



Editor-in Chief

Jerome M. Hershman, MD
Distinguished Professor of Medicine
UCLA School of Medicine
and VA Greater Los Angeles Healthcare System
Endocrinology IIID, 11301 Wilshire Blvd.
Los Angeles, CA 90073
Email: jhershmn@ucla.edu

Associate Editors:

Albert G. Burger, MD
Professor, University of Geneva
Geneva, Switzerland
Email: agburger@bluewin.ch

Jorge H. Mestman, MD
Professor of Clinical Medicine and OB/GYN
University of Southern California,
Keck School of Medicine
Los Angeles, CA
Email: mestman@usc.edu

Elizabeth N. Pearce, MD, MSC
Associate Professor of Medicine
Boston University School of Medicine
Boston, MA
Email: Elizabeth.pearce@bmc.org

Wendy Sacks, MD
Cedars-Sinai Medical Center
Department of Medicine
Health Sciences Assistant Clinical Professor
University of California, Los Angeles
email: wendysacks@cshs.org

Stephen W. Spaulding, MD
Professor of Medicine
Department of Medicine
University at Buffalo, SUNY
Email: medspaul@buffalo.edu

Cord Sturgeon, MD
Associate Professor of Surgery
Director of Endocrine Surgery
Northwestern University
Feinberg School of Medicine
Chicago, IL
Email: csturgeon@nmh.org

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Falls Church, VA 22041
Telephone: 703-998-8890
Fax: 703-998-8893
Email: thyroid@thyroid.org

Designed By
Karen Durland (kdurland@gmail.com)

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A MEK-Inhibitor Enhanced Radioiodine Uptake in Previously Dedifferentiated Thyroid Cancers

Jerome M. Hershman

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SUMMARY • • • • •

Background

Radioiodine-131 has been a mainstay of treatment for differentiated thyroid carcinoma (DTC) for over 50 years. Unfortunately, in many patients with aggressive tumors that recur and metastasize, dedifferentiation occurs and there is loss of iodine uptake by the cancer cells. In such patients, radioiodine therapy is futile and their prognosis is poor. In recent years there have been many basic studies to test agents that may cause a reexpression of the sodium-iodide symporter in thyroid cancer cells that lack this expression. Clinical studies have also been performed with agents, such as retinoids, to increase the uptake of radioiodine by thyroid cancers with very low or no uptake, but none of these studies have resulted in clinically meaningful uptake of radioiodine by tumors that did not show uptake beforehand. The current paper shows that this goal of redifferentiation is attainable with use of a mitogen-activated protein kinase kinase (MEK) inhibitor, as had been shown in animal models (1).

Methods

Patients selected for treatment with the MEK inhibitor, selumetinib, had radioiodine-refractory metastatic disease that was positive on PET scanning. The baseline iodine avidity of their lesion was first assessed with a recombinant TSH-stimulated ¹²⁴I PET-CT scan. Patients were then treated with selumetinib for 4 weeks. In the last week of treatment, a second TSH-stimulated ¹²⁴I PET-CT study was performed. Patients with ¹²⁴I dosimetry that predicted

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tumor uptake of less than 2000 cGy were excluded from further study. If the absorbed dose of radioiodine-131 in the lesion was predicted to be ≥ 2000 cGy, full dosimetry with iodine-131 was performed to calculate the maximum tolerable activity that could be administered safely. The patient then received a therapeutic dose of radioiodine-131 after preparation with recombinant TSH. Selumetinib was continued until 2 days after the therapeutic dose of ^{131}I . Thyroglobulin levels and the imaging response were evaluated at 2 and 6 months after this therapy.

Genotyping for oncogenic mutations was carried out on paraffin-embedded archival samples.

The primary end point was an increase in ^{124}I PET-quantified iodine uptake and the tumor response at 2 and 6 months; the secondary end point was a decrease in the serum Tg level.

Results

Twenty patients completed the study; 5 had classic papillary thyroid cancer, 8 had tall-cell variant papillary thyroid cancer, and 7 had poorly differentiated carcinoma. Nine patients had a BRAF V600E mutation, 5 had an NRAS mutation, 3 had RET/PTC rearrangements, and 3 had no detectable oncogenic mutations.

Twelve patients had increased ^{124}I uptake after selumetinib, and in 8 the uptake showed that the radiation dose in the lesion would be ≥ 2000 cGy with ≤ 300 mCi ^{131}I . These 8 patients were treated with ^{131}I . Only 1 of 9 patients with the BRAF mutation had increased ^{124}I uptake, but all 5 with NRAS mutations had increased uptake. Analysis of lesions showed dramatically increased uptake in some lung and bone lesions.

At the 6-month follow-up, there was a reduction in the size of target lesions in all patients. There was a partial response in six patients and stable disease in two others. The TSH-stimulated serum Tg was reduced by 80% at 6 months.

Side effects of selumetinib included fatigue, rash, and mild liver-enzyme abnormalities. One patient with a cumulative 976 mCi ^{131}I dose before the study received another 139 mCi as a result of the study. One year later he had a myelodysplastic syndrome that progressed to acute leukemia.

Conclusions

The MEK inhibitor selumetinib produced clinically meaningful increases in iodine uptake in a subgroup of patients with thyroid cancer that was refractory to radioiodine, resulting in good clinical responses to ^{131}I therapy.

ANALYSIS AND COMMENTARY ● ● ● ● ● ● ● ●

This is a very impressive study, the first to show that a drug caused clinically meaningful radioiodine uptake in DTC that had become dedifferentiated before treatment with the drug, in this case, the MEK inhibitor selumetinib. This therapy should be very useful for treatment of lung metastases that no longer concentrate radioiodine and for lesions in other areas that cannot be resected. The quanti-

tation of uptake with ^{124}I -PET scans is not likely to be available in many centers. Nevertheless, confirmatory studies with less rigorous protocols will be necessary before selumetinib can be approved for this purpose.

It is interesting but unfortunate that only 1 of 9 DTCs expressing the BRAF oncogene had a good response to selumetinib because DTCs with this oncogene

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have a poor prognosis (2). On the other hand, all 5 DTCs expressing NRAS responded very well to selumetinib. Because of the small numbers of patients, it is too early to assume that this prediction of response by genotyping oncogenes will hold up with further studies, but additional studies that include genotyping will be helpful.

The side effects of tyrosine kinase inhibitors, such as selumetinib, are substantial. Fortunately, the short duration of therapy limited the severity of the side effects in this study. Therapy for only several weeks should help to make this treatment method acceptable to patients.


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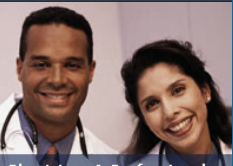
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