	02 (6.3%)	
Chronic Liver disease	01 (3.1%)	01 (3.1%)	
COPD		01 (3.1%)	
Histopathologic Grades			
Grade 1	06 (18.7%)	08(25.0%)	0.386
Grade 2	14 (43.7%)	10 (31.3%)	
Grade 3	12(37.6%)	14 (43.7%)	
TNM Staging			
Stage II	13(40.6%)	14 (43.7%)	0.853
Stage III	19(59.4%)	18 (56.3%)	
ECOG performance status			
ECOG PS 0	05(15.6%)	06(18.7%)	
ECOG PS 1	24(75.0%)	24(75.0%)	0.369
ECOG PS 2	03(9.4%)	02 (6.3%)	

SD: Standard deviation
COPD: Chronic obstructive pulmonary disease
TNM: Tumour, node and metastasis
ECOG: Eastern Cooperative Oncology Group
PS: Performance status.

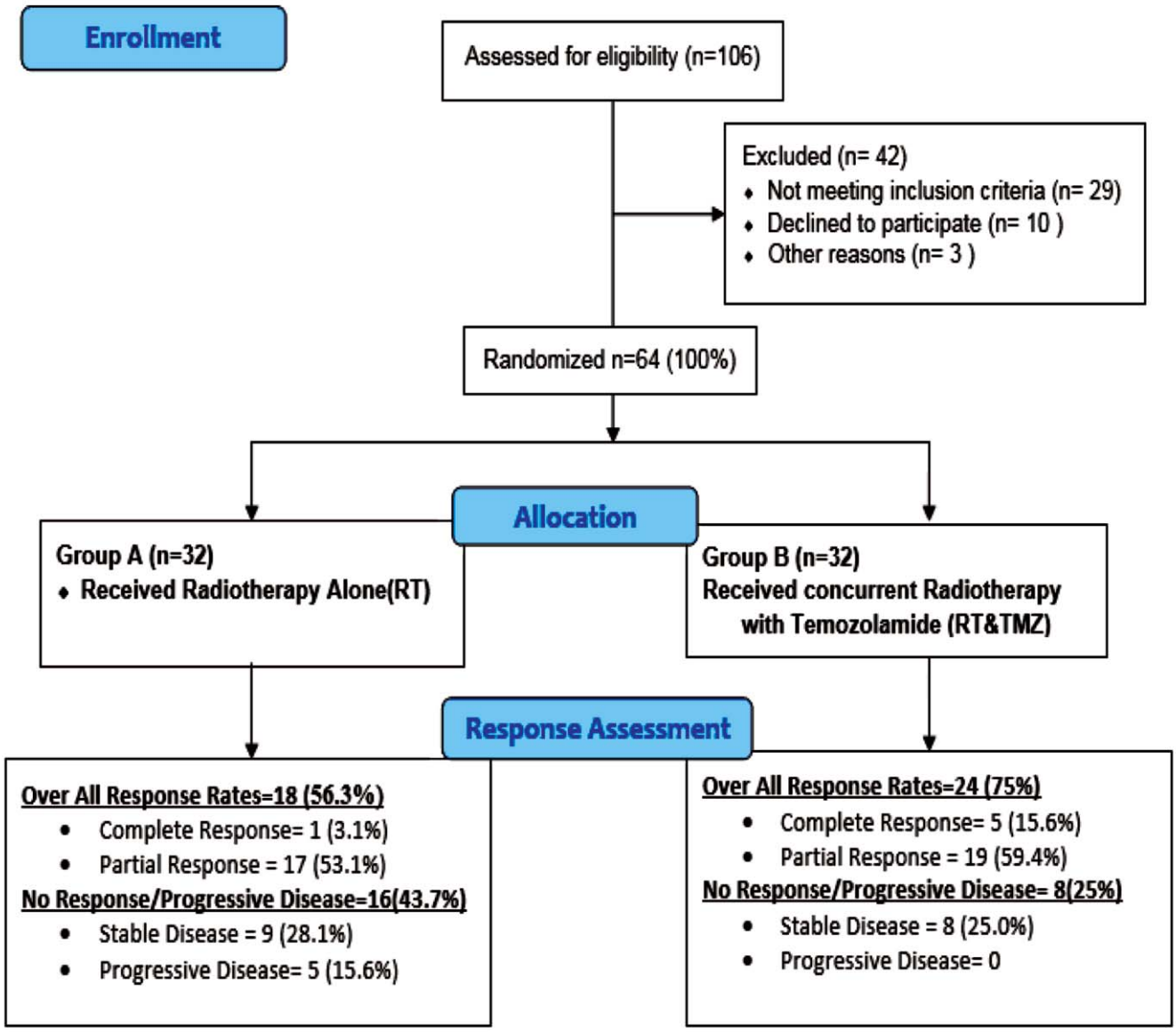

Figure: CONSORT Flow Diagram: A randomized comparison of radiotherapy alone with concurrent chemoradiotherapy plus temozolamide in locally advanced soft tissue sarcoma.[12]

Table-2: T-test of variables in two treatment groups.

Variables	Group-A (n=32)	Group-B (n=32)	P Value
Treatment Response			
Complete response	1 (3.1%)	5 (15.6%)	
Partial Response	17 (53.1%)	19 (59.4%)	0.12
Stable Disease	9 (28.1%)	08(25.0%)	
Progression	5(15.6%)	0 (0)	
Limb Sparing Surgery with Tumor Free Margins			
Yes	02 (6.3%)	03 (9.4%)	0.641
No	30 (93.7%)	29 (90.6%)	

*Group-A= Control (Radio therapy alone) and *Group-B= Temozolamide with Radio therapy.

study sample (Figure). Of them, 32(50%) patients were assigned to each of the two groups. The mean age of Group-A was 36.25±20.31 years (range: 18-76 years) and of Group-B 37.84±15.79 years (range: 19-70 years). There were 18(56.3%) males in Group-A and 20(62.5%) in Group-B (Table-1). In Group-A partial response was seen in 18(56.3%) patients, stable disease 11(34.4%) and progression 3(9.4%) patients. In Group-B partial response was seen in 21(65.6%) patients, stable disease 8(25%) and progression in 3(9.4%) patients. (p=0.12) (Table-2).

In terms of safety profile, neutropenia, mucositis, pain, rash

Table-3: Comparison of safety profile in Group A (RT) and Group B (RT & TMZ).

Toxicities	Group-A (n=32)	Group-B (n=32)	P Value
Neutropenia in Treatment Groups			
No Adverse Event	26 (81.3%)	22 (68.75%)	0.434
Grade-1&2	5 (15.6%)	7 (21.87%)	
Grade-3&4	1 (3.1%0	3 (9.37%)	
Mucositis in Treatment Groups			
No Adverse Event	14 (43.8%)	13 (40.6%)	0.68
Grade-1	12 (37.5%)	15 (46.9%)	
Grade-2	6 (18.8%)	4 (12.5%)	
Pain in Treatment Groups			
No Adverse Event	12 (37.5%)	16 (50%)	0.454
Grade-1&2	17 (53.1%)	12 (37.5%)	
Grade-3&4	3 (9.4%)	4 (12.5%)	
Rash in Treatment Groups			
No Adverse Event	29 (90.6%)	19 (59.4%)	0.013
Grade-1&2	3 (9.4%)	11 (34.4%)	
Grade-3&4	00 (0%)	2 (6.3%)	
Emesis in Treatment Groups			
No Adverse Event	23 (71.9%)	15 (46.9%)	
Grade-1&2	7 (21.9%)	12 (37.5%)	0.117
Grade-3&4	2 (6.3%)	5 (15.6%)	

RT: Radio therapy.
TMZ: Temozolamide.

and emesis were compared between the groups (Table-3).

Discussion

A growing number of studies are evaluating TMZ efficacy in combination with other anti-tumour agents or treatment modalities in those malignancies with extremely poor prognosis.[13] TMZ is an oral drug of 3-methyl-(triazen-1yl) imidazole-4-carboximide, the active metabolite of DTIC.[14] DTIC is an 'old' drug that is used in second-line or combination treatment for STS.[15] The introduction of TMZ combined with radiation in glioblastoma has substantially improved treatment outcome.[16]

A study[17] used TMZ for 5 days in a 28-day cycle and noted one partial remission, while 19 patients had progressive disease. Another study[18] achieved an overall objective response rate of 8% when administering TMZ twice daily on a 12-h schedule for 5 days of 200 mg/m^2, followed by 09 doses of 90mg/m^2 every 4 weeks. The best results were reported by a study[19] using a 6-week, continuous, oral schedule of 75-100mg/m^2 TMZ, which was also used in a successful glioblastoma trial.[20] In the STS arm of the study, the overall response rate was 15.5%. All these results show that the activity of TMZ is schedule-dependent, with the 6-week continuous dosing regimen being the most effective approach.[21] The partial response in our study was 21% with TMZ and RT.

In one study[22] on the toxicity and efficacy of preoperative intensity-modulated radiation therapy (IMRT) combined with TMZ to improve local tumour control in STS, no grade-4 toxicities occurred. Nausea and vomiting were the most frequent grade-3 toxicities. The most frequent toxicities of any grade were dermatological, gastrointestinal and haematological. Response was partial in 5, stable in 7, and progressive in 2 patients.[22] One study evaluated the activity and toxicity of TMZ given as an extended schedule in patients with advanced sarcoma. It noted 7 partial responses amongst 45 patients, for an overall response rate of 15.5% (95% confidence interval [CI]: 5-26%).[19] In the current study, in Group-A 5(15.6%) patients had grade-1 and 1(3.1%) had grade-2, while in Group-B 7(21.87%) patients had grade-1 and 3(9.37%) had grade-2 neutropenia.

TMZ is a cytotoxic alkylating agent that was developed as an oral and less toxic alternative to DTIC. Both exert their anti-tumour effects through the formation of (5-(3-N-methyltriazen-1-yl)-imidazole-4-carboxamide) (5-3-MTIC), the putative active chemical metabolite of DTIC.[19,23] TMZ has activity against malignant gliomas and metastatic melanoma.[24,25] Based on its similar mechanism of action to DTIC, TMZ has been evaluated in STS using a variety of dosing schedules.[17,18,26] TMZ has consistently achieved a 10% response rate across three phase-II studies, with some evidence of higher activity in patients with leiomyosarcoma.[17,19,27]

A study reported an overall response rate of 32% with a median duration of response being 11.4 months. Median time to progression and median overall survival were 2.8 and 15.4 months respectively.[28] The combination of TMZ and thalidomide has been tested in a phase II study in 23 patients with un-resectable or metastatic leiomyosarcoma. The combination induced one partial response lasting 23 months, and five stable cases which lasted >4 months. The study noted that TMZ was the active drug of the combination, while thalidomide was poorly tolerated and might have contributed to the toxicity of the regimen.[29]

In the current study, both treatment methods were effective for treating STS. Further studies are needed to prove the effective role of TMZ when added with RT. The limitation of our study was that we didn't obtain randomized controlled trial number, due to lack of awareness at the time of plan of this study.

Conclusion

There was no significant response to STS treatment with the addition of TMZ. However, the effect of treatment was encouraging in patients treated with RT-TMZ than RT alone. The TMZ-RT combination was found to be effective

in terms of partial response to treatment.

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Conflict of Interest: None.

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