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Management of toxicity in patients treated with tyrosine kinase inhibitors (TKI)

Emanuele Naglieri

Oncology Department, I.R.C.C.S. Oncology Institute of Bari, Italy

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ABSTRACT

The landscape of the treatment of metastatic renal cell carcinoma (RCC) has changed dramatically in the last two years. The most promising agents developed and tested were small molecule tyrosine kinase inhibitors, mammalian target of rapamycin inhibitors and monoclonal antibodies. Indeed, when compared to IFN-α, first-line therapy with Sunitinib, Bevacizumab and Temsirolimus showed an improvement of both progression free survival (PFS) and survival.

The occurrence and severity of side effects differ between these agents and may define the choice of the best drug to use in the first line therapy with a model of tailoring therapy.

The adverse events considered to be most important in routine clinical practice are dermatological toxicities, gastro-intestinal symptoms, stomatitis, hypertension and other cardiovascular toxicities, haematological toxicity, fatigue and fatigue-causing side effects including metabolic changes.

We have analyzed and compared the most frequently observed toxicities of these novel agents in the attempt to obtain an help in the decision making of the best therapy.

Altogether, side effects of targeted agents appear manageable and reversible. Discontinuation of treatment due to toxicity is rare. Despite side effects, these novel agents signify an important step forward.

Renal cell carcinoma (RCC) is a neoplasm highly resistant to both chemotherapy and radiotherapy.[1] Interleukin-2 and interferon-α have limited efficacy and are associated with considerable toxic effects.[2] In the last 2 years, four targeted agents were approved for the treatment of advanced renal cell carcinoma which are changing dramatically the landscape of the treatment of this pathology. Indeed, when compared to IFN-α, first-line therapy with sunitinib, bevacizumab and temsirolimus has shown an improvement of both progression-free survival (PFS) and survival.

Sunitinib was the first of a new class of drugs to demonstrate significantly greater efficacy than IFN-α in advanced RCC. Sunitinib is an orally active inhibitor of tyrosine kinases (TKI) including vascular endothelial growth factor receptor and platelet-derived growth factor receptor. These receptor tyrosine kinases play a role in the pathogenesis of clear-cell carcinoma and therefore are the optimal targets in the treatment of this neoplasm. In a phase III randomised multicentre, international trial, patients were treated with either 50 mg once daily in cycles of 4 weeks with 2 weeks of rest or 9 MIU of IFN-α 3 times per week until disease progression or study withdrawal.[3] Primary end-point was PFS and secondary end-points included objective response rate, overall survival (OS) and safety. PFS was 11 months for patients treated with sunitinib and 5 months for those treated with IFN-α ($p < .000001$) with a 58% reduction of the risk of progression or death. The objective response rates were 28% and 5%, respectively. The most common adverse events are listed in

E-mail address: e.naglieri@oncologico.bari.it
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Table 1 – Adverse events in patients treated with sunitinib

Adverse event	All grade (%)	Grade 3 (%)	Grade 4 (%)
Diarrhea	53	5	0
Fatigue	51	7	0
Nausea	44	3	0
Stomatitis	25	1	0
Vomiting	24	4	0
Hypertension	24	8	0
Hand–foot syndrome	20	5	0
Mucosal inflammation	20	2	0
rash	19	1	1
Asthenia	17	4	0
Dry skin	16	1	0
Skin discoloration	16	0	0
Changes in hair colour	14	0	0
Epistaxis	12	1	0
headache	11	1	0
Decline in ejection fraction	10	2	0
Pyrexia	7	1	0
Chills	6	1	0
Leukopaenia	78	5	0
Neutropaenia	72	11	0
Anemia	71	3	1
Thrombocytopaenia	65	8	0
Increased aspartate aminotransferase	52	2	0
hypotiroidism	71	0	0

Table 1. They were generally moderate and regressed with suspending the therapy. A total of 38% of sunitinib group had a dose interruption because of adverse events, whereas 32% had a dose reduction.

Bevacizumab is an anti-vascular endothelial growth factor recombinant humanised monoclonal antibody that has shown efficacy in first-line therapy of metastatic RCC. The efficacy of bevacizumab in combination with IFN-a as first-line therapy in metastatic RCC has been compared with that of IFN-a in two randomised Multicentre phase III trials: the first was conducted mainly in Europe (AVOREN)[4] and the latter in the United States (US) (CALGB 90206).[5] Treatment regimens in the two studies were similar. All patients received subcutaneous IFN-α 9 MIU three times weekly until disease progression or unacceptable toxicity (or for a maximum of 52 weeks). Those in the bevacizumab arm of each trial also received intravenous bevacizumab 10 mg/kg every 2 weeks until disease progression or unacceptable toxicity. In AVOREN study, the median duration of IFN-α in the bevacizumab arm was 7.8 months (dose intensity 91%). The primary end-point in both trials was overall survival; secondary end-points included progression-free survival and objective response rates. The combination resulted in a median PFS that was significantly longer than that seen with IFN-α: 10.2 versus 5.4 months in the AVOREN study and 8.5 versus 5.2 months in the CALGB 90206 study. Data for overall survival in both studies have not yet matured.[6,7] The addition of bevacizumab to IFN-α in the AVOREN study was generally well tolerated, and the adverse events are listed in Table 2. During the course of AVOREN, the IFN-α dosage was reduced from 9 to 6 or 3 MIU three times weekly in 41% of the association compared with 30% of the IFN arm. Dose reduction seem do not compromise the efficacy of the combination therapy.

Adverse events occurred in 97% of the combination recipients and 94% of IFN-α recipients in AVOREN. The corresponding incidences of serious adverse events were 29% and 16%. Bevacizumab-associated toxicities were generally mild in intensity. The most common grades 3–4 adverse events in AVOREN study were fatigue and asthenia. Severe adverse events were reported by 79% of the combination arm in CALGB study compared with 61% when IFN was administered alone. An approximately 4-fold reduction in incidence of grades 3–4 adverse events in the 6-week period after dose reduction compared with the 6-week period before dose reduction was observed both in bevacizumab plus IFN-α recipients (8% versus 28%) an placebo plus IFN-α (7% versus 29%) who reduced their IFN dosage during the course of treatment in AVOREN. The discontinuation rate due to adverse events was 28% in the association arm versus 12% in the IFN-α arm. For three bevacizumab recipients in AVOREN, the cause of death was deemed possibly related to the study drug (two haemorrhage events and one GI perforation).

Therefore, at present we have two regimens available for the first line of metastatic RCC with either good or intermediate prognosis. The occurrence and severity of side-effects differ between these agents and may define the choice of the best drug to use in the first-line therapy with a model of tailoring therapy.

For patients with poor prognosis the best treatment is temsirolimus. Temsirolimus is an inhibitor of mammalian target of rapamycin (mTOR) kinase, a component of intracellular signalling pathways involved in the growth and proliferation of cells[8,9] and the response of such cells to hypoxic stress.[10] The inhibition of angiogenesis by temsirolimus is clinically relevant because unregulated angiogenesis is prominent in RCC. In a phase III randomised trial, temsirolimus was compared with both IFN- and the association between the two drugs.[11] Temsirolimus was administered intrave-

Table 2 – Adverse events in patients treated with association between bevacizumab and interferon-alpha

Adverse event	All grade (%)	Grades 3 and 4 (%)
Diarrhea	20	2
Fatigue	33	12
Nausea	28	0
Stomatitis	30	0
Vomiting	14	0
Hypertension	26	3
Hand–foot syndrome	0	0
rash	0	0
Skin discoloration	0	0
bleeding	33	3
Decline in ejection fraction	1	0
Arterial embolism	1	0
Venous embolism	3	0
Neutropaenia	7	2
Anemia	10	3
Thrombocytopaenia	8	2
Proteinuria	18	0
Hypotiroidism	0	0

nously at 25 mg weekly until progression or unacceptable toxicity. Patients who received temsirolimus alone had longer overall survival (HR for death 0.73; $p = 0.008$) and PFS ($p = 0.001$) than did patients who received IFN alone. Overall survival in the combination arm did not differed significantly from that in the interferon group. Median overall survival times in the IFN group, the temsirolimus group and the combination therapy group were 7.3, 10.9 and 8.4 months, respectively. Adverse events occurred in at least 20% of patients in any group. Grade 3 or 4 asthenia was reported in 11% of patients in temsirolimus group and in 28% of those in combination group. As compared with patients in the IFN group, mild to moderate rush, peripheral oedema and stomatitis affected more patients who received temsirolimus either alone or in combination with IFN.

Another important tyrosine kinase inhibitor is sorafenib. Sorafenib is an orally active multikinase inhibitor with effects on tumour cell proliferation and tumour angiogenesis. In a phase III randomised, double-blind, placebo-controlled trial (TARGET)[12] sorafenib showed an improvement of PFS in patients with advanced clear-cell RCC in whom previous therapy had failed; median PFS of sorafenib group was 5.5 months compared with 2.8 months of the placebo group.

Diarrhoea, rash, fatigue and hand–foot skin reactions were the most common adverse events associated with sorafenib. Adverse events were mainly of grade 1 or 2, and are listed in Table 3. The proportion of patients who discontinued the study drug owing to adverse events was similar in the two groups (10% in the sorafenib group and 8% in the placebo group) and discontinuation was mostly due to constitutional, gastro-intestinal or pulmonary-upper respiratory tract symptoms. In the sorafenib group doses were reduced in 13 of patients and were interrupted in 21% of patients (mainly due to dermatologic and gastro-intestinal events). The median duration of these interruption was 7 d. Hypertension and cardiac ischaemia were rare but serious adverse events that were more common in patients receiving sorafenib than in those receiving placebo. Cardiac ischaemia or infarction occurred in 12 patients in the sorafenib group (3%). Of these events, 11 (including 2 deaths) were considered to be serious adverse events associated with treatment. Bleeding was seen in 15% of patients. Febrile neutropaenia or grade 4 thrombocytopaenia did not occur.

Table 3 – Adverse events in patients treated with sorafenib (TARGET)

Adverse event	All grade (%)	Grades 3 and 4 (%)
Diarrhea	43	2
Fatigue	37	5
Nausea	23	1
Stomatitis	21	6
Vomiting	16	1
Hypertension	17	4
Hand–foot syndrome	30	6
rash	40	1
Skin discoloration	0	0
bleeding	15	2
Cardiac ischaemia	3	3
Arterial embolism	0	0
Venous embolism	0	0
Neutropaenia	18	5
Anemia	8	3
Thrombocytopaenia	12	1
Proteinuria	0	0
Hypotiroidism	0	0

So far we have four new drugs for RCC. Side-effects may be related to the different targets of the single agents. Indeed bevacizumab side-effects are related to single target-specific VEGF. On the contrary, both sunitinib and sorafenib have multi-targeted-potential for non VEGF related toxicity.

The adverse events considered to be most important in routine clinical practice are dermatological toxicities, gastrointestinal symptoms, stomatitis, hypertension and other cardiovascular toxicities, haematological toxicity, fatigue and fatigue-causing side-effects including metabolic changes.

The dermatological toxicities affect mainly hands and feet predominantly on pressure points with dysaesthesia, paraesthesia, erithema, callus-like blisters and desquamation. These aspects are different from the hand–foot syndrome observed with chemotherapy. For grades 1–2 toxicity it is recommended to continue at same dose level with supportive measures. At the first occurrence of grade 3 toxicity, it is necessary to interrupt the treatment until recovery to grades 0–1 resuming the therapy at reduced doses, and subsequently increase to full doses adding supportive measures. At the second occurrence of grade 3 toxicity it is mandatory to interrupt the treatment until recovery, starting and maintaining the reduced doses in the next cycles. Skin toxicities are never life-threatening and are always reversible, may affect patient's daily life and require a close cooperation with dermatologists.

Diarrhoea is another important event bound to TKIs therapy. Treatment should start at very first signs and patient should be advised to take loperamide regularly following a special diet including bananas, rice and potatoes.

The management of cardiovascular side-effects with TKIs is more complex. It is manageable if the patient's blood pressure is regularly checked. Treatment interruption or dose reduction should not be necessary. Blood pressure measurements must be performed daily during the first 3 months of treatment. The choice of the antihypertensive medication depends on general cardiovascular status of the patient and is individualised for each patient.

The cardiac side-effects are observed so far predominantly in patients with TKIs. The relationship to TKIs treatment is unclear but likely in previously asymptomatic patients. The possible mechanism is the inhibition of HIF accumulation by TKI treatment. Side-effects may vary from the reduction of left ventricular ejection fraction to myocardial infarction. Before treatment, it is mandatory to evaluate the cardiac function with both ECG and echocardiography. During treatment an ECG must be repeated monthly and an echocardiography every 2–3 months. At the occurrence of cardiac symptoms it is necessary to interrupt TKI treatment, treat patients according to the findings and after recovery, resume treatment based on toxicity grade.

Cancer-related fatigue is a distressing, persistent, subjective sense of tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning. Hypotyroidism may be an

underlying cause of fatigue in TKI-treated patients. Thyroid function should be controlled prior to treatment and at regular intervals. Thyroid replacement therapy should be started at first increase of TSH.

Haematological toxicities occur mostly at grades 1–2 and are completely reversible. Intermittent treatment interruption or dose reduction may be required. Both anaemia and lymphopaenia do not require dose reduction. Complete blood counts should be taken before each treatment cycle and on day 14 of the first 3 months of treatment.

In conclusion, side-effects of targeted agents appear manageable and reversible. Discontinuation of treatment due to toxicity is rare. Despite side-effects, these novel agents signify an important step forward.

Conflict of interest statement

None declared.

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