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Entropy Increases in Kidney Cancer Treatment, but a Bit of Simplicity May Emerge From Chaos

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We know from the second law of thermodynamics that the spontaneous evolution of an isolated system can never lead to a decrease of its entropy (ie, its intrinsic disorder), as entropy always increases as long as the system evolves. Even though kidney cancer (the “system”) cannot be regarded as a purely isolated system, and even though we are actively attempting to modify it with all our therapeutic weapons, it is clear that this system has evolved dramatically in the past few years and that complexity (if not entropy/disorder) is the direct consequence of this evolution. What has happened in the past 6 years in the field of kidney cancer is both exceptional and unprecedented. Starting in 2005, when the results of the sorafenib TARGET trial were first disclosed at the American Society of Clinical Oncology (ASCO) annual meeting, almost each subsequent year saw the presentation of one novel drug or more for this once-orphaned disease. Subsequent to the recent presentation of the axitinib trial results, seven molecularly targeted agents have proven their activity against this tumor within large, randomized, phase 3 trials: the four multikinase inhibitors sorafenib, sunitinib, pazopanib, and axitinib; the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (given together with interferon- α [IFN- α]); and the two mammalian target of rapamycin (mTOR) inhibitors temsirolimus and everolimus. This list excludes compounds likely to enter the field soon (eg, tivozanib).

The picture is complicated further by the lack of randomized, head-to-head, comparative trials and the limited time we had to synthesize all of the data we have gathered. As a measure of such a huge complexity, several issues remain still open, none trivial: (1) the ideal first-line

treatment, (2) the role of combinations, and especially (3) how to better sequence the drugs we now have to maximize the clinical benefit for the vast majority of our patients.

As far as the first-line treatment for patients with good or intermediate prognosis (for poor prognosis patients, the situation seems a little more clear), sunitinib is by far the most commonly prescribed drug. However, phase 3 data suggest that a similar benefit, at least in terms of progression-free survival (PFS), also may be achieved with bevacizumab plus IFN- α or with pazopanib. In addition, recent data, although not coming from phase 3 trials, seem to challenge these few certainties. The results of the TORAVA randomized phase 2 trial—the only first-line comparison trial presently available—showed that bevacizumab plus IFN- α performed definitively better than sunitinib, especially in terms of resulting PFS [1]. Several drawbacks from the design of this phase 2 study may account for such a difference, but the data—and the relative doubts—remain.

As for the combination of bevacizumab plus IFN- α , the recently presented results of the BEVLiN single-arm phase 2 trial [2] are very provocative and, in some ways, in concordance with a well-known subanalysis of the AVOREN trial [3]. This concordance suggests that the combination of bevacizumab with low doses of IFN- α may lead to enhanced (although not well understood mechanistically) antitumor activity.

Sorafenib lost almost all of its attractiveness in first-line treatment after it proved not to be superior to IFN- α in a highly criticized randomized phase 2 trial [4]. However, it recently proved able—also within a randomized phase 2 trial—to achieve PFS of 9 mo [5], almost doubling the PFS reported in the first-line trial against IFN- α . This finding

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moved sorafenib closer to the other treatment options commonly used in first-line treatment. Again, huge biases exist but also the clear-cut feeling that we simply do not know all that we should about these drugs.

As far as combinations of molecularly targeted agents, the few data we have from several phase 1 and 2 trials and the above-mentioned randomized phase 2 TORAVA trial [1,6] suggest that, besides economical issues, tolerability appears to be the most relevant limitation of such an approach.

What to do after the failure of a first-line anti-VEGF receptor (anti-VEGFR) therapy is still a matter of debate. Physicians are lined up in opposite camps, the supporters of shifting to an mTOR inhibitor facing those convinced by the opportunity of continuing inhibition of the same pathway using a different multikinase inhibitor. In this issue of *European Urology*, Busch and colleagues have added another piece of evidence (albeit retrospective) to this already long-lasting quarrel. Their data show no relevant differences in terms of PFS (or overall survival) between the use of an mTOR inhibitor and a multikinase inhibitor after failure of a first multikinase inhibitor [7]. This finding is absolutely in agreement with other similar reports that clearly suggest that, besides those unfortunate patients who will not respond to anything from the very beginning (the *primary refractory* patients), all others may achieve some kind of benefit from almost all available drugs, and this benefit may be enhanced by the use of the higher number of possible of agents in sequence, even though the “ideal” sequence is still unknown. Second-line treatment was a particular object of controversy, despite several attempts to identify which patients will benefit from which second-line treatment [8], with the ultimate aim of helping physicians make reasonable choices in the real world of everyday clinical practice.

Interestingly, the mainly retrospective reports suggesting that continuous inhibition of the VEGFR pathway could be of benefit for advanced kidney cancer patients may not contradict the results of the prospective, randomized, phase 3 RECORD-1 trial, which demonstrated the activity of the mTOR inhibitor everolimus after one (or even two) multikinase inhibitors. The peculiar molecular pathogenesis of kidney cancer is heavily dependent on angiogenesis, due to the frequent mutation of the von Hippel-Lindau tumor suppressor gene in sporadic cases [9]. This makes it possible that presently available mTOR inhibitors (which indeed are just TORC1 complex inhibitors) could be active in this cancer due to their indirect inhibition of angiogenesis. But is this really true in clinical practice? Nobody really knows. Once again, apparently chaos is still ruling the system.

Physics tells us that chaos can be, and often is, a property of very simple systems, meaning that simple questions usually have complicated answers [10]. However, our only

way out could be by turning this concept upside-down: In a complex system (eg, kidney cancer) we should look for an easy—and credible—answer to our questions.

Such an answer is probably Chris Ryan’s “simplified algorithm” statement, courageously made during the educational program at the 2010 ASCO annual meeting: “Choose any agent you want. Use it well.” This is a statement on which we should all agree. It is a shortcut, for sure, but a smart one and also a bit of simplicity to move out from the fogs of chaos.

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