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Molecular Targeting Therapy to RCC: Current Status and Future Perspectives

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Renal Cell Carcinoma is highly resistant to current chemotherapeutic agents and the main focus of systemic treatment to date has been immunotherapy that offers only limited benefit. Interferon (IFN) yielded a 15% objective response rate (RR), but responses were rarely complete or durable. Interleukin-2 (IL-2) has elicited also a 15% objective RR in stage IV, but only 5% were complete, although this responses appeared to be durable in some patients.

The understanding of cellular processes underlying tumor biology, has permitted the development of novel molecular-targeted drugs with optimistic results in renal cell carcinoma (RCC). Mutations in the von Hippel Lindau gene (VHL) are found in 75% of sporadic RCC, which result in upregulation of several genes involved in angiogenesis such as VEGFR and PDGFR. Other activated pathways in RCC are the EGFR and the mTOR pathway which regulate survival and cell growth. In addition to temsirolimus (an mTOR inhibitor) two different strategies have been studied to inhibit these targets: monoclonal antibodies such as bevacizumab and small molecule tyrosine kinase inhibitors such as sorafenib, sunitinib and AG 013736. Phase II studies with these drugs have reported substantial clinical activity in advanced RCC. Survival benefit has been reported with temsirolimus, sunitinib and sorafenib in randomized trials which has led to the accelerated approval of sorafenib and sunitinib by the FDA and by the EMEA for advanced RCC. Nevertheless, as new therapies develop, new challenges arise regarding the optimal use of these targeted drugs.

The fact that novel agents are more likely to be cytostatic than cytotoxic brings up the relevance of endpoints such as progression free survival and disease stabilization. Trials with these drugs show tumor shrinkage that does not meet the traditional RECIST criteria which should therefore be revisited. In this sense, current studies are focusing in surrogate endpoints as plasma biomarkers of angiogenesis and new imaging techniques.

As the clinical activity of these molecules is further defined, questions related to scheduling need to be addressed. Carefully designed studies will help optimize issues such as continuous versus intermittent, lower chronic doses or sequencing treatment. Furthermore, the generally favorable safety profile of these targeted drugs should allow their use in combination with each other or with traditional agents.

Both the urologist and the oncologist should gain knowledge from lessons learned in other oncologic diseases like ovarian cancer or germ cell tumors. In particular, concepts such as the place and timing of nephrectomy and the role of interval or post-treatment surgical resection of metastatic locations in responding patients need to be defined. In addition, the role in the adjuvant setting will be clarified in the near future. Because of the potential expanded use of these new agents and their side-effects profile, clear guidelines for both urologists and oncologists need to be established.

With these novel molecular-targeted therapies, new and exciting challenges arise that will ultimately result in the benefit of our patients. However, because we are not yet curing our RCC patients these molecules should not be used indiscriminately and we should continue including patients in well designed prospective clinical trials.

References