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Off-label use of molecularly targeted therapy

Advances in technology allow for genetic and molecular profiling of tumors, findings that are useful for guiding molecularly targeted therapy. Molecularly targeted agents are usually tested and developed on groups of tumors based on histologic type and primary location, but many genetic abnormalities overlap across tumor types. For this reason, clinicians often use molecularly targeted therapies off-label, targeting other tumors that harbor the offending genetic alteration. Some nonrandomized studies have shown that using targeted therapies in this way has increased progression-free survival, but, to the authors' knowledge, no randomized controlled trials have been performed. According to the authors, this study represents the first to directly compare the use of molecularly targeted agents, in an off-label, histology-agnostic strategy, to the standard of care in a randomized trial. In the trial, patients who met the inclusion criteria of recurrent or metastatic solid tumors that were refractory to standard of care were screened. A biopsy or resection of a metastasis was examined by targeted next-generation sequencing, gene copy number analysis, and immunohistochemistry for hormone receptors. Patients qualified for the study if molecular alterations were identified in one of three molecular pathways—hormone receptor pathway, PI3K/AKT/mTOR pathway, or REF/MEK pathway—and the molecular alterations could be matched to one of 10 available targeted treatment regimens. The patients were then randomized to receive either the off-label molecularly targeted agent or treatment of the physician's choice. Demographics and tumor types were shown to be similar between the two groups. In both arms of the study, the treatments were administered according to standard protocols, and the primary endpoint of the study was progression-free survival. The median progression-free survival rate was 2.3 months in the experimental group versus 2.0 months in the control group (P=0.41). There was no significant difference in six-month progression-free survival (13 percent in the control group and 11 percent in the experimental group). In addition, adverse events were similar between the two groups. Overall, the use of molecularly targeted agents in an off-label, histology-agnostic manner was not shown to significantly improve progression-free survival. The authors note, however, that a few factors may explain the negative result. First, the nature of the study was highly variable, including many different tumor primary sites and histologic types. Second, the treatment algorithms were simple, and targeted therapies were given as single agents, potentially leading to reduced efficacy. Third, and perhaps most importantly, the patient population examined had refractory metastatic cancer and was previously treated extensively. The biology of tumors is inherently complex and becomes increasingly so as tumors grow, metastasize, and evade treatment. It's possible that it may be more beneficial to use targeted therapies earlier in tumor development, when fewer molecular alterations are seen, and when those that are present are more likely to be causative of tumorigenesis. While the findings of the study show that off-label use of targeted treatments should be discouraged, the authors encourage enrollment in clinical trials to discover the most effective therapies.

Le Tourneau C, Delord JP, Goncalves A, et al. Molecularly targeted therapy based on tumor molecular profiling versus conventional therapy for advanced cancer (SHIVA): a multicentre, open-label, proof-of-concept, randomised, controlled phase 2 trial. *Lancet Oncol.* 2015;16:1324–1334.

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