LETTER to the EDITOR

Is it Rational to Continue Anti-Neoplastics with Minimal Toxicity even after Progression in Patients with no other Options? Possibly Yes

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Dear Editor

In everyday medical oncology practice, anti-neoplastic therapy is continued unless there is further tumor growth or intolerable toxicity resulting from the treatment itself. To monitor the tumor response or progression, a baseline snapshot of measurable or evaluable lesions is obtained prior to onset of therapy. Then, 2-3 cycles are given and the same studies are repeated and comparatively read to evaluate interval change in sizes of malignant lesions, whether is it getting smaller or not. If there is a clear progression or intolerable toxicity despite the therapy, it is stopped and a new treatment is planned. In the remaining scenarios, namely tumor shrinkage or no change in size, the therapy is continued (Therasse et al., 2000). The decision algorhythm described above is based on the dogma that "not shrinking" or further growth in tumor size despite a specific therapy means a "resistance to that therapy." Is it really? It may well be imagined that progressing tumor would have had been "more progressed" without therapy than with therapy, or a stable tumor under therapy would have had progressed without it. It is like "going down the hill with or without brakes. It is of course clinically irrelevant to ask such questions in case of an agent with cumulative toxicity or a patient with bad performance status. However, it is not infrequent to have a therapy-demanding patient with good performance status and an agent without alternative and cumulative toxicity. In such patients, which one is better: To stop the current theapy or continue it? We have some comments:

What happens in a progressing tumor at cellular level despite systemic therapy can be explained by several scenarious: 1) Your agent has no cytotoxic-cytostatic effect on cancer cells at all and malignant cells continue to proliferate, 2) It has some cytotoxic-cytostatic effect on cancer cells, but overridden by dividing tumor cells. That is, cancerous cells proliferate more than the extend to which killed by the cytotoxic agent. In the first explanation, it can easily be imagined that stopping, or continuing with same therapy doesn't make any difference on tumor and it may cause additional toxicity without any benefit. In the second scenario, discontinuing the drug kiling a portion of dividing cells may cause accelerated tumor growth. Therefore, one can not talk about absolute and uniform futility for every patient with progressive disease.

Unfortunately, a benefit can not be definitely excluded without a randomized clinical trial. We do not think that such a trial will be conducted in the foreseeable future. There are some observations supporting the hypothesis above, though. For example, it has been showed that molecular targeted therapies like bevacizumab and trastuzumab show efficacy when continued after progression (Grothey et al., 2008), (Tripathy et al., 2004). In metastatic colorectal cancer, fluorouracil is part combination chemotherapies in first, second and third lines of treatment regardless of the names like FOLFIRI, FOLFOX. We usually subconsciously continue to give fluorouracil-oral or intravenous-from diagnosis to death, nobody thinks of fluorouracil resistance. It is highly likely that fluorouracil adds to the efficacies of 2nd and 3rd line chemotherapies.

Another interesting observation is the acceleration of tumor progression after discontinuation bevacizumab due to resistance in some tumors, supporting the notion that an agent can be beneficial even after the anatomical progression (Zuniga et al., 2010), (Cacheux et al., 2008).

In conclusion, we think that a chemotherapeutic agent can be continued even after progression if there is no alternative, or no toxicity in a therapy-demanding patient. A related phase III trial can be conducted.

References

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