CAPECITABINE (C) IN COMBINATION WITH IRINOTECAN (I) AND OXALIPLATIN (O) (XELOXIRI) AS FIRST LINE TREATMENT OF METASTATIC COLORECTAL CANCER (MCRC): RESULTS OF A PILOT STUDY BY GRUPPO ONCOLOGICO NORD-OVEST (G.N.O.O.)

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ABSTRACT (updated)

Background: The triplet drug regimen FOLFOXIRI demonstrated improved Response Rate compared to FOLFIRI. This phase II trial was designed to evaluate the safety and tolerability of escalating doses of capecitabine in association with irinotecan and oxaliplatin in metastatic colorectal cancer (MCRC) patients.

Methods: The GONO group comparing FOLFOXIRI to FOLFIRI demonstrated that FOLFOXIRI regimen is feasible with manageable toxicities and significantly improves response rates compared to FOLFIRI in metastatic colorectal cancer patients. A phase III trial by the GONO group comparing FOLFOXIRI to FOLFIRI demonstrated that FOLFOXIRI regimen is feasible with manageable toxicities and significantly improves response rates compared to FOLFIRI in metastatic colorectal cancer patients.

Results: The study design was completed on 10th May 2004 and the study was closed on 15th May 2004. A total of 36 patients were treated. The use of oral fluoropyrimidines simplifies the treatment and allows for better compliance and reduces the risk of toxicities. The combination of capecitabine, irinotecan and oxaliplatin is: 2000 mg/m²/day kept the observed toxicities manageable.

Conclusions: The combination of capecitabine, irinotecan and oxaliplatin is feasible with G3-4 diarrhea being the DLT. The recommended dose for phase II trials are 3 patients were hospitalized because of G3-4 diarrhea but no toxic deaths have occurred.

OBJECTIVES

Primary objectives
- To establish the recommended dose of capecitabine in combination with fixed doses of irinotecan and oxaliplatin.

Secondary objectives
- Safety profile
- Progression-free survival
- Overall survival
- Rate of post-chemotherapy radical surgery on metastases
- Pharmacokinetics

RESULTS: DOSE FINDING PHASE

MAX TOXICITY PER PATIENT

Adverse event G-1 G-2 G-3 G-4
NAUSEA 97% -
DIARRHEA 55% 40% 27% 14%
NEUROTOXICITY 54% 20% 14% 7%

CAPECITABINE: at recommended dose

IRINOTECAN: 165 mg/m² ev day 1
OXALIPLATIN: 85 mg/m² ev day 1 every 2 weeks

The use of oral fluoropyrimidines simplifies the treatment and allows to avoid the possible complications of a CVC.

STUDY DESIGN

PART 1: Dose finding study

Hypothetically confirmed adenocarcinomas of colon or rectum
Unresectable and measurable metastatic disease according to RECIST criteria
Male or female, aged > 18 and < 75 years
ECOG PS 0 or 1
At least 6 months from prior chemotherapy
At least 6 months from prior radiotherapy or surgery
Adequate renal, hepatic and haematological functions
ECOG PS = 0 for patients aged > 70 years
At least 4 weeks from prior radiotherapy or surgery
At least 6 months from prior chemotherapy

RESULTS: DOSE FINDING PHASE

MAX TOXICITY PER CYCLE

Type of DLT DIARRHEA NEUROTOXICITY THROMBOCITOPENIA

MAX TOXICITY per CYCLE

DIARRHEA NEUROTOXICITY THROMBOCITOPENIA

RESULTS: DOSE FINDING PHASE

DOSE LEVELS AND DLTS

CAPECITABINE IRINOTECAN OXALIPLATIN

N° patients 15 5 6
N° DLT 3 2 2

Phase III study by the GONO group comparing FOLFOXIRI to FOLFIRI demonstrated that FOLFOXIRI regimen is feasible with manageable toxicities and significantly improves response rates compared to FOLFIRI in metastatic colorectal cancer patients.

RESULTS: DOSE FINDING PHASE

Dose 3 grade 4 diarrhea was the dose limiting toxicity (DLT)

Grade 3-4 diarrhea: 3 patients were hospitalized because of G3-4 diarrhea but no toxic deaths have occurred.

PHASE II STATISTICAL DESIGN

Using the mini-max two stage Simon’s design with:
- pD = 50% (pH = 0.05)
- a error = 0.05
- b error = 0.20

The first step of the phase II study requires an accrual of 12 patients.

RESULTS: PHASE II

MAX TOXICITY per CYCLE

MAX TOXICITY per CYCLE

NAUSEA DIARRHEA NEUROTOXICITY THROMBOCITOPENIA

RESULTS: PHASE II

MAX TOXICITY per CYCLE

NAUSEA DIARRHEA NEUROTOXICITY THROMBOCITOPENIA

RESULTS: PHASE II

MAX TOXICITY per CYCLE

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RESULTS: PHASE II

MAX TOXICITY per CYCLE

NAUSEA DIARRHEA NEUROTOXICITY THROMBOCITOPENIA

REFERENCES

2. Folprecht G et al, Ann Oncol 2005

RESULTS: DOSE FINDING PHASE

RATIONAL

In metastatic colorectal cancer the best outcome is achieved in patients receiving fluoropyrimidines, irinotecan and oxaliplatin in the course of the disease.

The activity of the first dose treatment is correlated with the secondary rate of toxicities.

The use of oral fluoropyrimidines simplifies the treatment and allows to avoid the possible complications of a CVC.

Some patients receiving fluoropyrimidines, irinotecan and oxaliplatin in the course of the disease.

The study is still ongoing to better determine the activity and the safety profile of the combination at the recommended dose.

Thank you to all patients and investigators!