FAQ: I started an EGFR inhibitor two weeks ago but haven’t developed a rash. Does this mean it’s not working?

The short answer is no.

Since the introduction of the targeted agents that inhibit the epidermal growth factor receptor (EGFR), both the oral EGFR tyrosine kinase inhibitors (TKIs) like Iressa (gefitinib) or Tarceva (Erbitux), and the monoclonal antibody therapies against EGFR like Erbitux (cetuximab) have been identified as often having a rash as a leading side effect. Though often annoying and sometimes very difficult to manage, the development of a rash has also been identified as somewhat of a double-edged sword, as several early trials identified development of a rash as being associated with a better result on oral EGFR inhibitors, and even that there may be a correlation with best outcomes in patients who develop a more severe rash. Moreover, this same trend has also been seen in patients who receive Erbitux for lung cancer as well as for colon cancer.

Meanwhile, other corroborating tangents included the finding that smokers on Tarceva had fewer side effects and have also been consistently identified to not do as well with oral EGFR inhibitors as never-smokers or ex-smokers, very possibly related to faster metabolic breakdown of these agents in current smokers. It remains a possibility, though still not well studied and unproven, that a higher dose of EGFR TKI therapy may be more effective in current smokers.

First, it’s not clear whether the benefit is especially related to development of a rash as much as disappointing results being seen more generally in the population that doesn’t develop a rash. In the TRIBUTE trial, patients who received chemo and Tarceva and didn’t develop a rash trended toward a worse survival than patients on the arm that received chemo and placebo — so perhaps there is an element of worse outcome in patients who don’t have the immune response/constitutional features that are associated with rash. Similarly, the more favorable results of people on the FLEX trial who developed a rash may be because they received enough Erbitux to develop a rash or because they had the undefined features that characterize people who do better, and who also happen to develop a rash with Erbitux. In other words, is the rash part of the mechanism here, or is it just a marker of some other factor of people who do well?

More importantly, though, is the fact that this trend is useful in populations but is not very helpful in individuals: it is absolutely not uncommon for people who don’t develop any appreciable rash to experience significant and prolonged tumor shrinkage, while some patients who experience major skin symptoms demonstrate very early progression. A rash is absolutely not necessary nor sufficient for benefiting on an EGFR inhibitor. Therefore, experts feel that absence of a rash is not a reason to discontinue therapy or to presume that this is an ineffective therapy.
A related question is whether someone experiencing a problematic rash should be concerned that they need to experience the problematic side effects to benefit, since it is most appropriate to temporarily hold treatment and often to reduce the dose in patients who have significant skin toxicity. Corroborating the nearly universal finding that many of the best- and longest-responding patients on EGFR inhibitors are those who undergo dose reductions to manage the rash, a recent analysis demonstrated that patients who had Iressa dropped to a lower dose due to side effects do every bit as well as those who remain on the higher dose.