



©2011 Dustri-Verlag Dr. K. Feistle
ISSN 0946-1965

DOI 10.5414/CPP49096

A preliminary report of a Phase II study of folinic acid, 5-fluorouracil, irinotecan (FOLFIRI) plus sunitinib with toxicity, efficacy, pharmacokinetics, biomarker, imaging data in patients with colorectal cancer with liver metastases as 1st line treatment – a study of the CESAR central european society for anticancer drug research – EWIV**

K. Mross¹, M. Büchert², U. Fasol², U. Jaehde³, F. Kanefendt³, D. Strumberg⁵, J. Arends¹, J. Hense⁴, B. Moritz⁶, R. Fischer^{7*} and M.E. Scheulen^{4*}

¹Tumor Biology Center at the Albert-Ludwigs-University Freiburg,

²Magnetic Resonance Development & Application Center (MRDAC) of the

University Freiburg, Freiburg, ³Institute of Pharmacy, Clinical Pharmacy, University

Bonn, Bonn, ⁴Innere Klinik (Tumorforschung), West German Cancer Center,

Universitätsklinikum Essen, Essen, ⁵Department Hematology and Oncology,

University Hospital Herne, University Bochum, Bochum, Germany, ⁶CESAR Central

European Society for Anticancer Drug Research-EWIV, Vienna, Austria, and

⁷Department of Gastroenterology, University Hospital Freiburg, Germany

Key words

Phase II study –
FOLFIRI – sunitinib –
oncology – cytotoxics –
cytostatics – biomarker
– pharmacokinetics –
DCE-MRI – CEUS

*Both authors contributed equally.

Introduction

This investigator (KM) initiated Phase II trial (IIT) started in 2008. Inhibition of angiogenesis with bevacizumab has become standard treatment in combination with FOLFOX or FOLFIRI in patients with mCRC [1]. The rationale for this Phase II study came from a Phase I study demonstrating, that patients with mCRC can be treated very effectively and with acceptable toxicity with FOLFIRI plus sunitinib at 37.5 mg (instead of 50 mg) [2]. FOLFIRI was given in the conventional 2 weeks schedule (2qw) whereas sunitinib was given for 4 weeks with 2 weeks off. Therefore, one treatment cycle was defined as 3 times FOLFIRI given every 2 weeks (totally 6 weeks) with 4 week treatment with sunitinib followed by 2 weeks drug holiday. Nearly in parallel a large international multicenter randomized Phase III trial in patients with CRC

was initiated comparing FOLFIRI ± sunitinib. It was our aim to elucidate the anti-angiogenic activity of sunitinib via Dynamic-Contrast-Enhanced Magnetic Resonance Imaging (DCE-MRI) and Dynamic-Contrast-Enhanced Ultrasound Imaging (DCE-USI; CEUS). Initially we set the DCE-MRI and DCE-USI measurements over the whole period of 2 cycles (= 12 weeks). Due to these rather sophisticated imaging techniques it was defined that only patients with at least one liver metastasis > 2 cm in diameter were included to be sure that with a very limited number of patients a maximum of relevant data would be produced. During treatment of the first 4 patients it was recognized that the target lesion in the liver became too small for evaluation by DCE-MRI and DCE-USI due to the highly effective treatment. The protocol was amended to evaluate these imaging parameters earlier than originally planned to ensure that the size of the liver metastases was not too small to be quantified. In Figure 1 the intense research program during the first 2 cycles is depicted.

Methods

No final data can be shown as the full biometric evaluation and report have not yet

Correspondence to
Priv.-Doz. Dr. med.
K. Mross

Department Medical
Oncology, Clinical Trial
Unit, Breisacherstrasse
117, 79106 Freiburg
i.Br., Germany
mross@
tumorbio.uni-freiburg.de

**This extended abstract summarizes four lectures given by B. Moritz, M. Büchert, J. Arends and U. Jaehde in the Working Group Session "Phase I – III studies" during the 8th Annual Meeting 2010 of the Central European Society for Anticancer Drug Research (CESAR) held in St. Gallen, Switzerland, July 01 – 03, 2010.

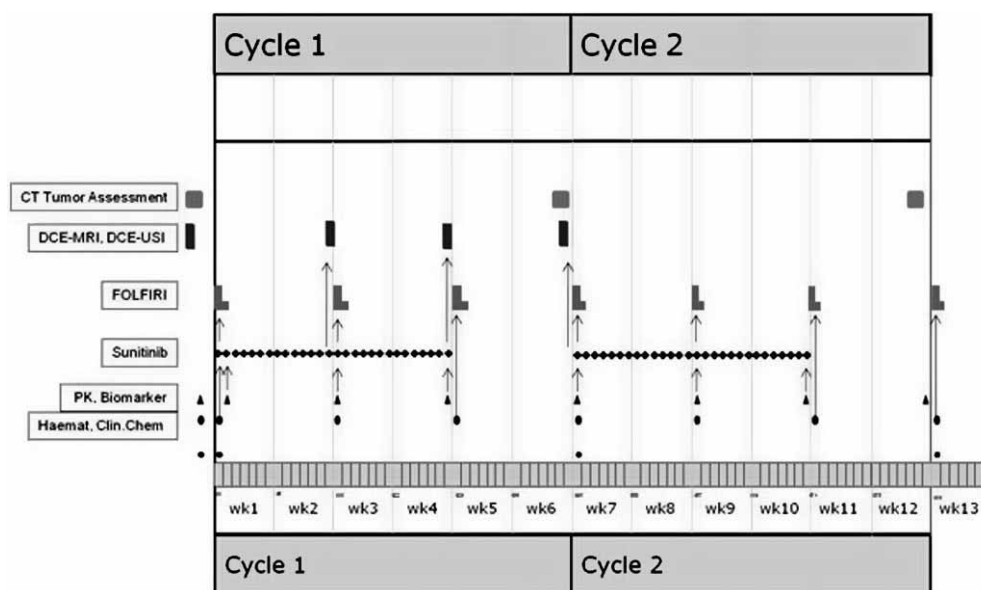


Figure 1. Time lines for PK, biomarker, treatment, DCE-MRI and DCE-USI and efficacy analysis.

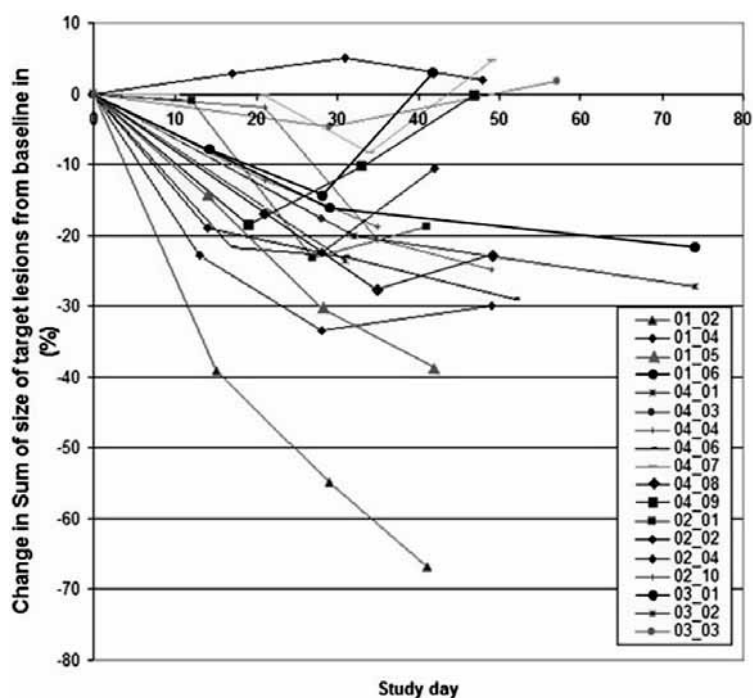


Figure 2. Analysis of the sum of target lesion sizes in liver. The % change compared to baseline is plotted for each patient.

been completed. Instead some important preliminary findings will be shown. 23 patients were included. From nearly all patients the toxicity data were documented. From most of the patient the concentrations of sunitinib, its main metabolite SU12662 and various biomarkers (VEGF-A, sVEGFR-2, sVEGFR-3) were measured in plasma. In the majority of the patients DCE-MRI data were

taken, but not always four times as it was originally planned. Up to now, it was possible to evaluate the DCE-USI data in one sub-group of patients only. Three different sonographic machines in 3 different study sites were used. In order to perform a central evaluation of the raw data from the 4 participating centers with the software package Qontrast[®] from Bracco Inc., transformation of the video sequence in different formats (DICOM, AVI 1 and AVI 2) will need to be successfully completed.

Results

23 patients received up to 8 treatment cycles (median 4 treatment cycles). The toxicity was significant. Neutropenia, leukopenia, thrombocytopenia, infection, hand & foot syndrome, rash, diarrhea, stomatitis and anal fissure were observed and led to dose reduction of the drugs applied. In 18 patients DCE-MRI data were generated. iAUC₆₀ and Ktrans were decreasing in the majority of the patients but in some patients just the opposite was seen. In 18 patients the sum of the target lesion sizes were calculated by MRI. Here again the majority showed a decrease while in some patients an increase was observed (Figure 2). The final analysis will include the complete staging data (with CT scans). The DCE-USI (CEUS) data are currently not ready for analysis.

The pharmacokinetic data fit well to the PK evaluated in healthy volunteers [3]. Plasma concentrations of VEGF-A increased immediately after administration exhibiting a large inter-individual variability. Maximum

response of the soluble receptor levels was observed at the end of each cycle with concentrations of 52 – 94% (sVEGFR-2) and 32 – 96% (sVEGFR-3) of the respective baseline values. All biomarker levels returned to baseline after 2 weeks “off treatment” [4]. Correlation analyses between PK/PD and DCE-MRI, response or toxicity are ongoing.

Conclusions

This IIT was challenging for logistical reasons and included a broad translational research program. Thus far, the analysis showed that standardization of each step within the study and at each center is essential for success. The drug combination of FOLFIRI and sunitinib is a very effective regimen (2 patients underwent potentially curative hepatic surgery), nonetheless, it is more toxic than initially thought and known from literature. In the meantime, the Phase III study was stopped based on a recommendation of the Drug Safety Monitoring Board (DSMB), as no advantage in antitumor efficacy could be shown. It seems that toxicity was remarkable, similarly as in our study.

Although anti-angiogenic effects could clearly be seen, this drug combination is associated with remarkable toxicity. Addition of an inhibitor of VEGFR-TK either to FOLFOX or FOLFIRI in treatment of patients with mCRC is obviously a difficult task [5] as some prominent drugs failed in similar situations

Acknowledgment

The trial was supported by an IIT grant of Pfizer Inc.

References

- [1] Mross K. Angiogeneseinhibition in der Onkologie. Bremen: UniMed Science Verlag; 2007.
- [2] Starling N et al. A phase I study of sunitinib in combination with FOLFIRI chemotherapy in treatment-naïve, metastatic colorectal cancer. Poster presented at ASCO GI, Orlando, Florida, January 19 – 21, 2007.
- [3] Lindauer A et al. Pharmacokinetic/pharmacodynamic modelling of biomarker response to sunitinib in healthy volunteers. Clin Pharm Ther. 2010; 87: 601-608.
- [4] Kanefendt F, Lindauer A, Kinzig M, Strumberg D, Scheulen ME, Mross K, Fischer R, Moritz B, Sörgel F, Jaehde U. Biomarker response on exposure to sunitinib and its primary metabolite (SU12662) in metastatic colorectal cancer patients. Int J Clin Pharmacol Ther. 2011; 49: 88-90.
- [5] Hecht JR et al. A randomized, double-blind, placebo-controlled phase III study in patients with metastatic cancer receiving first-line chemotherapy with FOLFOX4 and PTK/ZK or placebo (CONFIRM-1). J Clin Oncol. 2005; 23: 3.