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Original Research

Modified gemcitabine and oxaliplatin or gemcitabine + cisplatin in unresectable gallbladder cancer: Results of a phase III randomised controlled trial

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KEYWORDS
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Abstract ***Aim:*** To determine equivalence of modified gemcitabine and oxaliplatin compared with gemcitabine and cisplatin in unresectable gallbladder cancer (GBC). Primary end-point was overall survival (OS).
Methods: Open label, prospective, randomised phase III equivalence study. Inclusion criteria included histologically proven unresectable GBC, 18 years or older, adequate organ functions

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Equivalence

and Eastern Cooperative Oncology Group ≤2.
Sample size: 108 patients were required in each arm to have an equivalence margin of ±2 months with power of 80%.
Treatment: Modified gemcitabine and oxaliplatin (mGemOx)—gemcitabine 900 mg/m2, oxaliplatin 80 mg/m2, maximum 6 cycles; gemcitabine + cisplatin (CisGem)—gemcitabine 1000 mg/m2, cisplatin 25 mg/m2, maximum 8 cycles, all day 1 and 8 every 3 weeks.
Results: Two hundred sixty subjects were recruited between February 2011 and July 2015. Two hundred forty-three patients (119, mGemOx and 124, CisGem) received at least 1 dose and analysed for safety and efficacy (modified intention to treat). Median OS was 8·5 months for whole group (95% confidence interval [CI]: 7·9–9·1). Median OS in mGemOx was 9 months and 8·3 months in CisGem; p = 0·057 (hazard ratio = 0·78; 95% CI = 0·60-1·02). Restricted mean OS for follow-up limited to 30 months was 11·2 months (95% CI: 9·8–12·6) in mGemOx and 10·4 months (95% CI: 9·1–11·7) in CisGem. Difference of the mean was 0·8 months with 95% CI, exceeding 2 months (−1·1 to 2·7), hence rejecting equivalence. Peripheral neuropathy, thrombocytopaenia in mGemOx and nephrotoxicity was higher with CisGem.
Conclusion: This trial failed to show equivalence of eight cycles of CisGem to six cycles of mGemOx. Numerically OS was better with mGemOx. Toxicities were different. The trial was not powered to answer superiority.
Clinical trial registration: CTRI/2010/091/001406.

1. Introduction

Gallbladder cancer (GBC) is more common among females in the northern and the north-eastern regions of India. Highest age adjusted incidence (AAR) among women is 17·1 in Kamrup Urban District. In Delhi, GBC is the third commonest cancer among women (AAR of 11·8/100,000 population) [1].

About 90% of patients are unresectable. Chemotherapy options are gemcitabine with cisplatin or oxaliplatin [2,3]. Whether, cisplatin with emetogenicity and nephrotoxicity or oxaliplatin with myelotoxicity and neuropathy are equally effective is unknown.

ABC-02 trial confirmed superiority of gemcitabine and cisplatin (CisGem) over gemcitabine (only 36% were GBC) [2,4]. Superiority of modified gemcitabine and oxaliplatin (mGemOX) over 5FU/folinic acid or best supportive care alone in unresectable GBC was reported earlier [3]. Even pathological complete response (CR) was reported [5]. Dose and schedule of gemcitabine and oxaliplatin in mGemOX is different from earlier reported GEMOX [6].

This study was designed as equivalence study to compare overall survival (OS) with CisGem and mGemOx. Standard duration and doses as per available evidence were used [2,3]. Hypothesis was that 6 cycles of mGemOx (which was reported earlier) [2] is equivalent to 8 cycles of CisGem [3]. In this article, we report results for primary endpoint with last follow-up date being 31 December 2017.

2. Patients and methods

2.1. Study design and participation

An open label, prospective, randomised controlled single centre equivalence study conducted at the All India Institute of Medical Sciences, New Delhi. All the study data and informed consent were gathered in accordance with the Declaration of Helsinki. Institute Ethics committee approved the study protocol. All patients were given a written explanation and provided written informed consent before participating.

Detailed inclusion, exclusion criteria and investigations done at baseline, during treatment and during follow-up is available at online edition (Supplementary Methods available at EJC online).

Inclusion criteria included histologically proven unresectable/metastatic adenocarcinoma of gallbladder, age ≥18 years, adequate organs functions and Eastern Cooperative Oncology Group (ECOG) performance status of ≤2.

Contrast enhanced computed tomography scan of chest and abdomen was done at baseline, mid-way through treatment or early if clinically indicated and at the end of therapy. Thereafter, in patients with response or stable disease follow-up scans were done every 3 months for the first year; every 6 months in the second/third year and annually thereafter till progression. It was decided to do Fluorine18-fluoro-deoxy-glucose positron emission tomography-computed tomography (F18-FDG PET-CT) scan whenever possible.

Once disease progressed subjects were followed up for survival and safety.

2.2. Statistical consideration and analysis

Sample size was calculated taking median survival of 9·5 months in previous study with mGemOx [3] and 11·7 months with CisGem [2]. One hundred eight patients were required in each arm to declare equivalence with an equivalence margin of ±2 month with 80% power and an alpha value of 0·05 [7] Two months equivalence margin was chosen considering that this will be clinically meaningful. To account for major protocol violations or any losses on follow-up, an additional 22 patients in each arm were enrolled.

Descriptive statistics like mean, median, standard deviation and range, were used to describe baseline demographic and clinical profiles of all patients. To determine the association between two categorical variables, the χ^2 test was used. Continuous variables were analysed using the unpaired *t* test or Wilcoxon rank sum test. Survivals were depicted using Kaplan–Meier plots. Differences between groups were analysed using the log-rank test. The Cox proportional hazards regression model was used to calculate the hazard ratios (HRs), univariate and multivariate analysis. Equivalence was assessed using the confidence interval (CI) approach. The difference in the mean survival between the two arms and the 95% CI of the difference was used to assess the equivalence of the two study arms [8]. When survival curves overlap or intersect, the usual index of HR based on assumption of proportion of hazards may not be valid. In view of this, we chose restricted means of survival. We truncated analysis to 30 months at which time a reasonable number of cases were still available to have stable survival estimate. In our data, we had 10 subjects still available at 30 months. Detailed statistical methods (see Supplementary Methods available *EJC online*).

Data analysis was done using Stata, version 14·2 (Stata Corp, Texas, USA)

The study was registered at Clinical Trial Registry of India: CTRI/2010/091/001406.

The protocol is available online at CTRI site: http://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=2194&EncHid=&modid=&compid=%27,%272194det%27.

2.3. Randomisation and masking

Eligible study subjects were allocated to one of the treatment arms in a 1:1 ratio. Randomisation sequence (variable block size) was generated using software N Query Advisor. Treatment arm allocation was done in a sequential manner, and no stratification was done.

2.4. Treatment protocol

Arm A-mGemOx.
Injection oxaliplatin 80 mg/m^2 IVI day 1 and 8.
Injection gemcitabine 900 mg/m^2 IVI day1 and 8.
Repeated every 3 weeks for maximum of 6 cycles.
Arm B- CisGem.
Injection gemcitabine 1000 mg/m^2 IVI day1 and 8.
Injection cisplatin 25 mg/m^2 IVI day 1 and 8.
Repeated every 3 weeks for maximum of 8 cycles.
Dose modification (see Supplementary Methods available at *EJC* online).

Tumour response was assessed by Response Evaluation Criteria in Solid Tumours criteria, version 1·1.

Patients with adequate response were evaluated for possible radical resection. Patients were followed up until death or withdrawal from the study.

Responding patients not suitable for surgery were considered for locoregional radiotherapy to the tumour and surrounding lymph node region. A limited dose of radiotherapy, 30 Gy in 10 fractions over 2 weeks was delivered.

National Cancer Institute Common Terminology Criteria for Adverse Events criteria V 3·0 was used for toxicity assessment.

2.5. Outcome

Primary end-point was OS (date of randomisation to death or date last seen alive). Secondary end-points were progression-free survival (PFS) (date of randomisation to disease progression or death from any cause), response rates (CR or partial response), identification of genes predictive of responses in a subset of patients and role of PET CT in GBC patients predicting disease activity.

3. Results

Between February 2011 and July 2015, 260 patients were enrolled and randomised as shown in Fig. 1 (CONSORT diagram). Out of these; 243 received at least one dose of chemotherapy and were included in the final analysis (modified ITT analysis). Baseline characteristics were well balanced and are summarised in Table 1. As of 31stDecember 2017, only 12 (5%) patients are surviving.

Forty-three (36·1%) patients in mGemOx and 38 (30·6%) patients in CisGem arm completed assigned therapy. The reasons for discontinuation of therapy are given in Supplementary Table S1 *EJC online*, and main reason was disease progression. One patient in mGemOx arm received eight cycles instead of assigned six. Dose modification was required in 13 (11%) patients in mGemOx and 22 (17%) in CisGem. There were no statistically significant differences in dose delays or

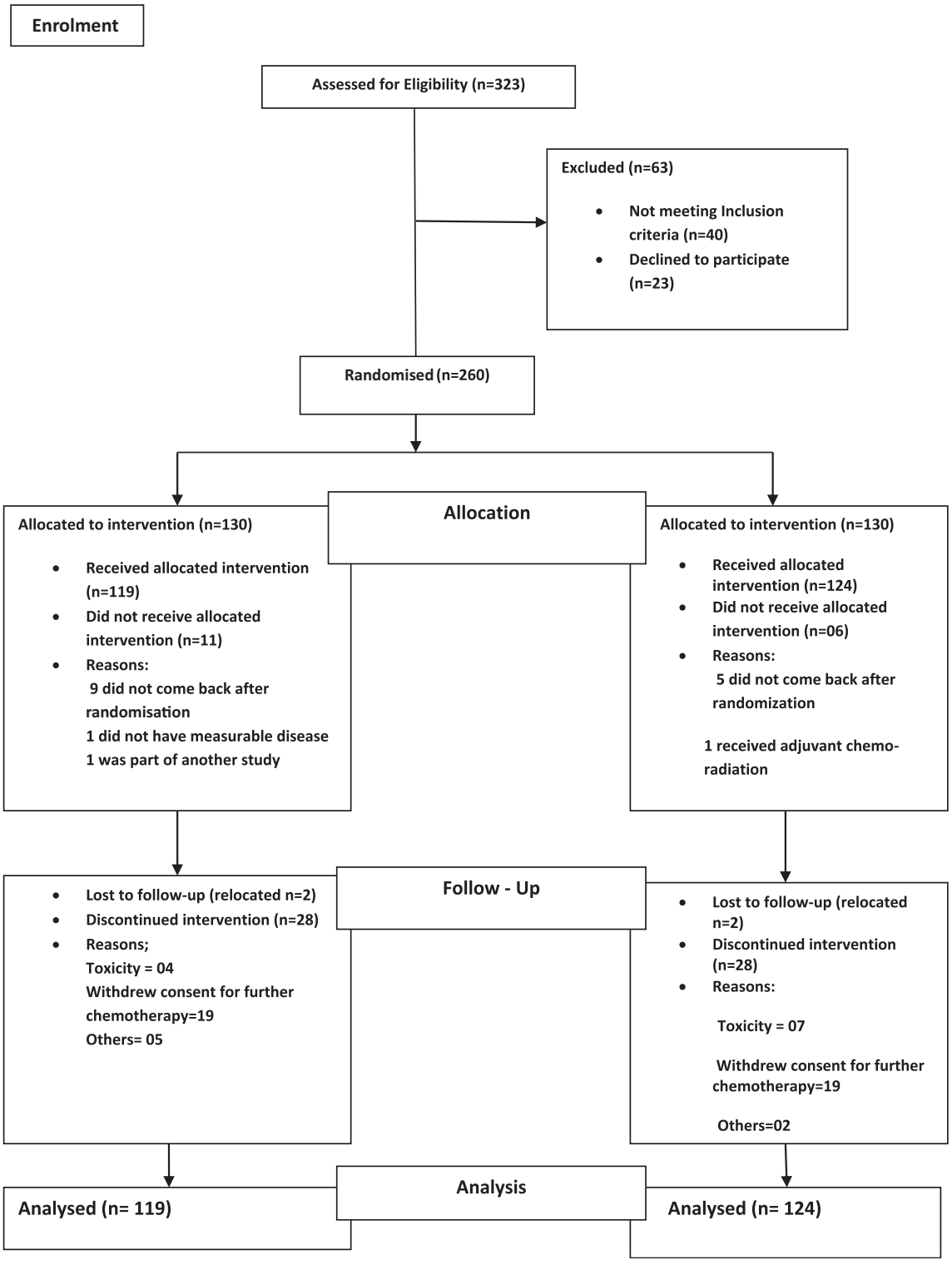

Fig. 1. CONSORT diagram.

reductions because of toxicity in two arms. Median number of cycles was 4.

Overall response was seen in 30 (25·2%) patients in mGemOx group and 29 (23·4%) patients in Cis-Gem group. Eight patients (6·7%) in mGemOx and five (4%) patients in CisGem achieved CR. Twenty-nine patients in mGemOx and 28 patients in CisGem had stable disease. On treatment, progression was observed in 39 patients and 46 patients in the two arms, respectively. Response could not be evaluated in 21 patients in each arm because of early death or lost to follow-up or consent withdrawal before response evaluation (Supplementary Table S2 *EJC online*).

Table 1
Baseline characteristics in two study arms.

Characteristic	mGemOx $N = 119$ (%)	CisGem $N = 124$ (%)	p
Sex:			
Males	43 (36·1)	39 (31·5)	
Females	76 (63·9)	85 (68·5)	0·44
Age in years:			
Mean ± SD	48.1 ± 9.92	47.8 ± 12.05	0·84
ECOG:			
0	7 (5·9)	7 (5·6)	
1	72 (60·5)	64 (51·6)	
2	40 (33.6)	53 (42·7)	0·33
0 + 1	79 (66·4)	71 (57·3)	0·14
High WBCs	5 (4·2)	7 (5·6)	0·54
Bilirubin >1N	20 (16·8)	30 (24·2)	0·15
SGOT/SGPT>N	31 (26·1)	29 (23·4)	0·66
SAP >N	78 (65·5)	74 (59·7)	0·34
Albumin <3·5	19 (16)	19 (15·3)	0·89
PET-CT scan done	21 (17·6)	13 (10·6)	0·11
Histology:			
Adenocarcinoma NOS	111 (93·3)	111 (89·5)	
Poorly differentiated	4	8	
Signet ring cell	0	1	
Mucinous	3	4	0·49
Prior therapy:			
Nil	73 (61·3)	66 (53·2)	
Simple cholecystectomy	17 (14·2)	14 (11·3)	
Radical cholecystectomy	5 (4·2)	17 (13·7)	
Biliary stenting	5 (4·2)	4 (3·2)	
Open and closure	7 (5·9)	6 (4·8)	
LAP cholecystectomy	12 (10·1)	14 (11·3)	
Surgery and adjuvant	0	1	0·18
Stage			
III	25 (21·4)	18 (14·5)	
IV	94 (78·6)	106 (85·5)	0·09

SAP, serum alkaline phosphatase; ECOG, Eastern cooperative oncology group; OS, overall survival; mGemOx, modified gemcitabine and oxaliplatin; CisGem, gemcitabine + cisplatin; WBC, white blood cells; N, normal; LAP, laparoscopic; NOS, not otherwise specified; SGOT, serum glutamic oxaloacitic transaminase; SGPT, serum glutamic pyruvic transaminase.

Eight patients, in mGemOx and five in CisGem were suitable for surgical resection. R0 resection was possible in eight patients including one pathological CR who received CisGem. Seven patients received adjuvant RT as per institutional policy and one patient received SBRT to liver after chemotherapy for small localised disease.

Median follow-up of surviving patients is 33·5 months (range 13·0–77·0), and of the whole group is 10·5 months. Median OS for whole group was 8·5 months (95% CI = 7·88–9·12) Supplementary Fig. 1 *EJC online*. Median OS in mGemOx was 9 months (95% CI: 7·9–10·3) and 8·3 months in CisGem arm (95% CI: 7·0–9·8); p = 0·057(HR = 0·78; 95% CI: 0·60–1·01). This is shown in Fig. 2. Mean OS was 11·2 months (95% CI: 9·8–12·6) in mGemOx arm and 10·4 months (95% CI: 9·1–11·7). Difference of mean (Standard group − test group) was 0·8 month (95% CI: −1·1 to 2·7). Difference of means between 95% CI exceeded the equivalence margin of 2 months, and hence equivalent was not established. Numerically, survival was better in mGemOx arm. Survival probabilities at 12 and 18 months was also calculated [9] The 12 months cumulative survival probabilities (±SE) for the mGemOx and CisGem arms were 32·2% ± 4·39% and 24% ± 3·9, respectively. Eighteen months cumulative survival probabilities (±SE) of the mGemOx and CisGem arms were 18·2% ± 3·6% and 7·5% ± 2·59, respectively, and this is shown in Table 2. Survival of subjects with ECOG 0–1 versus ECOG II (this was post hoc analysis) was analysed. Median OS was 10·0 month (95% CI: 8·06–11·93) in mGemOx arm and 9 months (95% CI: 7·81- 10·18) in CisGem arm. For subjects with ECOG II, median survival was 7·0 months in both groups (Supplementary Table S3 *EJC online*).

Median PFS in mGemOx was 5 months (95% CI: 3·2–6·0) compared with 4·0 months in CisGem arm (95% CI: 3·5–6·0); p = 0·047. As shown in Supplementary Fig. 2 *EJC online*.

Grade III or IV thrombocytopaenia was more in mGemOx group (24·4% versus 10·5%, p < 0·01), similarly grade III or IV peripheral neuropathy was more in mGemOx group (6·7% versus 1%, p = 0·01). Grade III/IV nephrotoxicity was more in CisGem arm (5·6% versus 0, p < 0·01). There was no significant difference in incidence of grade III and IV diarrhoea,

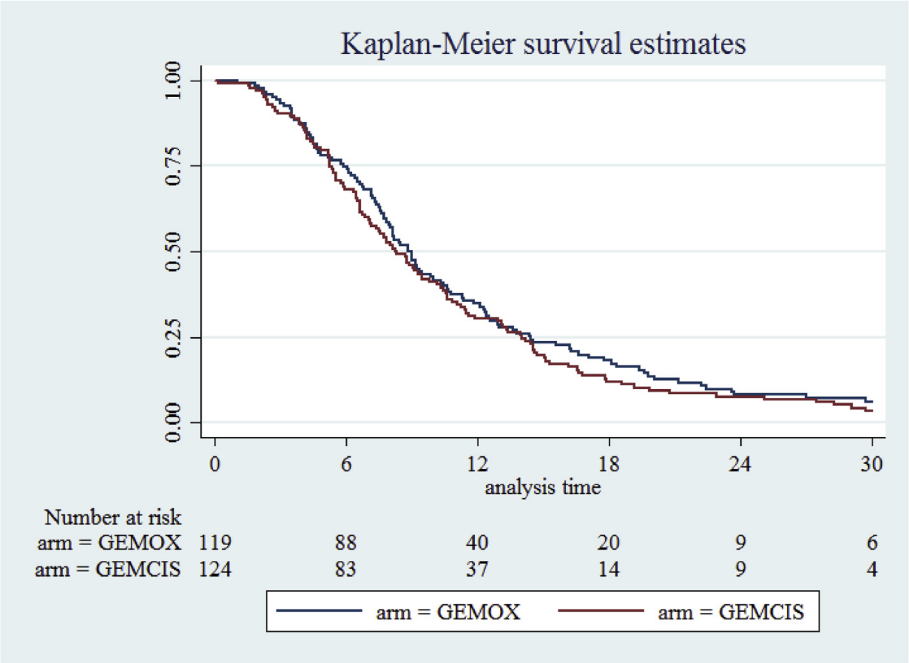

Fig. 2. Overall survival in mGemOx and CisGem group. OS, overall survival; mGemOx, modified gemcitabine and oxaliplatin; CisGem, gemcitabine + cisplatin.

neutropenia and vomiting. One patient in mGemOx arm developed stroke after the first cycle. Three patients developed deep vein thrombosis, one in mGemOx and two in CisGem arm. There were two toxic deaths, both in CisGem arm. One patient had sudden death at home and second died after grade IV diarrhoea and vomiting. Toxicity data are shown in Table 3.

Univariate and multivariate analysis were done to identify prognostic factors. Factors which were associated with poor outcome in univariate analysis were ECOG status 2, high bilirubin, high serum alkaline phosphatase, low albumin level, grade III or IV vomiting, grade III and IV other toxicity and no objective response (Supplementary Table S4 *EJC* online). ECOG status 2, low albumin, high serum alkaline phosphatase and no objective response were associated with poor outcome on multivariate analysis (Supplementary Table S5 *EJC* online only).

Unfortunately, utility of PET-CT scan and gene-expression profiling (GEP) could not be assessed as per protocol. PET-CT scan could be done only in 21 and 13 patients respectively in two arms. Though we collected the baseline samples for GEP, lack of organisation and infrastructure did not allow us to do it as per protocol.

4. Discussion

ABC-02 trial established CisGem as the preferred regimen for unresectable/metastatic biliary tract cancer.

Table 2
Survival (months) in the two treatment arms (OS, PFS and equivalence testing).

Parameter	Treatment Arm		Difference (95% CI)
	mGemOx (N = 119)	CisGem (N = 124)	
Median OS (95% CI)	9·0 (7·9–10·3)	8·3 (7·0–9·8)	
Mean OS (95% CI)	11·2 (9·8–12·6)	10·4 (9·1–11·7)	0·8 (−1·1–2·7)
Cumulative 30 months survival probability (%)	6·2 (2·69–11·75)	3·4 (1·13-7·90)	2·8 (−2·82-8·34)
PFS			
Median PFS (95% CI)	5·0 (3·2–6·0)	4·0 (3·5–6·0)	*P = 0·047*
Cumulative 30 months Surv. Prob. (%)	4·7 (1·59–10·32)	2·0 (0·38–6·22)	2·7 (−2·36 to 7·76)
Comparison of survival probabilities (%) at fixed time points[8]			
Time	Parameter	Surv. Prob. (%) ± SE	
		mGemOx	CisGem
12months	OS	32·2% ± 4·39%	24% ± 3·9%
18 months	OS	18·2 ± 3·6	7·5 ± 2·59
24 months	OS	8·1% ± 2·6%	5·0% ± 2·59%

OS, overall survival; mGemOx, modified gemcitabine and oxaliplatin; CisGem, gemcitabine + cisplatin; PFS, progression-free survival; CI, confidence interval; PET-CT, positron emission tomography-computed tomography.

Table 3
Toxicity and treatment modifications.

Characteristic	mGemOx $N = 119$ (%)	CisGem $N = 124$ (%)	p
Dose reduction			
Nil	106	102	
25%	10	19	
50%	3	3	0·25
Delay			
Nil	56	60	
<1 week	25	24	
1–2 weeks	27	26	
>2 weeks	11	14	0·93
Overall grade III or IV toxicity	65 (54·62)	69 (52·41)	0·78
Diarrhoea any grade	32 (26·89)	22 (17·74)	0·09
Grade III/IV	11 (9·24)	8 (6·45)	0·42
Vomiting			
Any grade	54 (45·37)	58 (46·77)	0·83
Grade III/IV	13 (10·92)	12 (9·67)	0·75
Absolute neutrophil counts			
Any grade	35 (29.41)	44 (35·48)	0·31
Grade III/IV	21 (17·64)	32 (25·80)	0·12
Platelets			
Any grade	58 (48·73)	46 (37·09)	0·07
Grade III/IV	29 (24·36)	13 (10·48)	<0·01
Anaemia			
Any grade	40 (33·61)	49 (39·51)	0·34
Grade III/IV	25 (21)	28 (22·58)	0·77
Peripheral neuropathy			
Any grade	20 (16.8)	5 (4·03)	0·001
Grad III/IV	8 (6·72)	1 (0·80)	0·02
Oral mucositis	3 (2·52	4 (3·22)	0·62
Renal			
Any grade	3 (2·52)	13 (10·48)	0·01
Grade III/IV	0	7 (5·64)	0·01
Toxic death	0	2 (1·61)	
Stroke	1 (0·84)	0	
Deep vein throbosis	1 (0·84)	2 (1·61)	
Dialysis	0	1 (0·80)	

Median OS was 11·7 versus 8·2 months in CisGem compared to gemcitabine ($p < 0·001$) [2]. Superiority of mGemOx over 5FU/folinic acid or best supportive care alone in unresectable/metastatic GBC was reported same year. Median OS was 9·5 versus 4·6 versus 4·5 respectively in (mGemOx, FUFA, and BSC, respectively [$p = 0·039$])[3].

The median age in current study is between 47 and 48 years similar to 47–52 years reported from India [3,10]. However, this is lower than 63–64 years reported in ABC-02 study [2].

A systematic review of studies using CisGem or GemOx was reported [11]. Eighteen studies involving 771 patients in CisGem and 15 studies involving 699 patients in GemOx were identified. Only two were phase III studies (one in each group), and five were phase II comparative studies. The primary objective was to assess the median of the median OS (mOS) and a weighted mOS. There was more heterogeneity regarding dose of cisplatin compared with oxaliplatin. Median of mOS was 9·85 months (ranges: 5–15·2 months) (95% CI: 8·6–11) in CisGem group and 10 months (ranges: 7·5–12·4 months) (95% CI: 8·8–11) in GemOx group. Weighted median of mOS was 9·7 months in CisGem group (95% CI: 9·0–10·5) and 9·5 months (95% CI: 9·5–10) in GemOx group.

A match pair analysis of GBC patients treated at a single centre in India using gemcitabine with either cisplatin or oxaliplatin was published [12] Total 316 patients were identified (163 in CisGem and 163 in GemOx). The median OS was 8·01 months in CisGem and 7·79 months in GemOx cohort ($p = 0·45$).

The current study is the first direct comparison of two gemcitabine base protocol (cisplatin or oxaliplatin) in unresectable/metastatic GBC. Overall response rates were similar. Even though the analysis was modified to intent to treat, the final analysis involved more than required number of 108 in each arm. Median OS in mGemOx was 9 months and 8·3 months in CisGem arm. Difference of mean was 0.8 month (95% CI: −1·1–2·7). 95% CI exceeded predefined equivalent margin of 2 months. Therefore, equivalence of 8 cycles of CisGem equivalent to 6 cycles of mGemOx could not be proven. The study was not powered enough to

answer the question of superiority of mGemOx over CisGem. The median OS in the current study was numerically lower than earlier reported median OS [2,3]. One possible reason may be enrolment of more patients with ECOG performance score of 2. In ABC-02 trial only 11·7% patients had ECOG performance of 2. In this current study, 33·6% of patients in mGemOx and 42·7% of patients in CisGem had ECOG performance of 2. Median PFS was significantly better in mGemOx arm (6 months) versus 4·5 months in CisGem arm, ($p = 0·047$). There had been differences in median PFS described in systematic review and match-pair analysis also. Fideti *et al.* have reported 6·3 months (95% CI: 4–8·5 months) in CisGem and 4·9 months (95% CI: 3·5–8·5 months) in GemOx cohort [10].

Oxaliplatin combination had more thrombocytopaenia and neuropathy whereas cisplatin-based combination was associated with more nephrotoxicity. Duration of treatment and hospital visits are important consideration, especially in palliative setting. Total duration of mGemOx is18 weeks for 6 cycles compared with 24 weeks for CisGem. Its implication on increasing cost of the treatment was not analysed.

4.1. Limitation

This was a single centre and open label study. Power of study was 80%. Because repeat imaging was planned at midway during treatment, it was not at identical time in two groups. As study included GBC patients only, we suggest caution in extrapolating these results to other ABC type.

5. Conclusion

Toxicity and survival are two important parameters which help in choosing one protocol over another. Current study has shown that 8 cycles of CisGem is not equivalent to 6 cycles of mGemOx, and mGemOx is definitely not inferior to CisGem. Toxicities are different. Shorter duration of treatment and numerically better survival with mGemOx suggest it may be preferred, especially if renal toxicity is a concern. Whether mGemOx is superior to CisGem can be only answered by an adequately powered study.

Authors' contribution

Protocol conceptualisation and design

A.S. contributed in protocol writing, patient recruitment, treatment, analysis and manuscript writing:

B.K.M., S.P.C., N.K.S., S.V.S.D., S.P., S.K., N.R.D, P.S., helped in protocol writing, patient recruitment, treatment, analysis and manuscript writing:

R.K.S., S.P., S.B., S.M., V.R. helped in patient recruitment, treatment and manuscript writing:

S.T., R.K., V.I. helped in patient recruitment, investigations (imaging, obtaining sample and pathology) and manuscript writing:

V.S. assisted in protocol writing, randomisation sheet generation, statistical analysis and manuscript writing.

All authors have seen and approved manuscript. All authors are also responsible for data integrity.

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This was an investigator-initiated trial and protocol was designed by first author (AS).

Conflict of interest statement

The authors have declared no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.10.004.

mGemOx, modified gemcitabine and oxaliplatin; CisGem, gemcitabine + cisplatin.

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