mTOR inhibition in advanced renal cell carcinoma: which criteria should be used to evaluate therapeutic outcome?

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With the implementation of mammalian target of rapamycin (mTOR) inhibitors in the systemic treatment of advanced renal cell carcinoma (RCC), considerable progress has been made regarding survival time and quality of life (QoL) compared with the treatment options used earlier. The prognostic factors used and the diagnostic measures taken to evaluate the oncological outcome and QoL of affected patients have not been adapted to this development adequately. This study analyses the recent phase III mammalian target of rapamycin inhibition trials for patients with metastatic RCC focussing on parameters for measurement of efficacy and QoL. It emphasizes the importance of adequate evaluation criteria for survival and QoL, as achieved by quality adjusted-time without symptoms and toxicity, in the palliative setting of advanced RCC. *Anti-Cancer Drugs* **22:18–23 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Renal cell carcinoma (RCC) shows a rising incidence especially in the Western countries with an estimated 200 000 new cases per year and approximately 40 000 RCC-related deaths [1,2].

To date, the only systemic treatment option for metastatic RCC (mRCC) was immunotherapy, as mRCC usually does not respond to traditional chemotherapy and radiotherapy treatments [3]. Despite the limited response rates (10–20%) and the restriction of therapeutic efficacy to patients with favourable prognostic factors, interferon-α (IFNα) and interleukin-2 represented the mainstay of treatment for patients with mRCC [4,5].

The increasing knowledge of RCC pathobiology on the cellular and molecular levels has led to the development of a number of new therapies. One promising strategy, the inhibition of the mammalian target of rapamycin (mTOR), a central element of the intracellular signalling pathway regulating metabolism, growth, proliferation and angiogenesis in RCC, shows growing evidence for the effectiveness in the treatment of mRCC in clinical settings [6].

Another major aim besides prolonged overall survival (OS) is the improvement of the quality of life (QoL) especially in the palliative setting [7,8].

With the implementation of mTOR inhibitors in the systemic treatment of advanced RCC, considerable progress has been made regarding survival time and QoL compared with the treatment options used earlier [9]. However, clinical benefit with regard to OS and the maintenance or improvement of cancer- and therapy-related QoL is limited to selected patients only [10]. It is, therefore, critical that the evaluation criteria in clinical trials are obligatory to focus on the patient's major individual needs such as OS time and QoL.

On the basis of this, the objective of this study is to first provide an insight into the commonly used evaluation criteria for oncological treatment in RCC, and second to critically analyse the methods used in the recent phase III mTOR inhibition studies for patients with mRCC, by which the oncological outcome (efficacy) and patients' QoL had been defined. Finally, the results of the phase III trial analyses will be discussed with particular focus on the evaluation criteria that concentrate on the OS and QoL.

Evaluation criteria in oncology

Efficacy/oncological outcome

In the past, direct therapeutic efficacy of anticancer treatment has been monitored through successive clinical and radiological evaluations of the size of tumour lesions. Nowadays, the evaluation of treatment response is integrated into the daily practice of every oncologist. It is also used in the investigational setting to define the antitumour activity of new anticancer treatments. Moreover, the level of anticancer activity is also associated with other indicators to document the therapeutic efficacy (clinical benefit) provided to the patients [11,12].

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The progress in cancer imaging, the importance given to the response rate endpoint and the growing number of novel agents have been other factors demanding a coordinated effort to revisit, update and possibly improve the existing criteria. Since 2000, the evaluation criteria have been summarized and implemented in the scientific world as the so-called Response Evaluation Criteria In Solid Tumours (RECIST) [13].

Quality of life

Together with the OS of oncological patients, the most important therapeutic objective is to maintain or improve the patient's QoL in clinical practice and trials [14]. Therefore, validated questionnaires have been designed to give an objective general insight into the impact of antitumour treatment on patients, evaluating the psychological, social and physical conditions of patients under therapy [15,16].

To more precisely determine the QoL of a patient with regard to his health status, excluding others factors such as secure social and occupational environment, financial security, spirituality, self-confidence and strong, supportive relationships, modified questionnaires have been introduced to assess health-related QoL (HRQoL).

Time without symptoms and toxicity/quality adjusted-time without symptoms and toxicity

Patients undergoing treatment for malignant diseases can be negatively affected by tumour symptoms or by adverse events (AEs) caused by the oncological treatment. Time without symptoms and toxicity (TWiST) is defined as the time interval during which patients, before disease progression (PROG), neither suffer from cancer-related symptoms nor from therapy-related toxicities (TOXs).

To give weight to the individual perception of the importance of each health state (TOX, TWiST, PROG), a more patient-centred modification of TWiST was developed: the quality-related-TWiST (Q-TwiST).

Q-TWiST is a utility measure that finds its application in the evaluation of the trade-off between treatment TOX and time-dependent clinical outcome of different oncological therapies. Therefore, it represents an instrument that integrates the quality and quantity of life and states an approach to assess the relative impact of a certain treatment on the patient's life. Thus, evaluating the combination of HRQoL and survival time in different health states, Q-TWiST is reported to be an adequate measure for the estimation of oncological efficacy and influence of anticancer substances on the patients' QoL [17,18].

Temsirolimus: phase III trial in metastatic renal cell carcinoma [19]

Oncological outcome/efficacy

In an international, multicentric phase III trial, 626 systemically untreated patients with advanced RCC and poor prognosis were randomized to receive TEMSR (25 mg intravenously weekly), IFN (3×3–18 million units weekly) or the combination of IFN (3×3–6 million units weekly) and TEMSR at a lower dosage (15 mg intravenously weekly). The primary endpoint of the study was the OS, and secondary endpoints included PROG-free survival (PFS), objective response rate and clinical benefit defined as stable disease (SD) or regression of the tumour over at least 24 weeks. Time to treatment failure and tolerance of therapy were assessed as well.

TEMSR showed a significant prolongation of PFS and OS compared with IFN monotherapy. Patients randomized to TEMSR showed an improved PFS of 3.8 versus 1.9 months in the IFN group (5.5 vs. 3.1 months after independent evaluation, $P < 0.001$) and OS was significantly longer (10.9 vs. 7.3 months, $P = 0.008$) for TEMSR compared with IFN. The advantage of TEMSR with regard to PFS and OS proved to be consistent for almost all enrolled patients independent from patient features that could have had an influence on treatment success. This was verified in subgroup analyses, taking into consideration variables other than the inclusion criteria.

Quality of life [20]

QoL was a predefined endpoint of the phase III trial. The assessment of QoL was carried out by applying the EurQoL-5D (EQ-5D) questionnaire, an instrument that is commonly recognised as a validated tool for the estimation of HRQoL in diverse health states. In addition, quality-adjusted survival was identified by the Q-TWiST method. All enrolled patients ($n = 626$) were available for the calculation of health state durations.

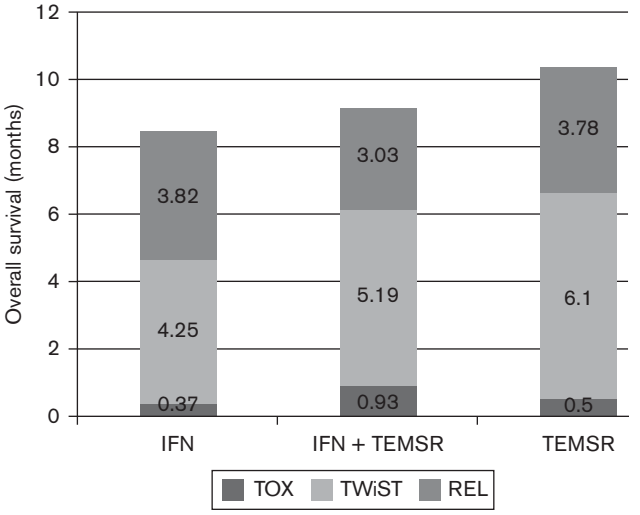
To monitor QoL in the course of the study, EQ-5D was completed at baseline, 12 and 32 weeks, at occurrence of any grade III/IV AE, at the time of disease PROG or at withdrawal from the trial. The return rate of EQ-5D was 96% (601 of the 626 patients) at baseline, 87% (260 of the 300 patients) at PROG and 40% (230 of the 570 patients) at incidence of grade III/IV AEs.

At baseline, the treatment groups (TEMSR vs. IFN vs. TEMSR + IFN) showed no difference in the median utility values based on the EQ-5D (0.689 vs. 0.656 vs. 0.689, respectively).

Furthermore, the patients' utility/preference values regarding the various health states (TOX, TWiST, PROG) were determined by the EQ-5D analysis at baseline. In all the treatment groups, the EQ-5D score for TWiST was consistent with the baseline score (0.689), whereas the scores for TOX and PROG were lower (0.585 and 0.587, respectively).

The distribution of the OS of the patients into the three health states across all the treatment groups is shown in Fig. 1.

Fig. 1



Distribution of overall survival (OS) into three health states across the treatment groups [mean OS 8.89 months interferon (IFN), 10.78 time without symptoms or toxicity (TEMSR), 9.41 (IFN + TEMSR)].

Thus, the time spent with therapy-related TOX was comparable in the IFN arm and TEMSR arm (0.37 vs. 0.5 months) and increased in the combination arm (0.93 months). Survival time with progressive disease was similar in the monotherapy groups (IFN 3.82 vs. TEMSR 3.78 months). In the combination group, life in PROG was shorter (3.03 months). With regard to TWiST, the time span was significantly longer in the TEMSR arm (6.5 months) compared with IFN-monotherapy ($P = 0.00048$) or in combination with TESMR (4.7 and 5.4 months, respectively; $P = 0.1288$). According to the investigators, the additional 1.9 months of OS (10.78–8.89) for the TEMSR group versus the IFN group were mostly accounted for by the difference in TWiST.

The evaluation of Q-TWiST showed an improved survival time in this quality-adjusted health state with a significantly longer Q-TWiST for TEMSR alone compared with IFN alone (7 vs. 5.7 months; $P = 0.0015$), whereas there was no advantage for Q-TWiST between IFN alone and IFN + TEMSR (5.7 vs. 6.1 months; $P = 0.3469$).

Everolimus (RAD-001): phase III trial in metastatic renal cell carcinoma [21]

Oncological outcome/efficacy

In a phase III trial, 410 patients with advanced RCC and tumour PROG after systemic treatment with sunitinib, sorafenib or both were randomised in a 2 : 1 ratio to receive the orally applicable mTOR inhibitor everolimus ($n = 272$; 10 mg once daily) or placebo ($n = 138$). PROG-free survival was defined as the primary endpoint of the study, diagnosed according to the RECIST criteria and assessed by a blinded, independent central review. Secondary endpoints included safety, objective tumour response rate, OS, disease-related symptoms and QoL. The termination of the study was planned to be executed after 290 cases of tumour PROG. The stratification of the enrolled patients followed the Memorial Sloan-Kettering Cancer Centre (MSKCC) prognostic score (favourable vs. intermediate vs. poor) and earlier oncological treatment (one vs. two tyrosine kinase inhibitors).

The results of an interim analysis showed an unexpected response to everolimus. Therefore, the study was interrupted ahead of schedule after 191 cases of PROG. At this point, progressive disease was observed in 37% of the patients in the everolimus arm compared with 65% in the placebo arm [hazard ratio: 0.3; 95% confidence interval (CI): 0.22–0.4; $P < 0.0001$]. The median time to PROG in the everolimus arm was 4 (95% CI: 3.7–5.5) compared with 1.9 months (95% CI: 1.8–1.9) in the placebo arm. On account of the crossover from placebo to everolimus, an estimation of OS remains impossible.

Quality of life

AEs were seen at a distinctively higher rate in the treatment arm with everolimus than the placebo arm. This observation was consistent for all the AE grades (NCI-CTC grade I–IV), the relation of AEs greater than or equal to grade III/IV was 10 : 1 for everolimus. The AEs for RAD-001 and placebo are listed in Table 1. QoL was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30. It is reported to be sustained in the treatment group compared with the control group despite the described incidence of TOXs in the everolimus arm.

Discussion

There is no doubt that patients affected by advanced oncological disease primarily express their basic desire to reach a maximum survival in an optimal way. This includes their wish to maintain or possibly improve the QoL, which can be impaired by cancer-related symptoms or treatment-associated TOXs. Related to these patients' requests, in accordance with the physicians' Hippocratic Oath and on account of the changes in treatment modalities as well, a critical reflection of the evaluation criteria for the assessment of the efficacy of anticancer treatment and its impact on the QoL of the concerned patients, therefore, seems to be a must for each physician involved in clinical trials and in daily practice.

Temsirolimus: phase III trial in metastatic renal cell carcinoma

Hudes *et al.* [19] showed that a weekly administration of TEMSR monotherapy is effective in prolonging median PFS and OS in patients with advanced RCC and poor prognosis compared with IFN or IFN + TEMSR. Moreover, patients treated with TEMSR alone showed a significantly improved HRQoL measured by the EQ-5D questionnaire. Yang *et al.* [22] recently published that

Table 1 Comparison of adverse events (all grades, grade III/IV) in the treatment arm (everolimus) vs. the control arm (placebo)

	Everolimus ($n=269$)			Placebo ($n=135$)		
Adverse events	All grades (%)	Grade III (%)	Grade IV	All grades	Grade III	Grade IV
Stomatitis	107 (40)	9 (3)	0	11 (8%)	0	0
Rash	66 (25)	2 (<1)	0	6 (4%)	0	0
Fatigue	53 (20)	8 (3)	0	22 (16%)	1 (<1%)	0
Asthenia	48 (18)	4 (1)	0	11 (8%)	1 (<1%)	0
Pneumonitis	22 (8)	8 (3)	0	0	0	0
Anaemia	244 (91)	24 (9)	1 (<1%)	103 (76%)	7 (5%)	0
Hypercholesterolaemia	205 (76)	9 (3)	0	43 (32%)	0	0
Hypertriglyceridaemia	191 (71)	2 (<1)	0	41 (30%)	0	0
Hyperglycaemia	135 (50)	31 (12)	0	31 (23%)	2 (1%)	0
Lymphopenia	114 (42)	38 (14)	4 (1%)	39 (29%)	0	0
Hypophasphataemia	87 (32)	12 (4)	0	9 (7%)	0	0

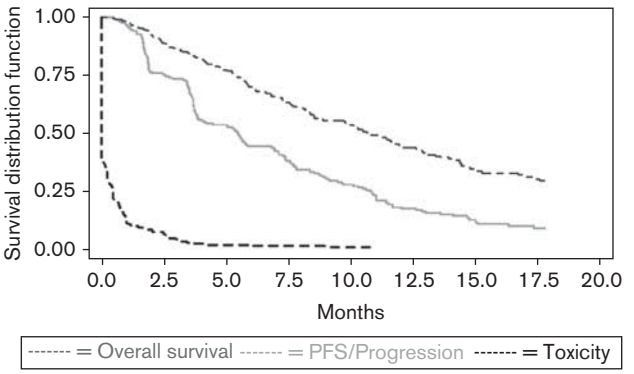
TEMSR is associated with significantly higher EQ-5D scores compared with IFN monotherapy in patients with untreated mRCC and poor prognosis.

In addition, the survival time of the patients was quality adjusted and diagnosed by the Q-TWiST method. In accordance with these results, patients with TEMSR alone experience a significant benefit with regard to OS, which is characterised by a significantly longer quality-adjusted TWiST compared with IFN alone. With the application of TEMSR as a monotherapy, the basic desires of the patients are met in this study, and the efficacy and tolerance have objectively been proved.

At the European Association of Urology Annual Meeting in 2009, Otto *et al.* presented data, originally reported by Mallick, indicating that the clinical status of patients with TEMSR therapy is decisive in predicting the QoL and its influence on life expectancy (Fig. 2). Using the Q-TWiST analysis for the evaluation of the health status TOX, PROG (progression after PFS) and TWiST, they found that patients presenting with the longest TWiST (no TOX, no symptoms) reported the best QoL. Moreover, these patients showed prolonged survival time compared with those experiencing early treatment TOX or cancer-related symptoms of PROG. Prolonged survival was mainly characterised by improved QoL [20]. In the much-awaited recent publication of the original data which were presented at the American Society of Clinical Oncology in 2007, these data have finally been published because of their great importance emphasizing the value of QoL in mRCC patients. Zbrozek *et al.* [23] point out that TEMSR monotherapy resulted in significantly longer Q-TWiST in patients with mRCC than in the IFNα treatment group.

Although affected by the less-controlled sources, yet nevertheless representing the important unique experiences in daily oncological practice – as claimed by Bellmunt and Guix [24] for the completion of recent anticancer treatment guidelines – TEMSR was shown to be well tolerated with regard to AEs in unselected patients with mRCC in a compassionate use programme [25,26].

Fig. 2



Time without symptoms or toxicity (TWiST): difference between progression-free survival (PFS) and time in toxicity.

Everolimus: phase III trial in metastatic renal cell carcinoma

Everolimus has been shown to improve PFS in patients with RCC compared with placebo in a second-line setting. On account of the crossover of patients from the placebo to the treatment arm, a statement regarding the impact of RAD-001 on OS cannot be made.

Whenever it is impossible to determine OS for any reason, it is even more essential to consider QoL so as to not worsen the remaining lifetime of the oncological patients by treatment measures. Motzer *et al.* specified a number of AEs related with everolimus in their placebo-controlled study. Drug TOX led to treatment discontinuation in 10% of the patients receiving everolimus, 34% of patients in the treatment arm required dose interruption and 5% required dose reduction. According to the investigators, the QoL under everolimus, compared with placebo, was maintained despite the more frequent incidence of AEs including all grades in the everolimus group, postulating no significant difference in the symptom scales of the European Organization for Research and Treatment of Cancer Quality of Life

Questionnaire-C30 used for comparing treatment and control [21]. The fact that the data verifying these results are yet to be published needs to be criticised.

Role of the Response Evaluation Criteria In Solid Tumours

Strikingly, mTOR inhibition studies showed a discrepancy between the tumour response rate measured by the RECIST criteria and clinical benefit in terms of life prolongation (PFS, OS). Hudes *et al.* [19] reported a negligible objective response rate (complete remission and partial remission) of 8.6%, but an OS prolonged by 49% and PFS by 77% both when compared with IFN alone. According to the results of a randomised phase II study investigating the efficacy and safety of TEMSR at different dosages in patients with advanced RCC, Atkins *et al.* reported a prolongation of PFS and OS compared with historical patient cohorts.

However, an influence on the objective tumour response rate (7% complete remission and partial remission) could not be shown [27]. This underlines the fact that the benefit from a therapy using mTOR inhibitors is based on the stabilisation of the disease rather than a cytotoxic effect decreasing the tumour burden, leading to SD secondary to unchanged tumour parameters [28].

The efficacy of anticancer treatment is commonly assessed using the RECIST criteria that document radiological changes in selected tumour lesions. So far, mTOR inhibition draws its main effect from tumour stabilization (SD), while leading to a significant OS and QoL benefit for patients with advanced RCC. Therefore, the RECIST criteria should play a minor role in the follow-up and monitoring of patients with advanced RCC treated with mTOR inhibitors. In contrast, for the evaluation of survival and QoL, clinical assessment, including TOX, TWiST/Q-TWiST and symptoms of PROG, should take the leading role in reasonably guiding patients with advanced RCC. In such a scenario, studies designed to measure the decrease of tumour masses as a sign of response to oncological therapy by positron emission tomography seem to contradict the objectives of patient-centred oncological management.

Stratification of patients in the era of novel therapies

Among others, the introduction of mTOR inhibitors has led to an emerging need to stratify patients according to tumour histology and risk of PROG (prognostic factors) and to introduce these patients to the most appropriate treatment available because of individual features (selection criteria).

The selection criteria for a distinct therapy that will lead to an ideal survival of the patient and the prognostic factors that will predict an optimal tumour response to treatment still remain unclear.

Recently, Baltaci [29] pointed out that despite common acceptance in the urological and oncological communities, the stratification of risk groups in RCC, which was introduced in 1999 and slightly modified in 2002 by Motzer *et al.*, is based on the experiences with immunotherapy trials and does not keep up with the development of novel targeted therapies, thus not taking into account the newly discovered factors such as tumour grade, stage, histological subtype and pathological/molecular tumour characteristics. Although guidelines and therapy algorithms for the systemic treatment of mRCC have already been established helping to facilitate the physicians' decision making [30], the inhomogeneous landscape of randomised controlled trials regarding the individual study designs has led to incomparableness of these trials investigating novel agents in cancer patients [24]. In addition, in this context, the clinical criteria for the evaluation of survival and QoL seem to be the most appropriate measure for the moment, as newly determined prognostic factors on the molecular level evaluating targeted therapies are still missing.

Conclusion

Through the inhomogeneous implementation of mTOR inhibitors in different settings (first-line vs. second-line; good vs. intermediate vs. poor risk, etc.) in randomised controlled trials, the search for a valid prognostic and QoL criteria has been complicated.

Despite the interesting discoveries and the unresolved questions, it is mandatory to focus on the patient's requests, that is, to reach a maximum OS and minimum treatment-related TOX (or optimum QoL) in a palliative setting.

Hudes *et al.* have shown that TEMSR alone compared with IFN alone fulfils these requirements in patients with mRCC and poor prognosis. Results from the study of Motzer *et al.* investigating everolimus lack information on OS and QoL and, therefore, cannot be recommended without limitations.

The introduction of mTOR inhibitors (among others) for patients with advanced RCC has led to the rapid use of TEMSR and everolimus in clinical trials and in clinical practice. The prognostic factors used and the diagnostic measures taken to evaluate the oncological outcome and QoL of the affected patients have not been adapted to this development adequately. The algorithm proposed by Parasuraman *et al.*, taking into consideration the clinical characteristics combined with the health state durations (measured by the Q-TWiST method), momentarily seems to be the most appropriate way to assess the prognosis and QoL of mRCC patients, and should therefore primarily be considered for the therapeutic management of patients with advanced RCC.

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