RMAC study

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RMAC study: A randomized study for evaluation of metronomic adjuvant chemotherapy in recurrent head and neck cancers post salvage surgical resection in those who are ineligible for re-irradiation

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Abstract:	Background Adjuvant re-chemoradiation after salvage surgery improves disease-free survival in recurrent head and neck cancer. However, most patients are ineligible for re-irradiation and are kept on observation. We investigated the efficacy of metronomic adjuvant chemotherapy (MAC) in this group of patients compared to observation. Methods This was a randomized integrated phase ⅔ clinical trial. Adults with recurrent head and

	neck cancer, who had undergone salvage surgery, but were ineligible for adjuvant re-irradiation were randomized in a 1:1 ratio to either MAC arm or observation. MAC consisted of weekly oral methotrexate (at a dose of 15 mg per square meter of body surface area) and celecoxib (at a dose of 200 mg orally twice daily) for 6 months. The primary endpoint of phase 2 was disease-free survival (DFS) while that of phase 3 was overall survival (OS). For phase 2, to detect an improvement in the hazard ratio (HR) 0.67 with MAC, with a type 1 error of 10% (1-sided), type 2 error of 30%, 105 patients were required. While for phase 3, with a target HR of 0.77, with a type 1 error of 5%, type 2 error of 20%, 318 patients were required.Results At a median follow up of 30.2 months (95% confidence interval (CI), 25.3 to 35.1) the 1 year and 2 year DFS were 59.4% (95% CI, 44.8 to 71.4) and 38.9% (95% CI, 25.1 to 52.5) in MAC arm whereas the corresponding numbers were 62.3% (95% CI, 47.8 to 73.8) and 54.2%(95% CI, 39.8 to 66.5) in observation arm, respectively (hazard ratio for progression, 1.42; 95% CI, 0.84 to 2.4;P=0.2). In the MAC arm the 1 and 2 year OS was 78.7% (95% CI, 64.9 to 87.6) and 48% (95% CI, 34.1 to 62).The corresponding figures in the observation arm were 79.2% (95% CI, 65.7 to 87.9) and 65.5% (95% CI, 50.9 to 76.7) (hazard ratio for death, 1.7, 95% CI, 0.94 to 3.08; P=0.08). Conclusion The adjuvant 6-month metronomic schedule was ineffective in improving outcomes in recurrent- relapsed head and neck cancers post salvage surgery who are ineligible for re-radiation. Trial registration Clinical trial registry of India (CTRI)- CTRI/2016/04/006872 [Registered on 26/4/2016]

RMAC study: A randomized study for evaluation of metronomic adjuvant chemotherapy in recurrent head and neck cancers post salvage surgical resection in those who are ineligible for re-irradiation

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Abstract

Background

Adjuvant re-chemoradiation after salvage surgery improves disease-free survival in recurrent head and neck cancer. However, most patients are ineligible for re-irradiation and are kept on observation. We investigated the efficacy of metronomic adjuvant chemotherapy (MAC) in this group of patients compared to observation.

Methods

This was a randomized integrated phase ⅔ clinical trial. Adults with recurrent head and neck cancer, who had undergone salvage surgery, but were ineligible for adjuvant re-irradiation were randomized in a 1:1 ratio to either MAC arm or observation. MAC consisted of weekly oral methotrexate (at a dose of 15 mg per square meter of body surface area) and celecoxib (at a dose of 200 mg orally twice daily) for 6 months. The primary endpoint of phase 2 was disease-free survival (DFS) while that of phase 3 was overall survival (OS). For phase 2, to detect an improvement in the hazard ratio (HR) 0.67 with MAC, with a type 1 error of 10% (1-sided), type 2 error of 30%, 105 patients were required. While for phase 3, with a target HR of 0.77, with a type 1 error of 5%, type 2 error of 20%, 318 patients were required.

Results

At a median follow up of 30.2 months (95% confidence interval (CI), 25.3 to 35.1) the 1 year and 2 year DFS were 59.4% (95% CI, 44.8 to 71.4) and 38.9% (95% CI, 25.1 to 52.5) in MAC arm whereas the corresponding numbers were 62.3% (95% CI, 47.8 to 73.8) and 54.2%(95% CI, 39.8 to 66.5) in observation arm, respectively (hazard ratio for progression, 1.42; 95% CI, 0.84 to 2.4;P=0.2). In the MAC arm the 1 and 2 year OS was 78.7% (95% CI, 64.9 to 87.6) and 48% (95% CI, 34.1 to 62).The corresponding figures in the observation arm were 79.2% (95% CI, 65.7 to 87.9) and 65.5% (95% CI, 50.9 to 76.7) (hazard ratio for death, 1.7, 95% CI, 0.94 to 3.08; P=0.08).

Conclusion

The adjuvant 6-month metronomic schedule was ineffective in improving outcomes in recurrent-relapsed head and neck cancers post salvage surgery who are ineligible for re-radiation.

Trial registration

Clinical trial registry of India (CTRI)- CTRI/2016/04/006872 [Registered on 26/4/2016]

Keywords

Recurrent; Head and neck cancer; Adjuvant; Metronomic; Salvage surgery

Introduction

Salvage surgery remains the cornerstone of management of recurrent head and neck cancer[1,2]. However, in spite of salvage resection, subsequent local and distant failure rates occur in 60 to 80% of patients, within 2 years of surgery[3,4]. Adjuvant re-radiotherapy with concurrent chemotherapy leads to improved disease-free survival (DFS) from 20% to 62% at 2 years when compared to observation alone[4]. However, not all patients are eligible for re-radiotherapy, either due to early failure or due to the presence of sequelae of previous radiation therapy[5,6]. As a considerable proportion of patients (30 to 92%) fail within 24 months of initial radiation, patients who are eligible for re-radiation are uncommon(Patil et al. 2019; Noronha et al. 2017; Laskar et al. 2019; Liao et al. 2008). At present these ineligible patients are kept under observation and the 2-year DFS in these patients is likely below 20%[3,4].

Metronomic chemotherapy consisting of methotrexate and celecoxib has activity in head and neck cancer[10,11]. We conducted a randomized study comparing oral metronomic chemotherapy, comprising methotrexate and celecoxib, with intravenous cisplatin in advanced head and neck cancer patients treated with palliative intent. Oral metronomic chemotherapy led to a 33% improvement in progression-free survival (PFS) and overall survival (OS)[10]. In an another matched pair analysis from Tata Memorial Hospital (TMH) Mumbai, patients with locally advanced head and neck cancers who received perioperative neoadjuvant and adjuvant metronomic chemotherapy with methotrexate and celecoxib,, had a 2-year DFS of 95% as opposed to 70% for those patients who did not.[12]. We investigated whether the same metronomic adjuvant chemotherapy (MAC) could improve patient outcomes in completely resected recurrent head and neck cancer subjects who are ineligible for re-radiation.

Methods

Trial design and conduct

This was a randomised parallel-group, integrated phase II/III clinical trial conducted at a premier tertiary cancer centre in India. The study protocol was approved by the Institutional Ethics Committee (IEC). All patients provided written informed consent prior to accrual in the study. The study was conducted according to the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2004, Good Clinical Practice (GCP) guidelines, the Indian Council of Medical Research (ICMR) guidelines, the schedule Y and was in compliance with applicable laws and regulations of India. The investigator complied with the study protocol, except when a protocol deviation was required to eliminate immediate hazard to a subject.

Participants

The patients eligible for this study were adult (age>18 years) recurrent head and neck cancer, post salvage surgery, ineligible for re-radiation, ECOG PS 0-2 and adequate organ function. The ineligibility for re-irradiation was decided in a multidisciplinary clinic. The ineligibility for re-irradiation was considered when at least one of following criteria was present; a short disease-free interval (relapse within 18 months of last radiation) or presence of severe late morbidity from previous radiation (example osteoradionecrosis or grade 3 lymphedema according to Common Terminology Criteria for Adverse Events (CTCAE) version 4) or coverage of planning target volume (PTV) would deliver a biologically equivalent dose in excess of 66 Gy3 to 10 cm of the spinal cord or 83.66 Gy3 to brainstem or treatment volume would require coverage of the posterior neck (level 5). Patients with prolonged QT_C interval, uncontrolled comorbidities or infection and pregnant or lactating women were excluded. Subjects should have fulfilled all of the inclusion criteria and none of the exclusion criteria to be eligible for this study (Study protocol-Supplementary appendix).

Randomisation

Randomization was done as block randomization with 1:1 randomization in both arms. The randomisation request was telephonically conveyed by the study coordinator to independent personnel. The randomisation was performed by this personnel and was conveyed to the study

coordinator telephonically. Neither the principal investigator (PI) nor the study investigators had access to the randomisation sheets.

Interventions

There were 2 arms in the study, metronomic adjuvant chemotherapy arm (MAC) and observation arm. Subjects in the MAC arm received weekly oral methotrexate (at a dose of 15 mg per square meter of body-surface area) and celecoxib (at a dose of 200 mg orally twice daily). A total of 6 cycles were administered, with each cycle consisting of 28 days. During treatment, subjects were assessed at the start of each cycle for the first 4 cycles. If subjects tolerated these cycles well, then they were assessed after 2 months. After completion of treatment, patients were followed up r every 3 months upto 2 years. Subjects in the observation arm were assessed at monthly intervals for 4 months, then at 6 months and then every 3 months 2 years. Patients underwent a comprehensive head and neck examination and blood tests (complete blood count, renal function and liver function tests) at each visit. European Organization for the Research and Treatment of Cancer (EORTC) C30 and HN-35 Quality of Life (QOL) questionnaires were administered to both arms at baseline and at each visit.

Outcomes

Disease-free survival (DFS) was defined as the time from randomisation until the first day disease recurrence was documented, or until death in the absence of recurrence. OS was defined as the time from randomisation until the death of the patient. Adverse events were documented in accordance with CTCAE version 4.02.

Sample size

The study was an integrated Phase II/III design. For the phase 2, to detect an improvement in the hazard ratio (HR) 0.67 with MAC, with an type 1 error of 10% and type 2 error of 30%, 105 patients were required. Analysis for this part of the study was planned after completion of enrollment and minimum follow up of 24 months of the last patient. If the DFS improvement was met, then the study would have entered phase 3. For phase 3, with a target HR of 0.77, type 1 error of 5% and type 2 error of 20%, 318 patients were required.

Statistical methods

Statistical package for social sciences (SPSS) version 20 and RStudio version 3.1.2 was used for statistical analysis. Futility analysis at the end of phase 2 was performed and descriptive statistics was also performed. Continuous variables were described using median and its 95% confidence interval (CI) while nominal and ordinal variables were described in percentages. Nominal and ordinal data was compared using Fisher's exact test while continuous data was compared using Mood's median test. Median DFS and OS with its 95% Confidence interval (CI) were estimated using the Kaplan Meier method and compared using the log-rank test. Brookmeyer and Crowley method was used for the construction of the 95% CI. COX regression analysis was used for calculation of hazard ratio (HR) with Efron's method of tie handling, with observation arm being considered as reference. The proportional hazard assumption was tested prior to performing the COX regression analysis. A P-value of 0.1 was considered as significant. Data was censored for analysis on 20th March 2020.

Results

Baseline characteristics

In the period from 8th June 2016 to 12th July 2018, 105 patients were recruited; 52 in the MAC arm and 53 in the observation arm. Baseline characteristics at the time of randomisation were similar between both arms (Table 1). The majority of patients had a primary in oral cavity (n=53,50.5%), with relapsed or residual (n=89,84.5%) being the commonest indication for salvage surgery. The prior tumour (prior to recurrence for which the salvage surgery was performed) and its treatment details are provided in supplementary appendix Table 1. The details of salvage surgery and histopathological details are provided in Table 2. The reasons for ineligibility for radiation were interval of less than <18 months from last radiation (n=85,81%), grade 3 or above previous radiation soft tissue sequelae (n=25,23.8%), risk of excess dose to critical organs at risk (n=89,84.8%) and presence of posterior fossa node which couldn't be safely encompassed in radiation portal (n=1, 1.9%) {Supplementary appendix Table 2}.

Treatment compliance

In the metronomic arm, all patients started metronomic chemotherapy and the median time to start was 29 days (Interquartile range 21-35.75)(Figure 1, supplementary Table 3). Thirty six patients (69.2%) completed 6 cycles. The reason for noncompletion of 6 cycles were recurrence in 12 (23%), adverse events in 2 (3.9%) and patients choice in 2 (3.9%).The adverse events leading to stoppage were febrile neutropenia & non-neutropenic infection in 1 (1.9%) patient each. Dose reduction of methotrexate was required in 1 patient after cycle 1 in view of grade 3 mucositis with febrile neutropenia. Dose reduction of 20% (from 15 mg/m2 weekly to 12 mg/m2) was done in subsequent weekly doses. reduced. Dose delays were seen in 4 patients (7.7%). The reasons were mucositis and myelosuppression, dysphagia, non-neutropenic fever and logistics, in 1 patient (1.9%) each.

Adverse event rate

Acute adverse events were available in all patients (Table 3). The rate of any grade mucositis (25% versus 3.8%), odynophagia (25% versus 7.5%), dysphagia (32.7% versus 13.2%), hyponatremia (30.8% versus 7.5%), hypomagnesemia (9.6% versus 0%) and anemia (61.5%

versus 26.4%) were higher in the MAC arm. Late adverse events were captured in 36 patients in both arms and were defined as occurring 90 days after randomisation. In the MAC arm, out of 52 patients, 12 patients progressed prior to occurrence of late adverse events and data was unavailable in 4 patients. In the observation arm, out of 53 patients, 12 patients progressed prior to the occurrence of late adverse events and data was unavailable in 5 patients. Incidence of any grade dysphagia was seen in 21 (58.3%) versus 11(30.6%) in the MAC and observation arm, respectively (P=0.032)

Outcomes

Disease-free survival

At a median follow up of 30.2 months (95% CI, 25.3-35.1), there were 32 and 25 events for DFS in the MAC and observation arm, respectively. The median DFS was 15.8 months (95% CI, 9.67-24.3) versus not reached (95% CI, 9.33-NA) in the MAC and observation arm, respectively (P=0.19). The 1 year and 2-year DFS was 59.4% (95% CI, 44.8-71.4) and 38.9% (95% CI, 25.1-52.5) in MAC arm whereas the corresponding numbers were 62.3% (95% CI, 47.8-73.8) and 54.2% (95%CI 39.8-66.5) in observation arm, respectively (Figure 2). The hazard ratio with observation arm as reference was 1.42 (95% CI, 0.84-2.4, P=0.2).

In the MAC arm there were 32 events (61.5%). These were failures in 26 patients (50%), second primary in 2 patients (3.8%), death due to unknown cause in 3 patients (5.8%) and death due to chronic comorbidity in 1 (1.9%) patient. The pattern of failures was local failure in 10 (19.2%), nodal failure in 8 (15.4%), local & nodal failure in 4 (7.7%), distant failure in 4(7.7%), local & distant in 1 (1.9%) and failure at local, nodal & distant in 1(1.9%) patient.

In the observation arm there were 25 events (47.2%). These were failures in 20 patients (37.7%), second primary in 4 patients (7.5%) and death due to unknown cause in 1 (1.9%) patient. The pattern of failures was local failure in 14 (26.4%), nodal failure in 2 (3.8%), local & nodal failure in 5 (9.4%), distant failure in 1 (1.9%), nodal & distant in 1 (1.9%) and failure at local,nodal & distant in 1(1.9%) patient.

Overall survival

At the time of data censoring, there were 45 deaths, 27 in MAC and 18 in the observation arm. The median OS in the MAC arm was 24 months (95% CI, 18.2-NA) while it was not reached

(95% CI, NA to NA) in the observation arm (P=0.08) (Figure 3). In the MAC arm the 1 and 2 year OS was 78.7% (95% CI, 64.9 to 87.6) and 48% (95% CI 34.1 to 62) while in the observation arm, they were 79.2% (95% CI, 65.7 to 87.9) and 65.5% (95% CI, 50.9 to 76.7). The hazard ratio with observation arm as reference was 1.7 (95% CI, 0.94-3.08, P=0.08).

The cause of death in MAC arm was disease-related in 22 (42.3%), unknown causes in 4 (7.7%) and due to chronic comorbidity in 1 (1.9%) patient. In the observation arm, 17 (32.1%) deaths were disease related while 1 (1.9%) death was due to an unknown cause.

Discussion

This was the first randomised study on adjuvant metronomic therapy in recurrent head and neck cancer who have undergone salvage resection and are ineligible for re-radiation. The study proves that the metronomic schedule of weekly methotrexate (at a dose of 15 mg per square meter of body surface area) with twice daily oral celecoxib 200 mg for 6 months failed to improve disease-free survival over observation alone. As a matter of fact, there was a negative trend towards higher relapse and deaths in the MAC arm. Hence, administration of this schedule in clinical practice as adjuvant therapy in post salvage surgery setting cannot be recommended.

The above-mentioned schedule of metronomic chemotherapy has a proven advantage over intravenous chemotherapy schedules in palliative settings[10] where there was improvement in progression free survival and overall survival. This was achieved at a low rate of adverse events and with improvement in quality of life scores. [10,13] With these encouraging results, as has been the case in oncology drug development, the schedule was tried as an adjuvant in post salvage resection patients who are at high risk of failure. However, it was not successful and this highlights an important aspect that results in a palliative setting does not necessarily translate into benefit the adjuvant setting. Multiple examples of other such scenarios are available like the FOLFIRI regimen in colon cancer[14], tyrosine kinase inhibitors in drug sensitive EGFR mutated lung cancer[15] and antiangiogenic therapy in colon[16], lung[17], renal clear cell carcinoma[18] and breast cancer[19]. Hence, a formal testing of regimens which are successful in a palliative setting is necessary in an adjuvant setting prior to their routine recommendation.

There can be multiple clinical reasons for this failure. Patients selected were those which were ineligible for re-radiation with multiple patients having short disease-free intervals (>50% below 1 year). In the palliative setting two-drug, metronomic schedules are effective in patients with longer disease free intervals.[10] It had limited action in patients with failures below 6 months[20]. Triple metronomic schedule consisting of methotrexate, celecoxib and erlotinib has activity in these patients[11] and should be considered for further adjuvant studies in this setting of low disease free interval. The dose of methotrexate was 15 mg per square meter of body surface area. This dose was chosen as it is approximately 1/3rd of the maximum tolerable dose of weekly methotrexate schedules of 40 mg per m^2.[2, 10] However, we have shown that a dose of 9 mg per square meter of body surface area of methotrexate has more activity and has higher

anti-angiogenic potential[11] and is considered to be the optimal biological dose of methotrexate. Future studies should consider this dose of methotrexate for metronomic action. The 2 drug schedule was administered for 6 months. The failure rates in head and neck cancer are high till 18 months[7,8]. Thus, an appropriate schedule could be up to 18 months. Such long adjuvant schedules have shown activity in ovarian cancer with bevacizumab[21] and with hormone blockade in hormone-positive breast cancer.[22,23]

There may be added biological reasons for these results. The local milieu is important for action of metronomic chemotherapy[24,25].. A similar phenomenon is seen with checkpoint inhibitors, where studies with Nivolumab in glioma as adjuvant therapy have failed.[26,27] However, when administered as neoadjuvant therapy it has shown promise[28]. It seems that the exposure to the local milieu is proposed as the reason for the same.[29] One of the mechanisms of metronomic action is via immunomodulation and hence the absence of local milieu will hamper this action.[24,25] This is further strengthened by the fact that in a phase 2 randomised study reported by Nair et al, administration of metronomic schedules prior to surgery in resectable oral cancer was associated improvement in outcomes[30]. A large phase 3 study from Tata Memorial Center addressing this issue is ongoing and has both neoadjuvant and adjuvant components (**CTRI**/2015/01/005405). Also, the phenomenon of angiogenic switch occurs in hours following surgery.[31–34] The metronomic schedules in the current study started weeks after surgery. It is possible that the efficacy would have been different if these schedules would have been given preoperatively and continued in the immediate postoperative period.

The study has its strengths and limitations. The strength of this study was that it was a randomised study which was adequately powered, studied an unaddressed issue in literature and had mature results with a median follow up of greater than 2 years. It was a single centre study, predominantly done in oral cancer settings and the surgery was performed by the expert head and neck surgeons, with an envious low rate of margin positivity. The margin positive rate in T3-T4 head and neck cancers in the Western world is in the range of to 32.4%[35,36] while those in our study were only 4.76% (n=5) patients.

Conclusion

Adjuvant 6-month metronomic schedule of methotrexate 15 mg per square meter of body surface area weekly with celecoxib 200 mg orally twice daily is ineffective in improving outcomes in recurrent- relapsed head and neck cancers post salvage surgery who are ineligible for re-radiation.

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Table

Table 1-Baseline Characteristics

Variable	Metronomic adjuvant chemotherapy arm (n=52)	Observation arm (n=53)	P-value
Age in years Median (interquartile range) Elderly-no(%)	 53(44.25-59) 5(9.6)	 53 (43.5-60) 7(13.2)	 0.761
Gender-no(%) Male Female	 47(90.4) 5(9.6)	 44(83) 9(17)	0.39
ECOG PS-no(%) 0 1	 2(3.8) 50(96.2)	 1(1.9) 52(98.1)	0.618
Habits-no(%)* Cigarette Beedi Smokeless tobacco Alcohol	 6(11.5) 16(30.8) 31(59.6) 6(11.5)	 7(13.2) 14(26.4) 38(71.7) 7(13.2)	 1 0.67 0.221 1
Comorbidities-no(%)* Hypertension Type 2 Diabetes mellitus COPD Ischemic heart disease	 12(23.1) 5(9.6) - -	 7(13.2) 10(18.9) 3(5.7) 1(1.9)	 0.214 0.265 0.243 1
Site of malignancy-no(%) Oral cavity Oropharynx Hypopharynx Larynx	 26(50) 16(30.8) 6(11.5) 4(7.7)	 27(50.9) 10(18.9) 6(11.3) 10(18.9)	0.277
Type of recurrence Relapse or residual Second Primary	 46(88.5) 6(11.5)	 43(81.1) 10(18.9)	0.416
Site of recurrence Local Nodal Local and nodal	 26(50) 17(32.7) 9(17.3)	 34(64.2) 12(22.6) 7(13.2)	0.366

Table 1- Baseline characteristics. ECOG PS- Eastern Cooperative Oncology Group Performance Status. COPD-Chronic obstructive pulmonary disease. *- patient may be represented under more than one subheading. Elderly is defined as 65 years or above.

Table 2- Salvage surgery and histopathological details

Variable	Metronomic adjuvant chemotherapy arm (n=52)	Observation arm (n=53)	P-value
Surgery type-no(%) Open Robotic	 50(96.2) 2(3.8)	 51(96.2) 2(3.8)	1.0
Margin status-no(%) Negative Close Positive	 42(80.8) 9(17.3) 1(1.9)	 44(83) 5(9.4) 4(7.5)	0.25
Number of lymph nodes dissected Median (Interquartile range)	 17.5(10.25-26.5)	 17(6.5-25.5)	0.773
Pathological T grouping-no(%) T0 T1 T2 T3 T4a T4b	 17(32.7) 4(7.7) 9(17.3) 4(7.7) 18(34.6) -	 12(22.6) 9(17) 5(9.4) 8(15.1) 18(34) 1(1.9)	0.277
Pathological N grouping-no(%) N0 N1 N2a N2b N2c N3	 22(42.3) 18(34.6) 2(3.8) 7(13.5) 2(3.8) 1(1.9)	 30(56.6) 12(22.6) 3(5.7) 7(13.2) 1(1.9) -	0.581
Stage grouping-no(%) I II III IVA IVB	 1(1.9) 7(13.5) 17(32.7) 26(50) 1(1.9)	 6(11.3) 2(3.8) 14(26.4) 29(54.7) 2(3.8)	0.123
Perinodal extension-no(%) Yes No	 21(40.4) 31(59.6)	 18(34) 35(66)	0.548
Adverse events-no(%) Poor differentiation Lymphovascular emboli Perineural invasion Depth of invasion > 1cm	 21(40.4) 5(9.6) 20(38.5) 11(21.2)	 24(45.3) 6(11.3) 18(34) 8(15.1)	 0.805 1 0.687 0.457

Table 2- Salvage surgery and histopathological details. *-All stagings are in accordance with the 7th AJCC-UICC edition of TNM staging. UICC- Union for International Cancer Control AJCC-American Joint Committee on Cancer.

Table 3-Adverse events

Acute adverse events	Metronomic adjuvant chemotherapy arm (n=52)		Observation arm (n=53)		P-value	
	Any grade	Grade 3 or above	Any grade	Grade 3 or above	Any grade	Grade 3 or above
Mucositis	13(25)	1(1.9)	2(3.8)	-	0.002	0.495
Odynophagia	13(25)	5(9.6)	4(7.5)	1(1.9)	0.018	0.113
Dysphagia	17(32.7)	7(13.5)	7(13.2)	2(3.8)	0.021	0.093
Weight Loss	7(13.5)	-	3(5.7)	-	0.201	-
Hyponatremia	16(30.8)	3(5.8)	4(7.5)	-	0.003	0.118
Hypokalemia	1(1.9)	-	-	-	0.495	-
Hypomagnesemia	5(9.6)	-	-	-	0.027	-
SGOT rise	2(3.8)	-	-	-	0.243	-
SGPT rise	4(7.7)	-	-	-	0.057	-
Anemia	32(61.5)	1(1.9)	14(26.4)	-	0.000	0.495
Neutropenia	2(3.8)	2(3.8)	2(3.8)	-	1	0.243
Thrombocytopenia	2(3.8)	2(3.8)	-	-	0.243	0.243
Late adverse events	Metronomic adjuvant chemotherapy arm (n=36)		Observation arm (n=36)		P-value	
	Any grade	Grade 3 or above	Any grade	Grade 3 or above	Any grade	Grade 3 or above
Xerostomia	26(72.2)	-	26(72.2)	-	1	-
Hyperpigmentation	23(63.9)	-	23(63.9)	-	1	-
Skin thickening	25(69.4)	12(33.3)	30(83.3)	18(50)	0.267	0.232

Lymphedema	25(69.4)	12(33.3)	29(80.6)	17(47.2)	0.415	0.337
Dysphagia	21(58.3)	4(11.1)	11(30.6)	5(13.9)	0.032	1
Dysguesia	17(47.2)	-	18(50)	-	1	-
Hypothyroidism	16(44.4)	-	17(47.2)	-	1	-
Creatinine rise	1(2.8)	-	1(2.8)	-	1	-

Table 3- Table depicting acute and late adverse events. Late adverse events were captured in 36 patients in both arms and were defined as occurring 90 days after randomisation. In the metronomic arm out of 52 patients, 12 patients progressed prior to occurrence of late adverse events and data was unavailable in 4 patients. In the observation arm out of 53 patients, 12 patients progressed prior to occurrence of late adverse events and data was unavailable in 5 patients. SGOT-Serum glutamic oxaloacetic transaminase. SGPT-Serum glutamic pyruvic transaminase.

Figures

Research in context

Evidence before this study

A PubMed search was done for studies published till 2014 with following items, " ((Salvage surgery) AND (Head and neck cancer)) AND (Adjuvant)". We identified 391 studies. The treatment paradigm of recurrent head and neck cancer was focussed primarily on systemic therapy, as it is applicable in over 90% of the patients. In contrast, salvage surgery, which offers sustained control, is an option in less than 10% of patients. What adjuvant therapy to give after salvage surgery was dealt only in a single randomised study. In this randomised study it was proven that patients undergoing salvage surgery need re-chemoradiation. But this treatment option is applicable only for a limited subgroup of patients. As often, majority of recurrences upto 90% occur within 2 years of the last radiation which preclude them from undergoing re-radiation. Such patients are currently kept under follow-up after salvage surgery. However, their outcomes are unsatisfactory. Neither any randomised or prospective single arm interventional studies had been done in this population of patients who undergo salvage surgery for recurrent/residual head and neck cancer and are ineligible for re-radiation. Hence we contemplated the current study.

Added value of this study

In this study conducted in patients undergoing salvage surgery in head and neck cancer who were ineligible for re-radiation, addition of metronomic oral methotrexate and celecoxib failed to improve the disease free survival and overall survival. The study confirmed the modest 2 year disease free survival 54.2% in the observation arm which can be used in future as a baseline for further studies.

Implications of all available evidence

Adjuvant metronomic therapy of weekly methotrexate and celecoxib does not improve outcomes when administered post salvage surgery in patients who are ineligible for radiation. The outcomes in this cohort are modest and further studies are required to improve the results.

Protocol Title: A randomized study for evaluation of metronomic adjuvant chemotherapy in recurrent head and neck cancers post R0 salvage surgical resection who are ineligible for re-irradiation.

(Short title**:** Metronomic adjuvant chemotherapy**)**

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- **Document type:** Clinical Research Protocol
- **Development Phase: II/III**

1) Introduction & Background :

Locally advanced head and neck cancer patients are usually treated with a multimodality approach. This multimodality approach for patients treated with curative intent is either surgery followed by radiation with or without chemotherapy, or radical chemo-radiation.(1-2) In spite of utilization of these approaches, rates of disease recurrence are high, with the majority of patients experiencing disease recurrence within 2 years (50-60 %).(3) Eighty percentage of disease recurrences are loco-regional.(4-5)

If detected early, a proportion 13-24 % of patients with loco-regional disease recurrence in the oral cavity, oropharynx, laryngeal sites or regional lymph nodes are able to undergo salvage resection of disease. However, in spite of secondary surgical (salvage) resection, subsequent local and distant failure rates are 60-80% within 2 years of surgery.(6-8)

Adjuvant radiotherapy following salvage resection of recurrent head and neck cancer is considered a standard treatment. In a randomized trial by Janot et al, patients post R0 salvage resection receiving reradiation had a disease-free survival (DFS) of 62% at 2 years, while those in the observation arm had 20% DFS at 2 years.(7) However, not all patients are eligible for reradiation as majority of patients (78%) fail within 2 years of initial treatment., where risk of substantial toxicity precludes further treatment. (9)

Metronomic chemotherapy in the palliative setting in oral cavity cancer has been associated with a response rate of 5.6% and with a clinical benefit rate of 66.7% (10). The combination of oral methotrexate and capsule celecoxib was well tolerated in a single arm phase II study of 30 patients; the reported rates of grade 3 – 4 toxities were; 3% grade 3 thrombocytopenia, 3% grade 3 anemia and 3% grade 4 mucositis. The median duration of treatment was 5 months. (10) In a another published matched pair analysis from Tata Memorial hospital, patients with locally advanced head and neck cancers who received neoadjuvant metronomic chemotherapy with methotrexate and celecoxib followed by adjuvant metronomic chemotherapy post completion of primary treatment for a total of 18 months had a 2-year DFS of 95% as opposed to 70% for those patients who did not receive adjuvant metronomic chemotherapy. These patients received 2-4 weeks of neo-adjuvant metronomic and 18 months of adjuvant metronomic chemotherapy. This also suggest that it is safe to administer this combination chemotherapy orally. (11) We also conducted a randomized study in palliative setting where oral metronomic chemotherapy with methotrexate with celecoxib was compared with IV chemotherapy. This study met its primary endpoint. There was more than 33% improvement in progression free survival with encouraging safety profile. . (12)

The combination of methotrexate and celecoxib has been demonstrated to be tolerable in patients with recurrent head and neck cancers. The purpose of this study is to determine whether metronomic chemotherapy has sufficient activity to improve patient outcome in the randomized study in completely resected recurrent head and neck cancer. If this trial meets its primary endpoint than we will plan a study with overall survival as a primary endpoint based on this study.

2) Aim

To determine whether metronomic chemotherapy leads to improved outcomes, in patients with recurrent head and neck cancers post R0 salvage surgical resection who are ineligible for re-irradiation.

3) Objectives:

Primary Objective:

To determine the activity of metronomic chemotherapy in patients with recurrent head and neck cancers post R0 salvage surgical resection who are ineligible for re irradiation .The primary endpoint would be overall survival.

Secondary Objectives (endpoints):

To determine the safety of metronomic chemotherapy (rates of adverse events)estimates of quality of life (scores from patient completed questionnaires)

- Disease free survival

Tertiary Objectives:

1. To investigate circulating biomarkers as prognostic and/or predictive markers for study endpoints (relating to survival, response and safety): including but not limited to circulating endothelial cells & endothelial progenitor cells
2. To investigate the potential prognostic and/or predictive value for study endpoints of tissue biomarkers including tumour VEGF level & microvessel density

Will be submitting a separate protocol for the biomarkers but will take consent from patients in the present protocol.

Patients blood will be collected after randomization and after 2-3 months. This will be stored in tumor tissue repository.

4) Hypothesis :

Metronomic chemotherapy will improve the outcome of the patients in this setting who are high risk for disease recurrence. .

5) Trial Design:

Randomized controlled study

6) Population & setting:

The proposed study will be conducted in the department of Medical Oncology, Tata Memorial

Hospital (TMH) in Mumbai, India. Patients attending the Out patient wing of the department of Medical Oncology (TMH) will be selected for the present study, subject to fulfillment of the following selection criteria.

7.1 Selection Criteria:

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial.

7.2 Target population

Adult population with recurrent head and neck cancer post R0 salvage resection who are ineligible for re-irradiation.

7.3 Inclusion criteria

1. Patients with recurrenthead and neck cancers with primary in oral cavity, oropharynx, larynx or hypopharynx who have undergone complete salvage resection (R0 resection)
2. Ineligibile for re-irradiation in target region after assesement in joint clinic.
3. Age ≥18 years
4. ECOG performance status PS 0-2
5. Adequate bone marrow function (Haemoglobin > 8 0g/L, platelets > 100 x 10^9/L, ANC > 1.5 x 10^9/L)
6. Adequate liver function (ALT/AST < 1.5 x ULN, serum bilirubin < 2mg/dl)
7. Adequate renal function (creatinine clearance > 50 ml/min)
8. Adequate cardiac function (LVEF >40%)
9. Study treatment both planned and able to start within 28 days of enrollment
10. Willing and able to comply with all study requirements, including treatment (able to swallow tablets), able to be followed up at regular intervals and/or nature of required assessments (e.g. able to have IV contrast if this is required for tumour assessments)
11. Signed, written informed consent for main study and tissue banking.

7.4 Exclusion criteria

1. QTc prolongation (QTc B prolonged more than 450 millisecond)
2. Any significant active infection, including chronic active hepatitis B, hepatitis C, or HIV. for these is not mandatory unless clinically indicated. Participants with known Hepatitis B/C infection will be allowed to participate providing evidence of viral suppression has been documented and the patient remains on appropriate anti-viral therapy.

3. Concurrent illness, including severe infection that may jeopardize the ability of the patient to undergo the procedures outlined in this protocol with reasonable safety; Serious medical (e.g. Diabetes Mellitus, Hypertension, COPD ,active Tuberculosis or psychiatric conditions that might limit the ability of the patient to comply with the protocol.
4. Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse.
5. Pregnancy, lactation, or inadequate contraception. Women must be post menopausal, infertile, or use a reliable means of contraception. Women of childbearing potential must have a negative pregnancy test done within 7 days prior to registration. Men must have been surgically sterilised or use a (double if required) barrier method of contraception.

7.5 Screening

Entry to this study is conditional on confirmation of R0 resection status of the salvage surgical resection and ineligibility to undergo re irradiation. The ineligiblity for re irradiation would be decided in a multidisciplinary clinic. The ineligibility for re irradiation would be recorded under the following headings

1. Short interval relapse (within 18 months)
2. Severe late morbidity from radiation in terms of osteoradionecrosis, Grade 3 lymphedema according to CTCAE version 4
3. The coverage of PTV would deliver a biologically equivalent dose in excess of 66 Gy3 to 10 cm of spinal cord or 83.66 Gy3 to brainstem
4. Treatment volume requiring coverage of the posterior neck (level 5)
5. Any other reason

7.6 Registration

Subjects must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial/study. There will be no exceptions made to these eligibility requirements at the time of registration.

Subjects must be registered before starting study treatment. Treatment should be planned to start within 15 days after registration. Registration should be done according to the instructions in the Study Manual only after all screening assessments have been performed and the responsible investigator has both verified the subject's eligibility, and signed the completed registration form.

Once the registration process has been completed as per the instructions in the Study Manual, the subject will be assigned a subjectEORTC

study number and written confirmation of registration will be provided to the site. Individuals only be registered once in this trial.

8) Randomization:

Randomization will be done as block randomization with 1:1 randomization in both arms.

Arm – A) – Patients will receive chemotherapy with methotrexate and celecoxib

Arm – B) – Patients will be kept under observation

9) Treatment Plan

9.1 Administration of study treatments

Metronomic chemotherapy is the study intervention in this trial. The metronomic chemotherapy consitutes of methotrexate and celecoxib.

Oral methotrexate tablet 15mg/m2 will be administered weekly i.e on D1,D8, D15 & D22 of every 28 day cycle. Capsule celecoxib will be self administered twice daily in a dose of 200 mg BD continuously from D1-D28. The cycle duration will be of 28 days or monthly. The combination will be continued to a maximum of 18 cycles; unless prohibitive toxicity or disease progression occurs prior.

Cost of the treatment will be taken care by the study budget.

9.2 Routine and precautions during administration

Methotrexate is available as a 2.5 mg tablet. The recommended dose should be rounded to the nearest multiple of 2.5 mg. All tablets should be taken with at least half a glass of water one hour prior to or two hours post food. Capsule celecoxib should be taken twice daily 12 hours apart one hour post meal.

9.3 Dose modifications

Instructions for treatment delays and dose modifications for adverse events are specified below. Adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.02. In general, treatment should be withheld during adverse events of severity G3-4, and not restarted until the adverse event has resolved to G0-1, at the investigator's discretion. Day 1 treatment may be delayed for a maximum of 14 days. If the adverse event has not resolved to G0-1 after delaying day 1 treatment for 14 days, then study treatment should be discontinued. Treatment should not be delayed or modified for alopecia of any grade.

Specified dose reductions apply to all subsequent doses of study drug. If a patient experiences several adverse events with differing recommendations, then the modification that results in the longest delay and lowest dose should be used. Dose escalations or dose re-escalations after reductions for adverse events are prohibited.

9.4 Dose modifications for haematological adverse events

PARAMETER	TIMING	RESULT OR PROBLEM	CTCAE GRADE	ACTION WITH STUDY TREATMENT **(Methotrexate unless otherwise specified)**
Neutrophils ($x10^9$/L)	Previous cycle	febrile neutropaenia, or infection with neutropaenia	G4	Delay D1 until resolved AND reduce dose of methotrexate by 20%
	D1	1.0-1.5	G2	Delay D1 until >1.5 AND If delay > 7 d but l <15d, reduce doses by 20% level. If delay □15d, discontinue.
		<1.0	G3-4	Delay D1 until >1.5 AND reduce doses by 20% level.
Platelets ($x10^9$/L)	Previous cycle	<25 or bleeding	G4	Delay D1 until resolved AND reduce doses by 20%
	D1	<100	G1-4	Delay D1 until >99 AND If delay > 7 d but l <15d, reduce doses by 20% level. If delay □15d, discontinue.
Haemoglobin (g/L)	First occasion	<80	G2	Transfuse to Hb >80 AND treat as scheduled.
	Second occasion	<80	G2	Transfuse to Hb >80, treat as scheduled, AND reduce doses by 20%

Day 1 treatment may be delayed for a maximum of 14 days. If the adverse event has not resolved to G0-1 after delaying day 1 treatment for 14 days, then chemotherapy should be discontinued.

**- No dose reduction in celecoxib recommended. However, if chemotherapy is discontinued then celecoxib should also be discontinued.

Table 1: Dose modification for hematological toxicity

9.5 Dose modifications for other adverse events

SYSTEM	CTC AE		OTHER DETAILS	ACTIONS WITH STUDY DRUG(S)	OTHER ACTIONS
	Term	Grade			
Hepatic	Bilirubin	G3-4	>3.0 ULN	Discontinue methotrexate	
	AST/ALT	G3-4	>5.0 x ULN AND □ 2 x baseline	Discontinue methotrexate	
Renal	Creatinine	G2-4	>1.5 x baseline AND > 1.5 x ULN	Withhold both methotrexate & celecoxib until <1.5 x baseline AND <1.5 ULN., then restart at 20% lower dose	
Infection	Infection	G2-4		Delay until G0-1 Restart when G0-1 Reduce doses by 20% of methotrexate	
GI	Nausea	G3-4		Delay until G0-1	
	Vomiting	G3-4		Restart when G0-1	
	Diarrhoea	G3-4		Reduce doses 20% of methotrexate	

	Oral mucositis	G3-4			
Cardio-vascular	Myocardial infarction	G3-4		Discontinue both methotrexate & celecoxib	
Vascular	Thombo-embolic event	G3-4	Venous (DVT, PTE)	Delay both methotrexate & celecoxib until adequately treated Restart at physician discretion	Anticoagulate with heparin, not warfarin, whilst on study drug
		G3-4	Arterial	Discontinue both methotrexate and celecoxib	
Skin	Various	G3-4		Delay methotrexate and celecoxib until G0-1 Restart when G0-1 Reduce subsequent doses l20%	
Day 1 treatment may be delayed for a maximum of 14 days. If the adverse event has not resolved to G0-1 after delaying day 1 treatment for 14 days, then chemotherapy should be discontinued.					

Table 2: Dose modification for non hematological toxicity

Start of a new cycle

Re-treatment on day 1 will require: haemoglobin > 8mg/dl, ANC count > 1500/mm3, platelet count > 1lakh/mm3, creatinine clearance rate >50 ml min, and resolution of all nonhaematological toxicities (except alopecia and fatigue) to baseline or less than grade 1.

If methotrexate is delayed or withheld and if the cause of the delay doesnt require a interruption in celecoxib then it will be continued. Subsequently methotrexate can be given on the next weekly scheduled day. The scheduled methotrexate which was omitted remains omitted. The cycle would be considered continued if celecoxib is continued. If both are delayed and the delay is less than 15 days then from the day of restart the remaining cycle would be completed. Apart from guidelines above investigator will take decision regarding dose modifications based on patient's safety.

9.6 Concomitant Medications/Treatments

9.6.1 Recommended

The following medications and treatments are recommended in this study:

- Antiemetics if required by the patient. The antiemetics recommended are 5HT3 antagonist with or without Prokinetics
- No other medications or treatments are specifically recommended in this study.

9.6.2 Permitted

The following medications and treatments are permitted in this study:

- Symptomatic medications like proton pump inhibitors, H2 blockers, antacids, anti-diarroheal agents and stool softeners

9.6.3 Use with caution

The following medications are best avoided whilst subjects are on study drug, and must be used with caution:

- GMCSF, erythropoetic agents and other haematopoetic agents should not be used to avoid dose reductions
- Include drugs whose metabolism may be affected by study drug eg allopurinol.
- NSAIDS for analgesia
- Aspirin up to a dose of 100mg
- Low molecular weight heparin

9.7 Compliance

Subject medication compliance will be determined at each clinic visit by interview of patient & relative and the patient will be counselled appropriately if significant non-compliance is determined.

9.8 Unblinding

This is not a blinded study. Unblinding is not applicable.

9.9 Treatment discontinuation

Study treatment will be permanently discontinued for any of the following reasons:

- Progressive disease (PD) is documented by the investigator.
- Unacceptable toxicity as determined by the patient or site investigator or as defined in Table 1 & 2
- Delay of treatment for 14 days due to treatment-related adverse events. For delays >14 days due to due to reasons other than treatment-related adverse events the treatment would be continued. The treatment would be discontinued.
- The investigator determines that continuation of treatment is not in the patient's best interest.
- Occurrence of an exclusion criterion affecting patient safety, e.g. pregnancy or psychiatric

illness.

- Required use of a concomitant treatment that is not permitted, as defined in section of prohibited medications.
- Failure to comply with the protocol, e.g. repeatedly failing to attend scheduled assessments. If a patient has failed to attend scheduled assessments in the study, the Investigator must determine the reasons and document the circumstances as completely and accurately as possible in the medical records and CRF.
- The patient declines further study treatment, or withdraws their consent to participate in the study.

The reasons for discontinuing treatment will be documented in the subject's medical record.

Follow up of subjects who stop study treatment should continue according to this protocol

9.10 Subsequent treatment

Treatment after discontinuation of study treatment is at the discretion of the patient's clinician.

10) Outcomes and endpoints

9.1 Outcome (Primary endpoint)

The primary outcome is to determine the activity of metronomic chemotherapy.

Primary endpoint is disease free survival .

9.2 Outcome (Secondary endpoint)

9.2.1 Adverse Events (worst grade according to NCI CTCAE v4.02)

The NCI Common Terminology Criteria for Adverse Events version 4 (NCI CTCAE v4.0) will be used to classify and grade the intensity of adverse events after each treatment cycle. CTCAE will be used to collect all events regardless of attribution, in order to ensure objective reporting, and in order to report trial data according to accepted international guidelines. The worst toxicity would be recorded. The results would be computed in a tabular form in which the proportion of people having highest grade of toxicity would be charted.

9.2.2 Quality of life analysis (EORTC QLQ-C 30 and EORTC QLQ -H&N 35)

EORTC OLQ-C 30 (English, Marathi, Hindi & bengali version) would be used to collect general well being of these patients. EORTC QLQ- H&N 35 would be used to capture head and neck cancer related outcomes. This will be collected before randomization and on subsequent follow up.

9.2.3 Tissue biomarkers

The postoperative tumor specimen, baseline blood with EDTA and serum in heparin would be collected and deposited in tumor tissue laboratory of Tata Memorial Center or ACTREC. These samples would be analysed later post completion of trial for tissue VEGF, Microvessel density, Circulating endothelial cells and circulating endothelial progenitor cells. In addition any other

potential prognostic and or predictive tumor marker would be tested.

9.3 Schedule of assessments

	Screening	Baseline	On treatment30 day safety	On follow up	End of study
Time period	Within 28 days of registration	Within 7 days of registration	On D1 of treatment cycle each (or within 3 days prior) cycle	On each schedule follow up visit	At completion of 24 months of follow up
Informed consent	X				
Clinic§ assessment,	X		X*	X	X	X
Haematology	X		X*	X	X	X
Biochemistry	X		X*	X	X	X
Urine pregnancy test	X		X*			
2 D ECHO & ECG	X©					
Concomitant medications	X		X*		X	X
Adverse Events			X	X	X	X
Baseline blood for biomarkers		X.				
Patient status &	X		X*	X	X	X

ECOG PS						
Quality of life assessments		X	X*	X	X	X

§- Clinical assesment would include history and physical examination. .

©- A 2 D ECHO or ECG within last 6 month would be considered adequate.

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Blood samples (5 ml in EDTA bulb & 5 ml in plain bulb to be depoisted in tumor tissue repository)

*- if investigations done during screening and run are within last 14 days of baseline then these investigations need not be repeated.

9.4 Assessment phase definitions, schedule of visits and special circumstances

9.4.1Screening

All screening procedures must be performed within 28 days prior to registration, unless otherwise specified.

9.4.2 Run-in

Additional procedures must be performed over the next 7 run-in to confirm patient eligibility.

9.4.4 on treatment

The schedule of visits during treatment will be on D1 of each cycle. C2 D1, C3 D1 , C4 D1 , C5D1 , C6D1 & C6 D29. Assessments during treatment may be performed within 3 days prior to the specified timepoint, unless otherwise specified. If patients tolerates initial treatment for 4 months has been well than the patients will be followed every 2 – 3 months.

9.4.5 On treatment with delay in chemotherapy

In case of chemotherapy wouldnt be delivered due to a adverse event or in case of a in appropriate results of blood investigations. delay the chemotherapy until recovery.

9.4.6 30 day safety assessment

A safety assessment would be performed to include any adverse events occurring within 30 days after the last dose of study treatment.

9.4.7 Follow-up after treatment

Subjects who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol until disease recurrence or completion of 2 years. The

follow up schedule after completion of treatment is 9 months,12 months, 16 months, 20 months and 24 months.

If a patient wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via phone contact

9.4.8 After study is closed

When the last patient is evaluable for 2 year assessment which is expected to be 48 months after the first patient is recruited.

We will be submit phase II part of the study result to IRB before phase III part of study is started.

10 Safety reporting

10.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

Adverse events include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses, including the worsening (severity, frequency) of pre-existing illnesses
- Injury or accidents.
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test).

Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device.

AEs are not required to be reported unless they meet SAE criteria.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the subject is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,

- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

(i) The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

(ii) Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

Statistical analysis

11.1 Sample Size

It is an integrated Phase II/III design. With DFS(Disease free survival) of 6 months in standard arm and hazard ratio of 1.5, 70% power and alpha of 0.1 we will require 105 patients for the phase II study. Analysis for this part of the study will be done after enrollment of the patients and minimum follow up of 6 months of the last patient enrolled. Subsequently with median OS (overall survival) for 16 months in standard arm and hazard ratio of 1.3, power of 80% and alpha of 0.05 we will require 318 patients for the Phase III part of the study. .

11.2 Statistical Analysis

OS will be defined as time from first dose of metronomic chemotherapy until the death of the patient. OS curve will be estimated and plotted using Kaplan-Meier method and compared by log rank test.

DFS will be defined as the time from first dose of metronomic chemotherapy until the first day disease recurrence is documented, or until death in the absence of recurrence. Patients who do not recur will be censored at the date of last disease assessment. If no post-treatment disease assessments were obtained for a patient, DFS will be censored at Day 1. Patients who receive other anticancer therapy prior to documented disease recurrence will be censored at the date of last disease assessment. A DFS curve will be estimated and plotted using the Kaplan-Meier method. DFS will be compared by log rank test.

Biomarkers

Descriptive analysis would be done. The median value of the biomarker would be selected. The whole of sample would be divided into 2 groups in accordance with the median level. The DFS in these 2 subgroups will be compared by log rank test.

12) QUALITY CONTROL AND QUALITY ASSAURANCE

Data Monitoring and Safety committee (DMSC) will be responsible for conduct of trial.

Ethics and regulatory compliance

Study conduct

- This study will be conducted according to the Indian Council of Medical Research (ICMR) guidelines and the schedule Y in compliance with applicable laws and regulations. The study will be performed in accordance with the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2004. The investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a subject.

Institutional review board (Ethics committee)

- The protocol will be reviewed by the Institutional Review Board (IRB) before any patient is entered on the trial.

Informed consent

- Patients will be given a full explanation, in lay terms, of the aims of the study and the potential benefits as well as the possible discomforts and risks involved in taking part in a study. It will be pointed out that they can refuse to take part in, or withdraw from the study without prejudice to further care and treatment. Informed consent will be given in writing.

Confidentiality

All data generated in this study will remain confidential. All information will be stored securely at the Medical Oncology Department, Clinical Trials secretariat, Tata Memorial Centre (TMC) Mumbai and will only be available to staff directly involved with the study, Ethics Committee members and Regulatory Authorities.

- Personal data identifying trial subjects will be held securely at the Clinical Trials secretariat for the purpose of follow up after the conclusion of the protocol-specified period and for 5 years thereafter.

Clinical study report

The Clinical Study Report or summary thereof will be provided to the institutional review board and ethics committee.

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Figure 1

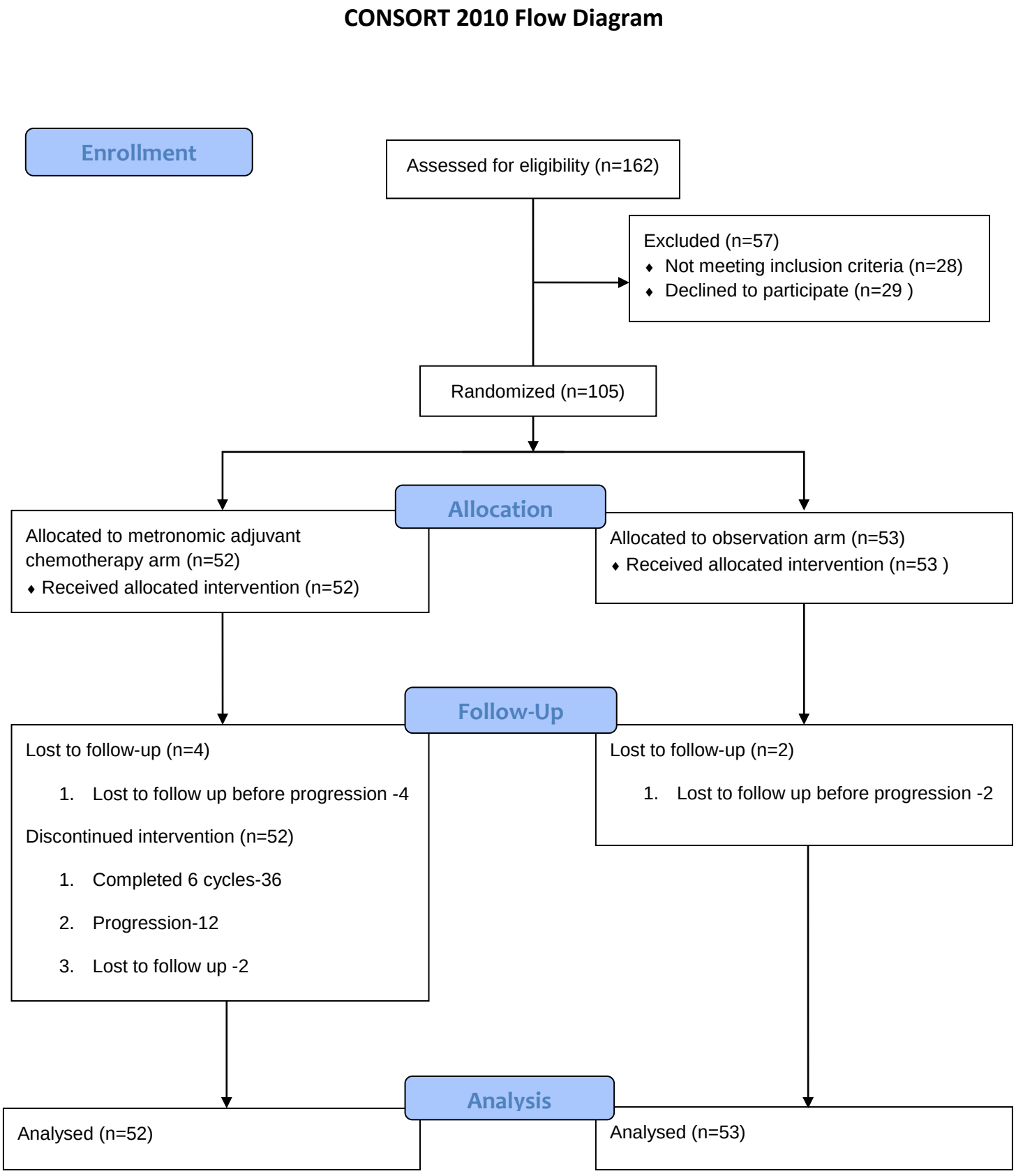
CONSORT 2010 Flow Diagram
Enrollment
Assessed for eligibility (n=162)
Excluded (n=57)
♦ Not meeting inclusion criteria (n=28)
♦ Declined to participate (n=29)
Randomized (n=105)
Allocation
Allocated to metronomic adjuvant chemotherapy arm (n=52)
♦ Received allocated intervention (n=52)
Allocated to observation arm (n=53)
♦ Received allocated intervention (n=53)
Follow-Up
Lost to follow-up (n=4)
1. Lost to follow up before progression -4
Discontinued intervention (n=52)
1. Completed 6 cycles-36
2. Progression-12
3. Lost to follow up -2
Lost to follow-up (n=2)
1. Lost to follow up before progression -2
Analysis
Analysed (n=52)
Analysed (n=53)

Figure 2

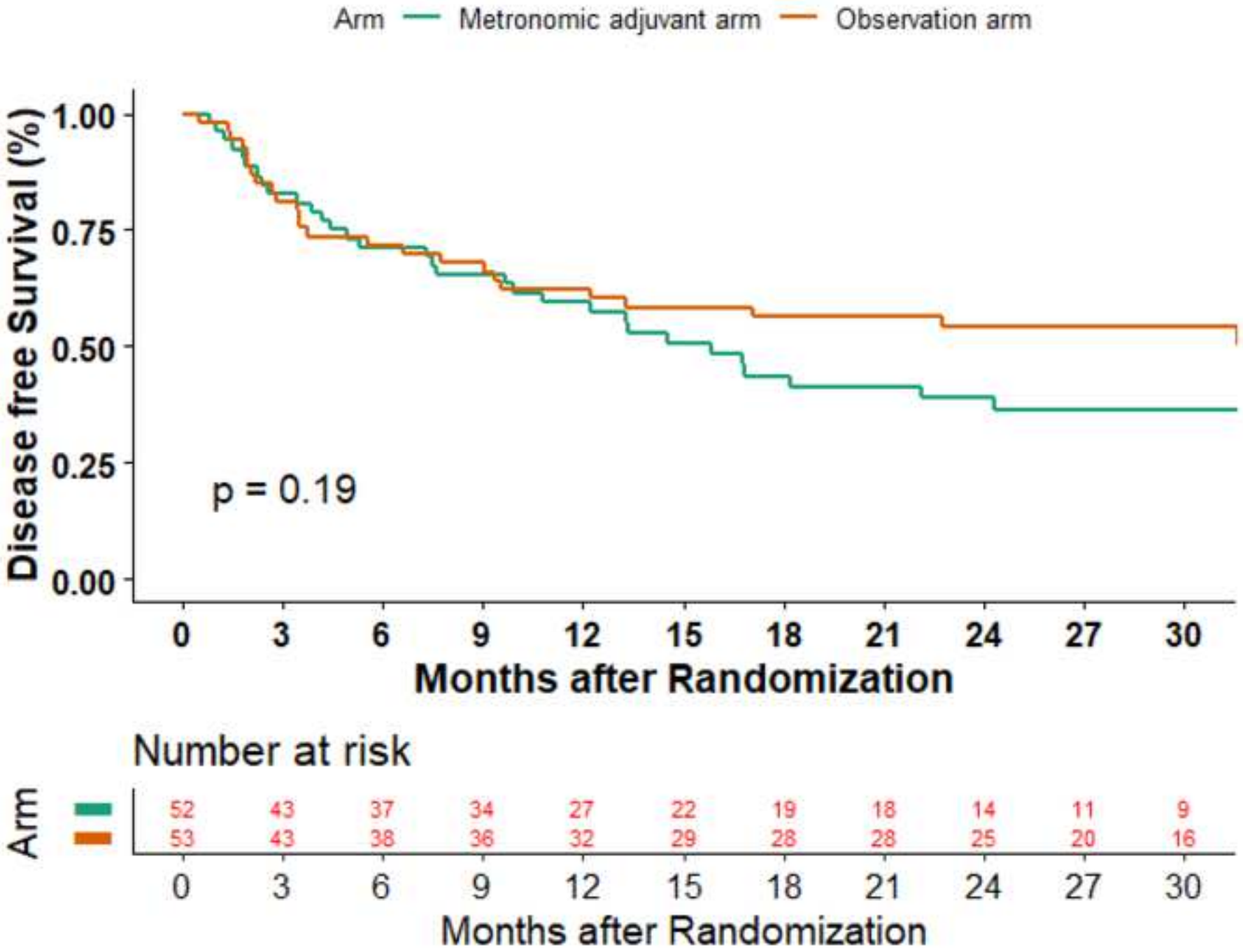

Figure 3