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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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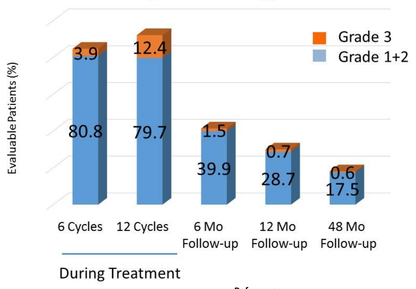
Background

- 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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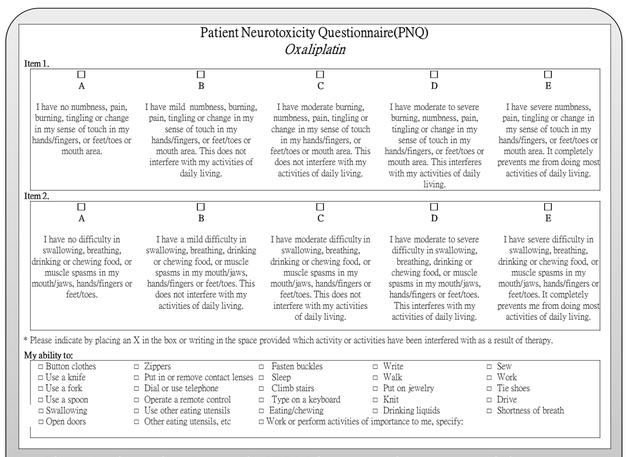
Objectives

- 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	B	C	D	E
I have no numbness, pain, burning, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area.	I have 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.	I have 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.	I have moderate to severe burning, 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.	I have severe numbness, pain, tingling or change in my sense of touch in my hands/fingers, or feet/toes or mouth area. It completely prevents me from doing most activities of daily living.

Item 2.

A	B	C	D	E
I have no difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes.	I have a mild difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. This does not interfere with my activities of daily living.	I have moderate difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. This does not interfere with my activities of daily living.	I have moderate to severe difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. This interferes with my activities of daily living.	I have severe difficulty in swallowing, breathing, drinking or chewing food, or muscle spasms in my mouth/jaws, hands/fingers or feet/toes. It completely prevents me from doing most activities of daily living.

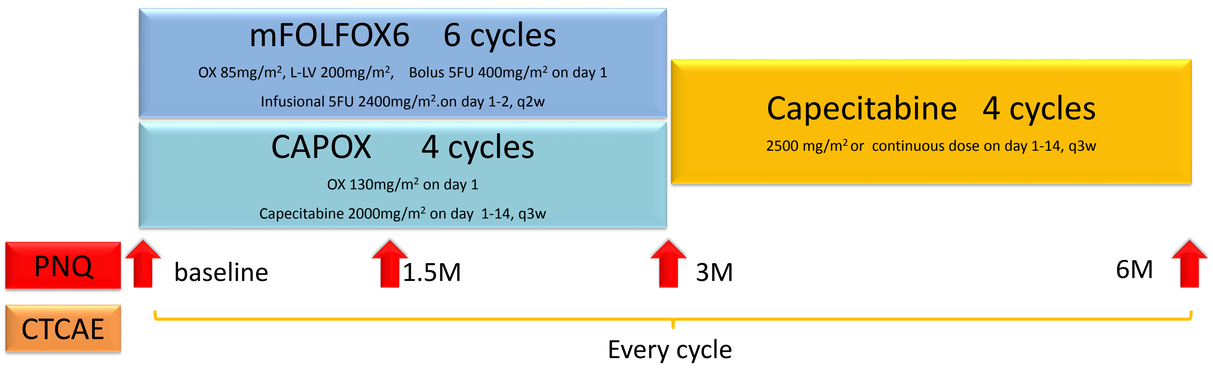
* Please indicate by placing an X in the box or writing in the space provided which activity or activities have been interfered with as a result of therapy.

My ability to:

□ Button clothes	□ Zippers	□ Fasten buckles	□ Write	□ Sew
□ Use a knife	□ Put in or remove contact lenses	□ Sleep	□ Walk	□ Work
□ Use a fork	□ Dial or use telephone	□ Climb stairs	□ Put on jewelry	□ Tie shoes
□ Use a spoon	□ Operate a remote control	□ Type on a keyboard	□ Knit	□ Drive
□ Swallowing	□ Use other eating utensils	□ Eating/chewing	□ Drinking liquids	□ Shortness of breath
□ Open doors	□ Other eating utensils, etc	□ Work or perform activities of importance to me, specify:		

- 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.

Adverse Events

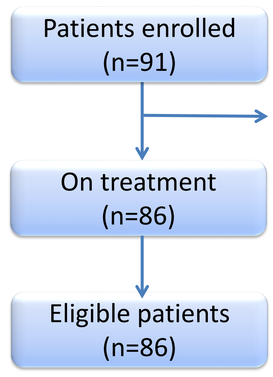
%	All Patients		mFOLFOX6(n=30)		CAPOX(n=56)		P value (Fisher test: All grade)
	All	G3≦	All	G3≦	All	G3≦	
leukopenia	34.9	0.0	33.3	0.0	35.7	0.0	1.000
neutropenia	57.0	9.3	53.3	3.3	58.9	12.5	0.653
anemia	53.5	0.0	70.0	0.0	44.6	0.0	0.040
thrombocytopenia	62.8	2.3	60.0	3.3	64.3	1.8	0.816
T-bil	9.3	0.0	6.7	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		mFOLFOX6(n=30)		CAPOX(n=56)		P value (Fisher test: All grade)
	All	G3≦	All	G3≦	All	G3≦	
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

Results

Consort flow diagram

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



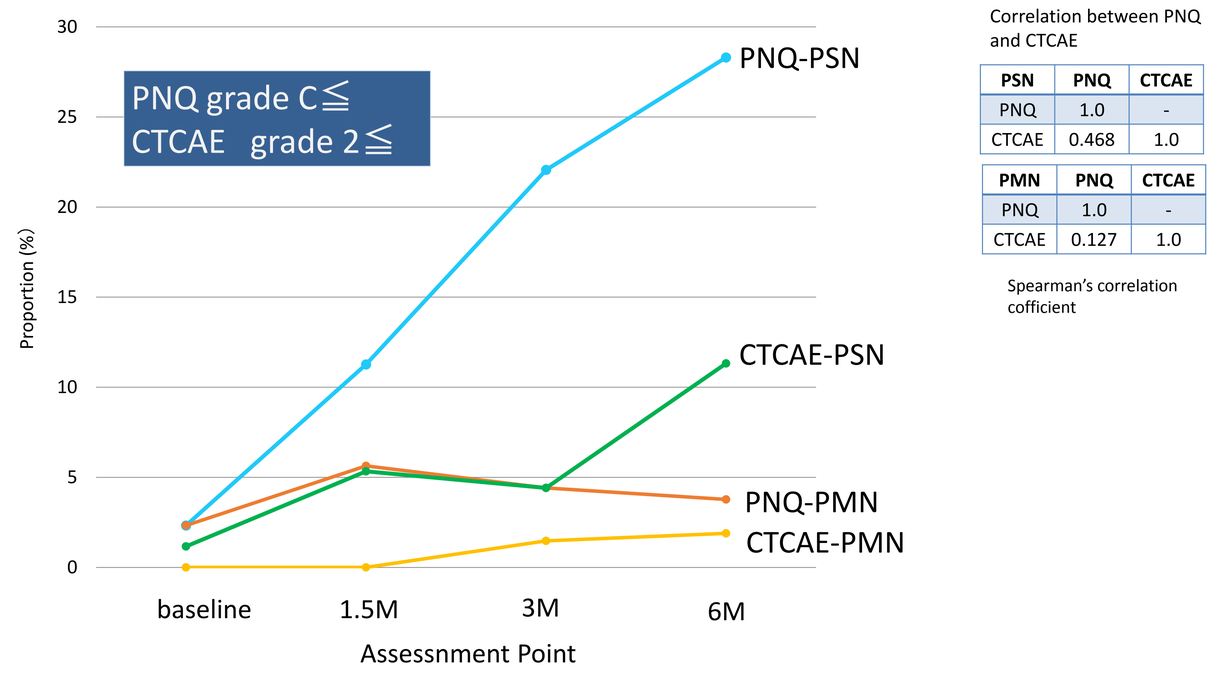
Characteristics of the patients

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)



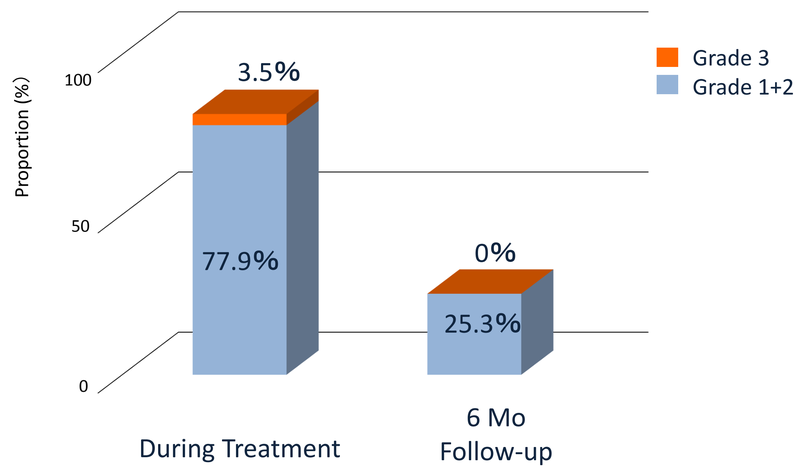
Correlation between PNQ and CTCAE

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



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.

Acknowledgement

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