The treating scenario in genitourinary oncology: what is new? Part 1

Sergio Bracarda*1, Rodolfo Montironi2, Camillo Porta4, Cezary Szczyllic4, Alessandra Bearz5, Giacomo Cartenì6 & Joaquim Bellmunt7

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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.

Treating kidney cancer (localized & advanced disease) before the American Society of Clinical Oncology Annual Meeting 2012

The session was opened by Alessandra Bearz, (Oncology Reference Center, Aviano, Italy) who provided a comprehensive overview on the state-of-the-art treatment of kidney cancer before the 2012 American Society of Clinical Oncology (ASCO) Annual Meeting (Chicago, IL, USA, 1–5 June 2012). In 2012, despite the fact that a series of targeted therapies (TTs) – four VEGF receptor inhibitors (sunitinib, sorafenib, pazopanib and bevacizumab) and two mTOR inhibitors (temsirolimus and everolimus) – are approved for the treatment of metastatic renal cell carcinoma (mRCC) many questions remain, including what the target is, when to treat, who to treat, what the best sequence of targeted agents is (if any) and how best to define the role of surgery in patients with mRCC [1].

Bearz began by outlining how choosing a first-line agent is complicated and requires consideration of the efficacy and toxicity profiles, and an understanding of an individual patient’s needs and disease-specific characteristics. As it is currently unclear if there are differences in efficacy among different drugs in the first-line setting, tolerability of TTs plays a large role in selecting a given therapy. For example, temsirolimus is frequently considered the first-line therapy of choice for patients with a poor prognosis; mTOR inhibitors are known to cause refractory diabetes and poor pulmonary function, while refractory hypertension is common with VEGF inhibitors. In addition, dosing schedules and the sex/age of patients play a part, and many elderly patients are not administered TTs owing to toxicity profile issues; however, data from six clinical trials and two expanded-access studies evaluating sorafenib monotherapy in >4600 patients with renal cell carcinoma (RCC) showed that it was well tolerated regardless of age in a heterogeneous population of RCC patients [2].

Bearz discussed the role of immunotherapy versus TTs and, despite the fact that immunotherapy was hailed as a major breakthrough 20 years ago, that difficulties exist with these agents as patients are always ‘on treatment’ and adverse events are problematic. A long-term analysis of patients with mRCC showed that a high dose of IL-2 can induce complete tumor regression in a small number of patients, with some patients experiencing extended disease-free intervals [3]. The problem is that favorable

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predictive characteristics are not known for immunotherapy; despite this, the authors concluded that high-dose IL-2 should still be considered as a first-line therapy in patients with mRCC who have an overall good performance status [3].

Response to targeted monotherapy varies between patients and as yet no validated biomarkers predictive of treatment outcome have been identified. Recently, Xu et al. suggested that germline variants in angiogenesis- and exposure-related genes may predict treatment response to TT monotherapy in patients with mRCC. If validated, these markers may explain why certain patients fail antiangiogenesis therapy and, therefore, the need to use alternative strategies to circumvent this issue [4]. It is also important to be aware of the patterns of disease progression, in that 10–25% of mRCC patients are refractory to primary therapy; 50–70% have early progression and 20–30% have late progression (durable response). To identify optimal first-line therapy (and subsequent second line) it is important to understand the mechanisms of resistance to TTs. By preselecting those patients most likely to respond to antivascular EGF therapy, clinicians can begin to optimize therapeutic strategies [5].

Choosing a second-line therapy in patients who have progressed on a first-line TT is also complex and many clinicians choose a second-line VEGF inhibitor based on the type of response to first-line VEGF inhibitor, without data supporting this practice. A study conducted to determine the association of response to second-line VEGF inhibitor with response to first-line VEGF inhibitor showed that clinical response to a second-line VEGF inhibitor was not dependent on response to the first-line VEGF-inhibitor [6]. Further studies are needed to define clinical parameters that predict response to second-line therapy.

While TTs are currently the standard-of-care in patients with mRCC, the role of surgery remains poorly defined. There are two main areas: cytoreductive nephrectomy and metastasectomy. In a retrospective study cytoreductive nephrectomy was independently associated with prolonged overall survival in patients with mRCC treated with TTs, although the benefit was small in patients with a poor prognosis [7]. Similarly, results of recent studies have better defined prognosis in mRCC patients with/without metastasectomy. Overall it appears that patients with mRCC should be considered for multimodal therapy, including surgery of metastatic lesions, and that a proportion of patients will achieve long-term survival with aggressive surgical resection [8].

In summing up, Bearz drew the following conclusions:

- In an ever-changing field, the optimal first-line TT is still to be determined and treating physicians make therapeutic decisions based on many factors, including patient age and prognostic factors, toxicity profiles of TTs, physician/patient preference, mode of administration, reimbursement considerations and surgical procedures;

- Much work is currently being carried out to identify suitable biomarkers, but it is currently difficult to draw definitive conclusions. It is important that physicians can predict what therapies will be effective, thus minimizing the time on treatment for those patients who are resistant to a given agent and, ultimately, optimizing costs and containing toxicities;

- Toxicity may predict response as it may be a reflection of adequate drug dosing;

- Results of ongoing clinical trials designed to identify the best first-line therapy and subsequent sequence of drugs are eagerly awaited.

**Preferred abstract of the year 2012 from European & American Congresses**

The purpose of this session was for presenters to select their preferred abstract presented during 2012 at major international congresses. Matteo Brunelli (Ospedale Policlinico ‘GB Rossi’, Verona, Italy) selected two abstracts from the United States and Canadian Academy of Pathology Annual Meeting 2012 (Vancouver, BC, Canada; 17–23 March 2012) entitled “Xp11.2 Translocations in Adult RCCs with Clear Cell and Papillary Features” [9] and “Molecular confirmation of t(6;11)(p21;q12) renal cell carcinoma in archival paraffin-embedded material using a break-apart TFEB FISH assay expands its clinicopathologic spectrum” [10]. Brunelli’s presentation generated much interest as did his conclusions:

- Translocation RCCs have to be recognized: Chan et al. showed that Xp11.2 translocation RCCs were identified in 3% of adult RCCs that had clear cell and papillary changes (CCP) [9]. These tumors appear to present
with smaller tumor size, lower stage and better prognosis in comparison with non-Xp11.2 CCP RCCs. In addition to Xp11.2 translocation carcinoma, coexistence of CCP features may be present in other subsets of tumors that have yet to be characterized;

- Immunohistochemistry (TFE3, TFEB and cathepsin-K) can be useful and FISH analysis overcomes problematic cases by using break-apart probes. A subset of RCCs is characterized by t(6;11)(p21;q12), which results in fusion of the untranslated α-MALAT1 gene to the TFEB gene. These RCCs differ from conventional RCCs in that they consistently express melanocytic immunohistochemical markers, such as HMB45, melan A and the cysteine protease cathepsin-K, but are often negative for epithelial markers such as cytokeratins. Argani et al. reported the development of a TFEB FISH – a clinically validated assay – that can confirm the diagnosis of t(6;11) RCC in archival material and should allow a more comprehensive clinicopathologic delineation of these newly recognized neoplasms [10].

The optimal surgical margin size for partial nephrectomy has not been clearly defined. Current surgical techniques attempt to preserve the maximum amount of non-neoplastic renal tissue, although it is unknown if closer surgical margins translate into improved preservation of renal function. Filippo Annino (UO di Urologia dell’Ospedale San Donato, Arezzo, Italy) discussed this important subject by selecting an abstract presented at the American Urological Association (AUA) Annual Meeting 2012 (Atlanta, USA; 19–23 May 2012) entitled “Viability of Glomeruli Adjacent to Tumor in Partial Nephrectomy Specimens for RCC” [11]. Fifty three partial nephrectomy cases containing RCC were retrospectively reviewed, and the authors concluded that the immediate peritumoral rim of non-neoplastic tissue is abnormal and populated with a mixture of nonviable, minimally viable and viable glomeruli. Distance from the tumor correlates with increased viability of glomeruli, which should be considered when defining the optimal surgical margin size for partial nephrectomy.

**Landmark studies on target agents: an overview**

Results of new landmark clinical trials on TT agents were the subject of Michele Sisani’s (UOC Medical Oncology, Arezzo, Italy) presentation, which discussed the COMPARZ and INTORSECT trials [12,13]. COMPARZ was a Phase III randomized, open-label study comparing pazopanib and sunitinib as first-line therapy in mRCC [12]. The study involved 1100 patients with clear cell mRCC who had not received previous treatment. The primary end point was to establish noninferiority of progression-free survival (PFS) with safety and quality of life secondary end points. The results indicated that the two drugs were similarly effective, with a median PFS of 8.4 and 9.5 months, respectively (slightly more than 10 months for both, according to the investigator evaluation). Patients reported adverse events with both drugs, but those recognized to be bothersome for patients, such as fatigue and skin sores, occurred less often with pazopanib than with sunitinib. Quality-of-life questionnaires were in favor of pazopanib over sunitinib. There was a higher incidence of liver function test abnormalities with pazopanib, but no differences in the rates of discontinuations due to adverse events.

The INTORSECT trial was a multicenter, randomized, open-label Phase III trial comparing the efficacy and safety of temsirolimus and sorafenib in patients with mRCC who had failed prior therapy with sunitinib [13]. It was the first head-to-head trial comparing a VEGF inhibitor with an mTOR inhibitor in mRCC. Overall, 511 patients with RCC from 112 sites, whose disease had progressed after first-line sunitinib and who had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 were included. Median PFS was 4.28 months with temsirolimus and 3.91 months with sorafenib. Median overall survival for the temsirolimus group was 12.27 months compared with 16.64 months for those who had received sorafenib. Overall, temsirolimus did not improve survival over sorafenib in the second-line setting, suggesting that VEGF inhibitors may be a better option than this mTOR inhibitor for patients who have progressed after treatment with sunitinib.

Mimma Rizzo (Cardarelli hospital, Naples, Italy) discussed two further large scale trials with TTs – the PISCES [14] and the TIVO-1 [15] studies. The PISCES study, a randomized, double-blind, placebo-controlled, crossover study, was designed to evaluate whether treatment with sunitinib or pazopanib results in clinically meaningful differences. Given the relationship between adverse events and quality
of life, patient preferences were the primary end point. Patients were randomized to receive either pazopanib (800 mg daily) or sunitinib (50 mg daily) for 10 weeks. After a 2-week washout period, patients were crossed over for another treatment period of 10 weeks. At the end of 22 weeks, patient preferences were assessed with questionnaires. Overall, 70% of patients preferred pazopanib, 22% preferred sunitinib and 8% had no preference. The reasons cited for drug preference included better quality of life; less fatigue; fewer changes in food tastes; less soreness in the mouth and throat; reduced nausea and vomiting; reduced soreness in hands and feet; and reduced loss of appetite.

At the ASCO 2012 Annual Meeting, Motzer et al. reported initial results from a randomized, multicenter, international, open-label, Phase III trial comparing tivozanib, a potent and selective inhibitor of VEGF receptors 1, 2 and 3, and sorafenib in patients with mRCC [18]. The primary end point was superior PFS superiority in patients receiving tivozanib versus sorafenib as a first-line therapy. Overall 517 patients were randomized to receive either tivozanib (n = 260; 1.5 mg/day), on a schedule of 3 weeks on and 1 week off, or continuous sorafenib (n = 257; 400 mg/day). Tivozanib had superior efficacy over sorafenib with a median PFS of 11.9 versus 9.1 months (p = 0.042). Important safety differences were observed, with patients on tivozanib experiencing higher rates of hypertension. As previously discussed by Bearz, it appears that development of hypertension is associated with tivozanib efficacy since toxicity of TTs may predict response as a reflection of adequate drug dosing.

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References


12. Motzer RJ, Hutson TE, Reeves J et al. Randomized open-label Phase III trial of
