The treating scenario in genitourinary oncology: what is new? Part 2

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The objectives of this innovative meeting were to discuss developments in the management of genitourinary cancer worldwide and how Italian clinicians could harness these innovations in their everyday practice. The 2-day meeting was divided into two sessions covering kidney and prostate cancer, and a large part was given over to the presentation and discussion of new recently presented data at major international congresses in 2012. There were no restrictions on content and all subjects from pathology, surgery and genetics to therapy and patient outcomes were covered.

Conference Scene

Future Oncology

Top two abstracts presented at international meetings in 2012

Attendees at the meeting voted for the top two abstracts, which were coincidentally both by Robert Motzer (Memorial Sloan–Kettering Cancer Center, NY, USA) – on the TIVO-1 and the COMPARZ trials. Interestingly, both abstracts were reports of Phase III trials of targeted therapies showing that, although the back-to-basics approach is gathering strength, physicians are interested in information on new products and how they compare with existing agents used as first-line therapy and/or sequentially. Although there are many new therapeutic options now available, there is clearly an unmet medical need in metastatic renal cell carcinoma (RCC). While not in the top two abstracts, the PISCES study – the first patient-oriented study in RCC – was highly rated. PISCES considered how patients feel when they take a drug over many months – a factor that traditional adverse event reporting does not reflect. The general feedback was that, although PISCES opened the door for other studies, the methodology needs to be revisited. In ‘real-world’ medicine, patients feel more able to have open and free discussions about their treatment and symptoms with nurses rather

than physicians (despite their best efforts) and this needs to be recognized when designing patient-oriented studies.

RCC: selecting first-line therapy

Having listened to state-of-the-art lectures and new developments from international congresses, the next piece in the therapeutic jigsaw was to open the discussion to practicing clinicians and their opinions on how best to manage patients with RCC. Giuseppe Di Lorenzo (University Federico II, Naples, Italy) put forward the case for selecting first-line therapy in favor of less toxicity, while Cezary Szczylic (Military Institute of Health, Warsaw, Poland) discussed the evidence in favor of more efficacies. All targeted agents tend to show a progression-free survival (PFS) benefit and, although there is a trend towards improved survival, they fail to meet overall survival criteria. It appears that there is no inherently ‘right or wrong’ therapeutic choice for clinicians; however, there is a ‘right and wrong’ way in which these agents are used. For now, the choice of first-line therapy needs to be based on available data. Physicians should choose a therapy that best addresses the patient’s clinical conditions, comorbidities and their attitude toward risk.

Keywords

■ genitourinary cancer
■ prostate cancer ■ renal carcinoma ■ targeted therapies

Future
Medicine part of

RCC: selecting second-line therapy

Sequential therapy has the potential to change metastatic RCC into a chronic disease that can be managed long term through the administration of targeted agents in sequence. Currently, approximately 50% of patients go on to receive second-line agents and 10–15% third-line and subsequent lines of therapy. Although prospective trials have shown the efficacy of different target therapies, choosing the best second-line agent was the subject of the RCC debate – is a tyrosine kinase inhibitor (TKI)–TKI sequence or a TKI–mTOR inhibitor sequence better? Camillo Porta (Policlinico San Matteo, Pavia, Italy) eloquently put forward the evidence for the former and Roberto Sabbatini (Policlinico di Modena, Modena, Italy) for the latter.

In favor of TKI–TKI sequencing

Large retrospective studies have shown that in TKI primary refractory patients (irrespective of the definition used), shifting to a drug with a different mechanism of action (i.e., an mTOR inhibitor) is not only not useful, but also potentially detrimental [1–2]. Continuing the same TKI on which the tumor has progressed could be better than shifting to a different drug. Porta believes that, since the mTOR pathway is so tightly linked to HIF, in a neoplasm such as kidney cancer, which is so dependent on angiogenesis, mTOR inhibitors may be considered as ‘weak’ antiangiogenic agents compared with TKIs. The results of the recent AXIS trial provide further evidence of the advantage of not switching the mechanism of action for second-line therapy. AXIS was an international randomized Phase III trial comparing axitinib (a potent inhibitor of VEGF receptor 1, 2 and 3) versus a sorafenib as a second-line therapy in patients with metastatic RCC. Results showed that the VEGF receptor is still a viable target in sunitinib-resistant patients, although the incremental benefit with further VEGF receptor inhibition may not be large [3].

In favor of TKI–mTOR inhibitor sequencing

Sabbatini discussed how each targeted agent possesses a unique biological profile and how patients refractory to one targeted agent may benefit from treatment with a different agent, especially if it has a different target. mTOR inhibitors (everolimus and temsirolimus) interfere with the mTOR intracellular pathway, which is upstream of HIF synthesis and distinct from VEGF signaling. The rationale for sequencing VEGF inhibitors with mTOR

inhibitors is the expectation that the efficacy of the second drug will be unaffected by the resistance of the tumor to the first drug [4]. There is no documented evidence for cross-resistance between these two classes of agents. Patients who have experienced disease progression on a VEGF inhibitor have been shown to achieve additional PFS benefit with an mTOR inhibitor. Toxicities of these two classes do not overlap and a full dose of each drug is delivered, enabling maximum benefit. Importantly, to date, everolimus is the only agent registered for second-line treatment of failed TKI metastatic RCC patients.

Despite both presenting their cases convincingly and comprehensively, the jury is still out on the ‘best sequence’ as there are many factors to be taken into account, including age, extent of disease, prior regimen utilized, response and duration of response to the first-line regimen, toxicity of the prior agent, presence of symptoms, patient wishes and comorbidities. The debate about using a second-line therapy in patients with comorbidities was discussed and it was felt that patients should not be excluded just because they have comorbidities, but it is important to choose an agent based on its toxicity profile – *primum non nocere*. Giuseppe Procopio (Istituto Nazionale Tumori, Milan, Italy) went back to basics and asked if sequencing was really necessary and if it was really a good idea to change – why not continue with existing therapy? Both presenters agreed the question was not whether to change, but when to change – it was vital that therapy was only changed when there was real evidence of progression or when toxicity was such that it could not be adequately managed – for example, if a patient had an hypertensive episode with a given drug it was important not to change therapy but to optimally manage hypertension.

In a look to the future, Szczylik concluded that inhibition of angiogenesis in treatment of metastatic RCC is temporarily effective, but that targeting other angiogenetic pathways offers the possibility of prolonging this effect and increasing PFS and overall survival. He suggested that further improving the efficacy of inhibitors for other molecular pathways responsible for cell proliferation/survival should be considered.

Joaquim Bellmunt (Hospital Del Mar, Barcelona, Spain) reviewed the different types of biomarkers and, while biomarkers provide a clear opportunity to provide truly personalized medicine and optimized patient outcomes, further research is needed into how they can best be applied to clinical practice.

Prostate cancer session

As in the RCC session, experts in the field selected their preferred abstracts from international congresses – European Association of Urology (EAU), European Society for Radiotherapy and Oncology (ESTRO), European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO) and the US and Canadian Academy of Pathology (USCAP) including:

- Distinct transcriptional programs mediated by the ligand-dependent full-length androgen receptor (AR) and its splice variants in castration-resistant prostate cancer (CRPC) [5]. Suppression of AR signaling is a therapeutic goal of CRPC therapy. An experimental study by Hu *et al.*, conducted in cellular models of CRPC, showed that suppression of the AR-FL signaling by targeting the AR-LBD can increase the expression of AR-V [5]. In prostate cancer cells and CRPC xenografts treated with MDV3100 or abiraterone, an increase in expression of two constitutively AR-Vs – namely AR-V7 and ARV567ES – but not AR-FL, was associated with an increased expression of *UBE2C*, a cell-cycle gene whose expression is driven by the AR. In addition, the expression of AR-V7, but not that of AR-FL, was associated with the expression of *UBE2C* in specimens of CRPC. The authors conclude that these results could lend support to the hypothesis of an adaptive shift toward AR-V-mediated signaling when AR-LBD is rendered inactive in a subset of CRPC tumors. This finding may suggest a new, potentially relevant mechanism that contributes to drug resistance in CRPC patients;
- Association of baseline corticosteroid with outcomes in a multivariate analysis of the Phase III AFFIRM study of enzalutamide (ENZA), an AR signaling inhibitor [6]. ENZA increased median survival by 4.8 months versus placebo in metastatic CRPC patients post-docetaxel in the AFFIRM study. Corticosteroids are known to activate AR signaling in nonclinical models. Patients were randomized 2:1 to ENZA 160 mg/day or placebo, and efficacy end points included overall survival, radiographic PFS and time to PSA progression. While patients on baseline corticosteroid had worse outcomes, ENZA was consistently superior to placebo for overall survival, PFS and time to PSA progression regardless of baseline corticosteroid use;

- Tasquinimod mechanism of action biomarkers: correlation with PFS and survival in men with metastatic CRPC treated in a randomized Phase II trial [7]. In total, 201 men with CRPC were randomized and received once-daily treatment with tasquinimod (an oral quinoline-3-carboxamide derivative that binds to S100A9 and displays immunomodulatory, antiangiogenic and antimetastatic activity) or placebo (134 tasquinimod and 67 placebo), with 41 placebo patients crossing over to tasquinimod after 6 months or disease progression. Tasquinimod treatment for 8 weeks was associated with an increase in median circulating levels of VEGF-A (40%) and TSP-1 (21%), and a decrease in bone alkaline phosphatase (14%) compared with placebo. An increased ratio (week 8:baseline) was associated with more rapid progression and shorter survival for TSP-1. The authors reported that the PFS and overall survival observed after tasquinimod treatment are encouraging, and that changes in the levels of TGF- β , TSP-1 or VEGF-C may be markers for treatment benefit.

The abstract by Hu *et al.* at USCAP 2012, presented by Sara Moscovita Falzarano (Pathology and Laboratory Medicine Institute, Cleveland Clinic, OH, USA) was described as outstanding. The take-home messages were succinctly summarized by Falzarano:

- An adaptive shift toward AR-V-mediated signaling occurs in at least a subset of CRPC patients following effective therapies targeting the AR-LBD;
- Early detection of the shift toward AR-V signaling may indicate CRPC progression and guide treatment selection to overcome resistance;
- Novel agents for the treatment of CRPC are being designed to suppress the activation of transcriptional programs directed by AR-Vs.

The meeting continued with presentations on second-line and subsequent options in the management of CRPC with hormone therapy and chemotherapy, and a discussion about whether targeting bone metastases is still recommended in CRPC.

Concluding remarks: the genitourinary cancer scenario in 2013

Sergio Bracarda (UOC Medical Oncology, Arezzo, Italy), in his concluding remarks, said he held the view that 2013 will be a very important

year for all involved in the management of genitourinary cancer, including a number of aspects:

- Identification of prognostic factors will be at the forefront of research in order to forecast the response to a given treatment and predicate toxicity to treatments;
- Nephron-sparing surgery to preserve renal function has been recommended, but little is known about perioperative morbidity and long-term functional outcome after elective nephron-sparing surgery compared with radical nephrectomy in patients with larger renal tumors;
- Treatment of bone metastases from urological cancers with single-dose therapy may be a therapeutic option to improve the quality of life of patients. To date the optimum therapy for metastatic bone disease remains uncertain but Bracarda believes new drugs are becoming available that could change the clinical course of the disease;
- Regarding RCC, the situation is more complex. For first-line therapy there are two (perhaps three) equivalent therapeutic options, while for second-line treatment the optimal therapy is still under discussion and the extreme heterogeneity of the disease makes precise recommendations problematic.

Bracarda closed the meeting by thanking everyone for taking part and inviting all to the 2nd

World Top Communications of the Year in Genitourinary Oncology (Arezzo, Italy; 7–8 November 2013) where he believes major advances in many of the still unresolved issues in genitourinary cancer will be presented and discussed.

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