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Inhibition of the Hedgehog Pathway in Advanced Basal-Cell Carcinoma... a place to start from?!

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Oncological pathology is probably one of the most studied medical subjects and one of the biggest health problems today.

From the discovery of Hedgehog signaling pathway and its implications in tumorigenesis, scientists managed to develop new therapies targeting tumors of all types involving this signaling pathway, especially skin cancers.

Normally, the hedgehog signaling pathway send certain informations towards the cells that are needed for the proper embryo development. When the pathway malfunctions, it can result in diseases like basal cell carcinoma.The hedgehog signaling pathway is one of the key regulators of animal development conserved from flies to humans. The pathway takes its name from its polypeptide ligand, an intercellular signaling molecule called Hedgehog (Hh) found in fruit flies (Drosophyla). Mammals have three Hedgehog homologues, of which Sonic hedgehog is the best studied.

Drugs that specifically target hedgehog signaling to fight this disease are being actively developed. Recently, a study involving 33 patients with basal cell carcinoma was published in the NEJM, with promising results. It was an open-label, multicenter, two-stage phase 1 trial to evaluate the safety and tolerability of GDC-0449 in patients with a variety of solid tumors that were refractory to standard therapy (either metastatic or locally advanced basal-cell carcinoma). GDC-0449 is an inhibitor of a molecule (SMO) involved in the hedgehog signaling pathway. The hedgehog pathway is inactive in adult tissues. However, most basal-cell tumors have mutations in the hedgehog signaling pathway that inactivate PTCH1 (loss-of-function mutation) or, less commonly, constitutively activate SMO (gain-of-function mutation). By blocking this molecule, the tumorigenesis process is stoped.

Three doses of the study drug were used: 150mg/day for 17 patients, 270mg/day for 15 patients and 540mg/day for one patient. The response to the study drug was assessed using physical examination and RECIST criteria (Response Evaluation Criteria In Solid Tumors, a set of published rules that define when cancer patients improve ("respond"), stay the same ("stabilize"), or worsen ("progression") during treatment).

The median duration of the study treatment was 9.8 months. Of the 33 patients, 18 had an objective response to GDC-0449, according to assessment on imaging (7 patients), physical examination (10 patients), or both (1 patient). Of the patients who had a response, 2 had a complete response and 16 had a partial response. The other 15 patients had either stable disease (11 patients) or progressive disease (4 patients). Eight grade 3 adverse events that were deemed to be possibly related to the study drug were reported in six patients, including four with fatigue, two with hyponatremia, one with muscle spasm, and one with atrial fibrillation. One grade 4 event, asymptomatic hyponatremia, was judged to be unrelated to GDC-0449. One patient withdrew from the study because of adverse events.

In conclusion, the investigators found evidence of hedgehog signaling in tumors that responded to the treatment. ❑

Comment on the paper:

Von Hoff DD, LoRusso P, Rudin CM et al – Inhibition of the Hedgehog Pathway in Advanced Basal-Cell Carcinoma. *N Engl J Med* 2009 Sep 17; 361:1164-1172