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Biomarker response on exposure to sunitinib and its primary metabolite (SU12662) in metastatic colorectal cancer patients*

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Key words

sunitinib – biomarker – colorectal cancer – VEGF – PK/PD modeling

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Objectives

Sunitinib is a multi-tyrosine kinase inhibitor and approved for metastatic renal cell carcinoma (mRCC) and imatinib-resistant gastrointestinal stromal tumors (GIST). Currently it is also being tested in metastatic colorectal cancer (mCRC) [1]. For sunitinib and other anti-angiogenic drugs, the potential of individualized dose adaptation based on pharmacokinetic parameters and biomarker measurements has not been explored yet since the understanding of the dose-exposure-effect relationship is still limited. It has been shown for healthy volunteers [2] as well as for cancer patients that sunitinib influences the plasma concentrations of various circulating proteins which can serve as biomarkers for its anti-angiogenic properties [3]. In this investigation plasma concentrations of the drug and its main metabolite, SU12662, and three biomarkers (VEGF-A, soluble VEGFR-2, and soluble VEGFR-3) were determined in mCRC patients within the CESAR C-II-005 study [see Mross et al., this issue, p. 96]. Based on these data, the changes in biomarker concentrations on exposure to sunitinib and its active metabolite SU12662 were investigated.

Patients and methods

23 patients with mCRC were enrolled into this prospective study. A daily dose of 37.5 mg of sunitinib was administered on a 4-week on/2-week off treatment schedule in addition to folinate, fluorouracil, and irinotecan (FOLFIRI) as first-line therapy. The dose was

reduced to 25 mg/day in case of toxicity. Samples were drawn at baseline and at seven pre-defined time-points during the Weeks 1, 3, 5, 7, 9, 11, and 13. Blood samples were taken prior to sunitinib administration to obtain drug trough concentrations. Plasma levels of sunitinib and SU12662 were determined by LC-MS/MS and those of VEGF-A, sVEGFR-2, and sVEGFR-3 using commercially available (R&D Systems, Minneapolis, USA) and previously validated immunoassays (unpublished data). Six patients were excluded from the analysis due to missing data. Plasma concentrations of the active drug and biomarker response were compared to a dataset previously obtained in healthy volunteers (n = 12) [2]. Furthermore, data were compared with corresponding predictions of appropriate pharmacokinetic/pharmacodynamic models previously developed for this healthy population. The two populations differed mainly in median age and BMI with 40.5 (range 27 – 54) years vs. 60 (range 33 – 75) years and 22.7 (range 20 – 26.7) kg/m² vs. 26.7 (range 19.3 – 39.9) kg/m², respectively. The ratio of male/female was 6/6 and 10/7 for healthy volunteers and mCRC patients, respectively.

Results and discussion

A total of 17 patients received 37.5 mg sunitinib daily during the first cycle. Only in one patient the dose reduced to 25 mg/day due to toxicity. Assuming a linear dose-concentration relationship [4] the drug concentrations were normalized to the dose given to

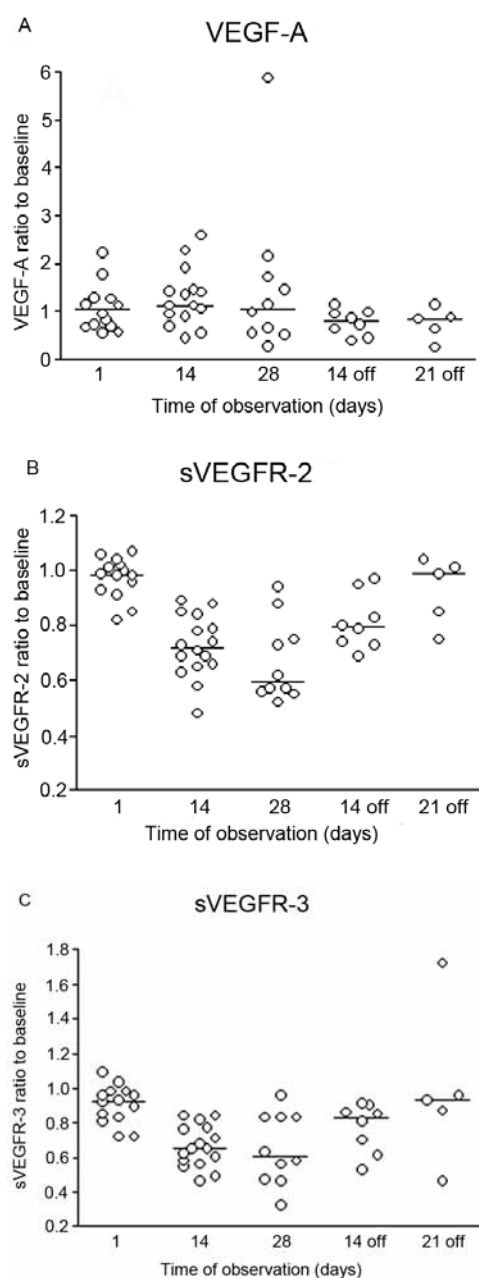


Figure 1. VEGF-A (A), sVEGFR-2 (B), and sVEGFR-3 (C) levels (relative to baseline) after a daily dose of 37.5 mg sunitinib on a 4-week on/2-week off schedule.

compare the results with those observed in healthy volunteers who received a daily dose of 50 mg sunitinib for 3 ($n = 4$) and 5 consecutive days ($n = 8$) [2]. After 1 day ‘on treatment’ median plasma concentrations of 12.40 (range 7.96 – 21.18) ng/ml and 3.14 (range 1.60 – 6.74) ng/ml were observed for sunitinib and SU12662 ($n = 14$), respectively, which were described satisfactorily by the predictions of the pharmacokinetic model, developed previously for healthy volunteers [2]. Maximum median concentrations were

observed after 4 weeks for sunitinib and after 2 weeks for SU12662 with 45.74 (range 18.83 – 52.67) ng/ml ($n = 16$) and 18.56 (range 7.18 – 40.29) ng/ml ($n = 10$), respectively. Median concentrations and their variability were comparable to the model predictions at all measured time-points. This is in contrast to a recently published meta-analysis on patients with other types of cancer (mainly metastatic renal cell carcinoma and GIST) where the tumor type was identified as a covariate for the CL/F of sunitinib and SU12662 [4].

VEGF-A concentrations exhibited large inter-individual variability with no significant changes in the median from baseline level (Figure 1A). The lack of a change in the median is in contrast to previous studies conducted in healthy volunteers [2] and cancer patients [3] where plasma concentrations of VEGF-A increased after drug administration. The reason for this difference remains unclear. Sample processing has been shown to have a large influence on the measured VEGF-A concentrations [5] and therefore the differences in handling of the samples in the four participating centers may have masked a potential pharmacological effect.

Maximum response of sVEGFR-2 and sVEGFR-3 was observed at the end of each cycle with concentrations of 52 – 94% and 32 – 96% of the corresponding baseline value, respectively (Figure 1B, C). All biomarker concentrations returned to baseline after two weeks ‘off treatment’. These observations were comparable to data previously published for various tumor types (mRCC, GIST, metastatic breast cancer, neuroendocrine tumor, mCRC) (1; 3; 6; 7). In comparison with the predictions of the PK/PD model developed for healthy volunteers, changes in the median of the soluble receptors relative to the baseline value tended to be greater in mCRC patients. Possible reasons for these observations, e.g. differences in treatment, treatment duration, and/or the influence of the tumor on biomarker response, as well as the effect of specific patient covariates (gender, age, weight etc.) on PK and PD will be further investigated.

Conclusions

Plasma concentrations of sunitinib and SU12662 seem to be comparable in mCRC patients and healthy volunteers when the differences in administered dose and treatment duration are considered. After one day ‘on treatment’ the prediction interval of the pharmacokinetic model previously developed for healthy volunteers describes the concentrations in mCRC patients satisfacto-

rily. With the exception of VEGF-A, changes in biomarker levels relative to the corresponding baseline value were comparable to data previously observed in cancer patients with other tumor types. The available PK/PD models will be further developed to provide the basis for a PK/biomarker-guided dosing strategy.

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