Strategic Options on Behalf of Patients with Metastatic Colorectal Cancer: Mass Tumor Murder versus Serial Tumor Killing

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At nearly every conference on the treatment of metastatic colon cancer the organizers engage an opinion leader to address whether it is more effective to deploy chemotherapy agents all at once in an attempt at maximal response or to administer single or double agents to extend options, moderate toxicity, and mitigate the costs of treatment. At the podium, in the literature, and in practice there are proponents of both approaches, but those advocating mass tumor cell murder seem to outnumber those who prefer the serial killer option these days. Also at the podium there is likely to be an opinion leader who is engaged to consider the merits of infusing 5-fluorouracil (5-FU) compared to substitution of capecitabine or alternative oral agents for it.

In the report by von Moos et al. in this issue of ONKOLOGIE the investigators embrace the philosophy of administering three cytotoxic agents at once and set out to find a safe capecitabine dose to substitute for 5-FU infusion [1]. Their work is a logical successor to a prior SAKK phase I–II study in which oxaliplatin and irinotecan were administered on alternating weeks with 5-FU as the common companion given weekly [2]. Patients enrolled in that trial had a promising overall survival exceeding 25 months without the use of a first line biologic agent, although the sample size was small and this favorable outcome may not hold up if the regimen was tested in a larger population of patients.

In this effort the oxaliplatin and irinotecan doses imported from that trial were fixed and the mission was to establish a safe dose of capecitabine. The investigators did that by enrolling 23 patients at 6 centers in what appears to be a well conducted study as would be expected from this group of experienced investigators. Despite the combination of 3 cytotoxic agents toxicity was moderate. One could argue whether myocardial fibrosis and Meniere's disease are really dose limiting toxicities related to this regimen and if the dose level could have been pushed a bit higher. One could also assert that in a

23 patient study with 5 different dose levels and no extended cohort at the maximum tolerated dose the authors should not have succumbed to the temptation to make remarks about their disappointment in the response rate.

Has this report helped to hone our approach to the management of patients with metastatic colorectal cancer? There are many reports of regimens that deliver irinotecan and oxaliplatin on the same day with either 5-FU or capecitabine such as the FOLFOXIRI regimen advocated by Falcone et al. [3]. Other groups have alternated various 5-FU or capecitabine plus irinotecan regimens such as FOLFIRI with 5-FU plus oxaliplatin regimens such as one of the FOLFOX regimens delivering each combination once a month on a 2-week alternating schedule [4,5]. All have led to similar outcomes and there are no clear data to make a determination whether one approach should be preferred over another.

This regimen's variation on those themes is to alternate irinotecan and oxaliplatin weekly rather than every other week. One could postulate that the alternating approach could be an effective strategy to moderate toxicity because of the interrupted exposure to the side effects of irinotecan perhaps lessening its associated alopecia and diarrhea and interrupted exposure to the side effects of oxaliplatin perhaps easing the associated neuropathy and myelosuppression. Others might theorize that cytotoxic drugs work best against cancer cells when given as often as possible at as high doses as possible to minimize the chances of tumor cells developing early drug resistance as a consequence of nonlethal damage. Proponents of that approach would not alternate regimens but instead move from one to the next when the tumor progresses. It's not clear that either of those theoretical issues have practical implications on an individual patient's likelihood of a response, quality of life, or their longevity.

In the end I would assert that this study will have, at best, a modest impact on the quest to improve patient care for

individuals with metastatic colon cancer. It is likely that those who embrace the use of three cytotoxic agents at once will opt for FOLFOXIRI as there is phase III experience with that regimen. For the same reasons those who prefer an alternating approach will opt for alternating a variation of FOLFOX with FOLFIRI or CapeOx with CapeIri. A few oncologists will still probably have a preference to administer serial single agents. Most oncologists will also consider adding a biologic agent to first line therapy. It seems that the arguments we have about using more cytotoxic agents versus the serial use of cytotoxic agents and about oral versus intravenous 5-FU parallel political arguments on managing terrorism. Discussing whether it is better to adopt a ‘shock and

awe’ approach or to ‘target the terrorists one at a time’ is not very satisfying approach to eradicating political conflict and likewise in the war against cancer an emphasis on fine tuning cytotoxic regimens in advanced colorectal cancer seems somewhat unrewarding. The point is that we need to think differently. We must individualize management approaches based upon a better understanding of the heterogeneous nature of colorectal tumors rather than assuming all are alike. We have to practically exploit the growing recognition of variable patient biology (pharmacogenetics). And finally we should prioritize the testing of new agents rather than to keep fiddling with variations on our current tactical approaches.

References

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