Research Highlight

The complexity of sunitinib dosing in renal cell cancer patients

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Sunitinib is an oral multityrosine kinase inhibitor, targeting - among others - vascular endothelial growth factor receptor (VEGFR) and platelet derived growth factor receptor (PDGFR). Sunitinib is one of the first so called targeted therapies which is approved as first line treatment for metastatic renal cell carcinoma (mRCC), and for second line in Gastro intestinal stromal tumors (GIST) and Pancreatic neuroendocrine tumors (PNET). Its introduction in 2006 introduced a new era in the treatment of mRCC, but also raised a lot of clinical relevant questions. One of these is which dosing schedule is most efficient with the lowest toxicicity and the best quality of life. The approved schedule for sunitinib is 50 mig oid in the so called "4 weeks on and two weeks off" (4/2 schedule). This is a remarkable schedule against the background of the Von Hipple Lindau (VHL) mutation induced overexpression of angiogenic vascular endothelial growth factor (VEGF) in clear cell RCC, which is the main target of sunitinib. Furthermore, in GIST it has been showed that during the two weeks off period the intratumoural metabolic activity as measured by FDG-PET can increase (1).

Motzer *et al*. addressed this question in The *Journal of Clinical Oncology* (2) by publishing a phase II randomised study comparing the approved daily 50 mg dose oid 4/2 schedule with a continuous daily dose (CDD) schedule of 37.5 mg oid in 292 treatment naïve clear cell mRCC patients. No significant difference in median time to progression (TTP, defined as time between random assignment and documented progression) or median progression free survival (PFS), median overall survival (OS) and objective response rate (ORR 4/2 *vs*. CDD; 32% *vs*. 28%) was found, although a trend towards a longer TTP in the 4/2 schedule patients was mentioned [9.9 *vs*. 7.1 months, Hazard Ratio (HR) 0.77, P=0.09].

Although randomisation was stratified according to their MSKCC risk category, more patients in the CDD group were classified as poor risk (14% *vs*. 8%), with worse clinical condition (Karnofsky score 70 12% *vs*. 3%) and presence of liver metastases (25% *vs*. 16%). Both univariable and multivariable analyses did not show independent relationships, although again a trend towards longer TTP was confirmed. Time to deterioration, one of the secondary endpoints assessed in a post hoc analysis, which was a composite endpoint of death, progression and self reported disease-related symptoms was longer with the 4/2 schedule than with the CDD schedule. (HR 0.77, P=0.034, median time to the composite end point 4.0 *vs*. 2.9 months). This secondary endpoint is not frequently reported and it's clinical relevance above the commonly reported endpoints as OS, PFS and quality of life is unclear. Since treatment with sunitinib and its analogues can be maintained for years, adequate treatment of adverse events and care for quality of life is essential. The self reported disease-related symptoms are interesting, but quality of life data are unfortunately missing.

Three other non-randomised phase II studies on continuous sunitinib dosing have been published, including more than three hundred patients in total (3-5). The ORR varied between 20-35%, median PFS from 8.2 to 13 months and median OS from 19.8 to 25 months, all comparable to the current study of Motzer *et al*. (2) and also to the keystone study of 4/2 sunitinib *vs*. interferon-α (ORR 31%, median PFS 11 months and med OS 26 months) (6,7). In conclusion, CDD or the 4/2 schedule do not really differ in terms of efficacy.

When no difference in efficacy can be claimed, perhaps a difference in safety and tolerability, or quality of life, can be a reason to have a preference for one of both

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schedules. However, the toxicity profile of both schedules was comparable as was the amount of patients who discontinued sunitinib because of adverse events (4/2 *vs*. CDD; 11% and 15%). Interesting to see is the high amount of patients needing drug interruptions (4/2 *vs*. CDD; 65% *vs*. 62% of which 29% and 13% for more than 7 days) or dose reductions (4/2 *vs*. CDD; 36% *vs*. 43%). The dose intensity was 91% in the 4/2 group and only 78% in the CDD group. Also interesting is the, clinically recognisable, pattern in self reported outcomes in the 4/2 group. Patients report rising amounts of adverse events during the 4 weeks on part of the schedule, and recovery during the 2 weeks off. In the other phase II CDD studies (3-5) 43-50% of the patients needed dose reductions and 10-16% of the patients discontinued treatment due to adverse events which is again comparable to the current Motzer study (2). In conclusion, no preference for either 4/2 or CDD can be given based on the reported toxicity in this study.

What should be also taken in account when trying to get the maximum benefit from sunitinib treatment? Houk *et al*. showed that higher exposure of sunitinib (measured as area under the curve during steady state, AUCss) significantly correlates with a higher probability of ORR and with longer TTP or OS, but also with increased risk of adverse events (8). Two frequently occurring adverse events of sunitinib, hypertension and hypothyroidism, are associated with better clinical outcome and suggested as efficacy biomarkers (9,10). In case of hypertension which needs multidrug treatment, a CDD schedule can be helpful in reaching a stable blood pressure, because the risk of hypotension within the 2 weeks of period, and the, sometimes big, changes in blood pressure. There is also a suggestion that a third adverse event, the hand foot syndrome (HFS) is a potential biomarker of efficacy. On the ASCO GU 2011 a retrospective study in 770 patients was presented, in which HFS was significantly and independently associated with improved ORR, PFS and OS (abstract 320).

Furthermore, in a subset of patients treated with sunitinib, a flare up syndrome occurs after discontinuation of treatment. This syndrome consists of tumour related complaints which can occur within days after stop of treatment (11,12). Reintroduction of even the same tyrosine kinase inhibitor can treat the flare up phenomenon. The pathobiology of the syndrome is not well understood. Patients in the 4/2 schedule can experience this flare up syndrome during the 2 weeks off period. These patients should turn over to a CDD schedule.

An alternative treatment strategy would be intrapatient dose escalation until reaching one of the clinical efficacy biomarkers, e.g., hypertension or hypothyroidism, for as far as tolerated. This would fit in the data of exposure - response relationship and the well known high interpatient variability of both treatment response as well as experienced toxicity. This strategy needs more research and pharmacokinetic as well as molecular imaging research may be helpful in this.

All together, this illustrates the complexity of adequate sunitinib treatment in individual patients. The choice for a 4/2 or CDD schedule has to be based on the individual patient. In terms of PFS or OS efficacy, no significant difference between the both schedules has been shown. The combination of the exposure related ORR chance results of Houk *et al*. and the somewhat lower ORR in part of the CDD phase II studies suggests that the 50 mg 4/2 schedule perhaps is better for the patient subset needing a rapid volume response, for example in case of obstruction, pain or neo-adjuvant treatment. On the other side, a CDD schedule can be more helpful in patients with severe hypertension or flare up syndrome after discontinuation.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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