Feasibility study of sequential adjuvant chemotherapy with three months oxaliplatin-based regimen (modified FOLFOX6 or CAPOX) followed by three months capecitabine in patients with stage III and high risk stage II colorectal cancer: (JSWOG C2)

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Hiroaki Tanioka[1], Kazuki Yamashita[2], Akihito Tsuji[3], Hideo Okumura[4], Yasuo Oka[4], Atsushi Tsuruta[4], Michio Inukai[5], Toshiki Yamakawa[6], Tomoki Yamatsuji[7], Yoshimitsu Masanori[8], Kazuhiro Toyota[9], Taketoshi Yamano[10], Yuji Yamamoto[11], Takeshi Nagasaka[12], Masazumi Okajima[13]

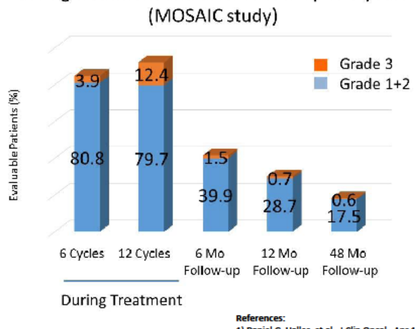
1) Department of Medical Oncology, Okayama Rosai Hospital, 2)Department of Surgery, Okayama Rosai Hospital ,3) Department of Medical Oncology, Kobe City Medical Center General Hospital ,4) Department of Digestive Surgery, Kawasaki Medical School Hospital , 5) Department of General Medicine, Kagawa University Hospital, 6) Department of Surgery, Kagawa Prefectural Central Hospital, 7) Department of General Surgery, Kawasaki Medical School, 8) Department of Surgery, Hiroshima City Asa Hospital , 9) Department of Surgery, National Hospital Organization Higashihirosima Medical Center , 10) Department of Surgery, Kurashiki Medical Center , 11) Department of Digestive Surgery Oncology, Ehime University Hospital, 12) Department of Digestive Surgery, Okayama University Hospital, 13) Department of Surgery, Hiroshima City Hospital

Background

- Six months oxaliplatin (OX)-based chemotherapy (modified FOLFOX6 or CAPOX) is the standard adjuvant chemotherapy for completely resected stage III colorectal cancer (CRC) in Japan.
- However neurotoxicity is the most frequent toxicity of these chemotherapy regimens and often decline their QOL.
- OX induced neurotoxicity is well known to be appeared by dose-dependently and progresses to irreversible in some cases.
- Six months OX regimen has been reported to leave neurotoxicity after treatment in patients with cmpletely resected stage III CRC.

Study	Regimen	Proportion of completion in therapy (%)	Median dose of OX (mg/m²)	PSN during treatment All grade (G3/4) (%)
XELOXA (NO16968) 1) 2)	XELOX (n=942)	69	874 (max1040)	78 (11)
MOSAIC 3)4)	FOLFOX4 (n=1108)	74.7	810 (max 1020)	92 (12.5)
				18.1 (0.6) 3yr
NSABP C-07 5)6)7)	FLOX (n=1247)	-	677 (max 765)	85.3 (8.4)
				29.9 (0.4) 1yr

Peripheral sensory neuropathy (PSN) during treatment and after follow-up to 3 years (MOSAIC study)



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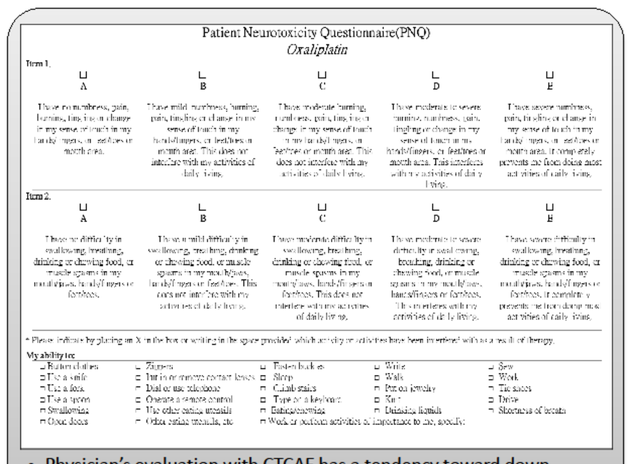
Objectives

- To investigate the feasibility of sequential approach with three months OX-based regimen followed by three months capecitabine in Japanese patients with stage III CRC, in addition to high-risk stage II CRC. (UMIN000004934)
- Primary endpoint
  - Frequency and Grade of peripheral sensory and motor neuropathy (PSN/PMN) (CTCAE v4 and PNQ)
- Secondary endpoints
  - Proportion of completion in oxaliplatin base therapy
  - Proportion of completion in adjuvant chemotherapy
  - Proportion of treatment selection
  - Adverse event
  - Compare FOLFOX to CAPOX in efficacy or adverse event


Patient Neurotoxicity Questionnaire(PNQ)
Oxaliplatin

Item 1.

A: Those no numbness, pain, burning, tingling in fingers or toes or change in my sense of touch in my hands/fingers, or feet/toes or mouth area.

B: Those mild numbness, burning, pain, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. This does not interfere with my activities of daily living.

C: Those moderate burning, numbness, pain, tingling, or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. This does not interfere with my activities of daily living.

D: Those moderate to severe numbness, pain, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. This interferes with my activities of daily living.

E: Those severe numbness, pain, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. It is so severe it prevents me from doing most activities of daily living.

Item 2.

A: Those no difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/throat, including difficulty in speech or facilities.

B: Those a mild difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/throat, including difficulty in speech or facilities. This does not interfere with my activities of daily living.

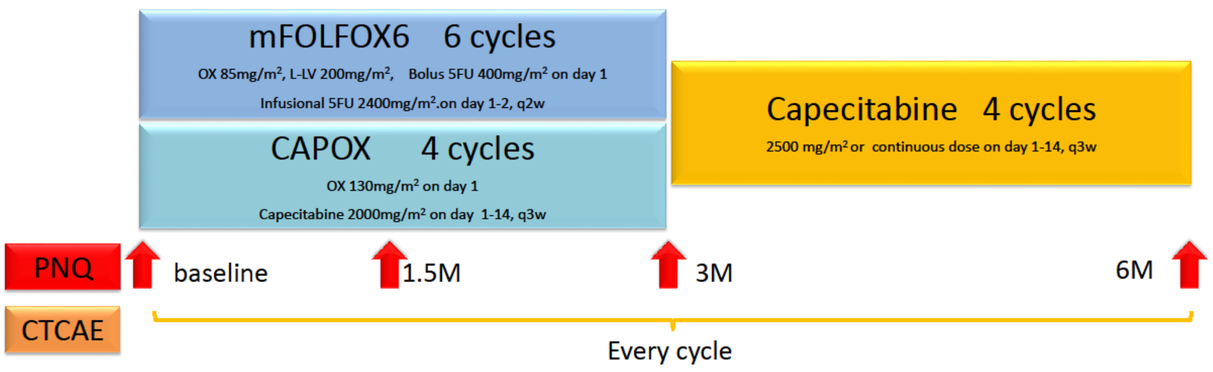
C: Those moderate difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/throat, including difficulty in speech or facilities. This does not interfere with my activities of daily living.

D: Those moderate to severe difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/throat, including difficulty in speech or facilities. This interferes with my activities of daily living.

E: Those severe difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/throat, including difficulty in speech or facilities. It is so severe it prevents me from doing most activities of daily living.

- Physician's evaluation with CTCAE has a tendency toward down grading and Patient-reported outcomes are important for detecting adverse events.
- Patient Neurotoxicity Questionnaire (PNQ) to evaluate the neurotoxity of OX is a self-reported questionnaire.

Study Design



Eligibility

- Main inclusion criteria
  - histopathologically confirmed colorectal cancer.
  - StageIII (or high risk stageII) and R0 resection.
  - After resection, it is possible to begin the adjuvant chemotherapy within 8 weeks
  - Age: ≧20 years
  - ECOG PS: 0-1
- Main exclusion criteria
  - more than grade 1 (CTCAE v4.0) PN

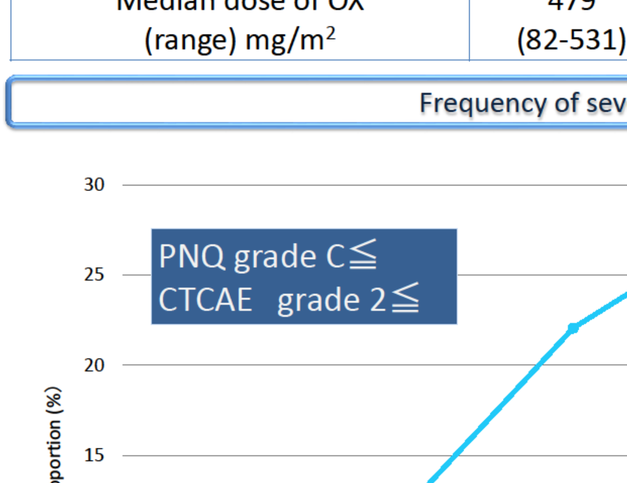
Statistical Design

- While attempting to detect a frequency of 3.9% with 95% probability for the occurrence of PSN (≧Grade 3 CTCAE), we determined that the sample size would include 80 patients.

Results

Consort flow diagram

91 patients enrolled in 11 institutes (between 2011 and 2014)



Characteristics of the patients

All patinets (n=86)	
Age median (range)	65 (36-81)
ECOG PS(0/1)	81/5
Sex (Male/Female)	49/37
Tumor site (rectal/non-rectal)	32/54
Histologic appearance (well/mod/por/others)	14/65/5/2
Disease stage (Ⅱ/Ⅲa/Ⅲb)	15/47/24

Proportion of completion and Dose of OX

		All patients	mFOLFOX6	CAPOX	P value
Number		86	30	56	
Proportion of completion (%)	OX-based therapy	83.7	80.0	85.7	0.544
	All treatments	65.1	63.3	66.1	0.816
Median dose of OX (range) mg/m²		479 (82-531)	467 (82-512)	490 (120-531)	0.123

Frequency of severity (PSN, PMN)

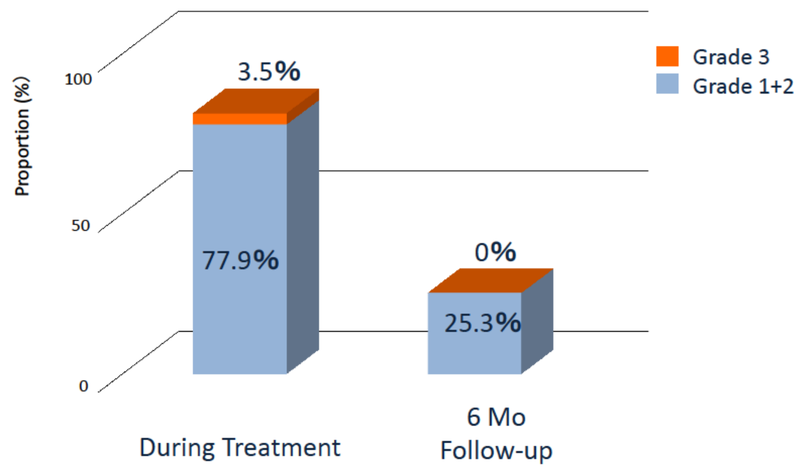
Correlation between PNQ and CTCAE

PSN	PNQ	CTCAE
PNQ	1.0	-
CTCAE	0.468	1.0

PMN	PNQ	CTCAE
PNQ	1.0	-
CTCAE	0.127	1.0

Spearman's correlation cofficient

PSN during treatment and after 6 Mo follow-up



Adverse Events

%	All Patients All	All Patients G3≦	mFOLFOX6(n=30) All	mFOLFOX6(n=30) G3≦	CAPOX(n=56) All	CAPOX(n=56) G3≦	P value (Fisher test: All grade)
leukopenia	34.9	0.0	33.3	0.0	35.7	0.0	1.000
neutropenia	57.0	9.3	53.3	3.3	58.9	12.5	0.653
anemia	53.5	0.0	70.0	0.0	44.6	0.0	0.040
thrombocytopenia	62.8	2.3	60.0	3.3	64.3	1.8	0.816
T-bil	9.3	0.0	6.7	0.0	10.7	0.0	0.708
AST	67.4	0.0	73.3	0.0	64.3	0.0	0.473
ALT	47.7	5.8	56.7	6.7	42.9	5.4	0.262
ALP	25.6	1.2	16.7	0.0	30.4	1.8	0.202
Cre	8.1	1.2	13.3	3.3	5.4	0.0	0.232

%	All Patients All	All Patients G3≦	mFOLFOX6(n=30) All	mFOLFOX6(n=30) G3≦	CAPOX(n=56) All	CAPOX(n=56) G3≦	P value (Fisher test: All grade)
HFS	50.0	3.5	63.3	3.3	42.9	3.6	0.113
Anorexia	47.7	4.7	56.7	0.0	42.9	7.1	0.262
Diarrhea	26.7	8.1	23.3	10.0	28.6	7.1	0.799
Nausea	30.2	1.2	26.7	0.0	32.1	1.8	0.632
Mucositis Oral	25.6	1.2	46.7	3.3	14.3	0.0	0.001
PSN	81.4	3.5	86.7	3.3	78.6	3.6	0.402
PMN	22.1	1.2	16.7	0.0	25.0	1.8	0.427

conclusions

- The proportion of grade3 PSN (3.3%) and PMN (1.2%) during treatment was lower than 6 months OX-based adjuvant treatment previously reported.
- At 6 months after the end of treatment, there was no grade3 PSN patient.
- Sequential approach with 3 months OX-based regimen followed by 3 months capecitabine is a safety adjuvant treatment for CRC.
- PNQ appears to detect OX induced neurotoxicity earlier than CTCAE.

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