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Restoring Radioiodine Uptake in *BRAF V600E*–Mutated Papillary Thyroid Cancer

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In recent years, sorafenib [1] and lenvatinib [2] have demonstrated efficacy in the first-line setting for advanced or metastatic differentiated thyroid cancer refractory to radioactive iodine (RAI). During the same time, the specific inhibition of BRAF in *BRAF*-mutated tumors showed important efficacy [3], including in papillary thyroid cancer (PTC) [4]. Furthermore, the ability of targeted therapies to induce tumor redifferentiation and the possibility of restoring RAI uptake with kinase inhibitors in iodine-resistant PTC has been described [5, 6]. The optimal treatment strategy in *BRAF*-mutated PTC therefore remains to be established.

An 83-year-old man was diagnosed with a mutated *BRAF V600E* tall-cell variant of PTC in the left thyroid lobe, staged pT3N1bR1 after total thyroidectomy and unilateral left lymph node dissection.

Fig. 1(A): The first post-^{131}I therapy scan (3.7 GBq after levothyroxine withdrawal) revealed a right cervical remnant but no ^{131}I uptake in the pulmonary metastases and cervical lymphadenopathies, which were otherwise fluorine 18 fluorodeoxyglucose (18F-FDG) avid on postoperative positron emission tomography (PET)/computed tomography (CT) imaging [maxium standardized uptake value (SUVmax): cervical lymphadenopathies, 19.1; right pulmonary macrometastasis, 14.8]. This inverse relationship reflects dedifferentiation ("flip-flop phenomenon").

Fig. 1(B): After the patient had received vemurafenib for 3 months (plasma concentration, 63.9 mg/L; target concentration >40 mg/L) the post-^{131}I therapy scan (5.5 GBq) revealed restored iodine uptake in known lesions and a pulmonary miliary (^{131}I uptake was 0.26% of the ingested dose in the left cervical nodes and 2.46% in the lungs). PET/CT showed shrinkage of known lesions and less 18F-FDG avidity (SUVmax: cervical lymphadenopathies, 3.4; right pulmonary macrometastasis, 2.9). This inversion in the flip-flop phenomenon reflects redifferentiation, which could explain the thyroglobulin rise.

Fig. 1(C): The third ^{131}I therapy scan (5.5 GBq) was performed shortly after the discontinuation of vemurafenib because of poor tolerance. Almost no RAI uptake was documented (^{131}I uptake was 0.016% in the left cervical nodes and 0.095% in the lungs). The plasma concentration of vemurafenib was 3.8 mg/L, consistent with an absence of substantial

Abbreviations: 18F-FDG, fluorine 18 fluorodeoxyglucose; CT, computed tomography; PET, positron emission tomography; PTC, papillary thyroid cancer; RAI, radioactive iodine; SUVmax, maximum standardized uptake value.

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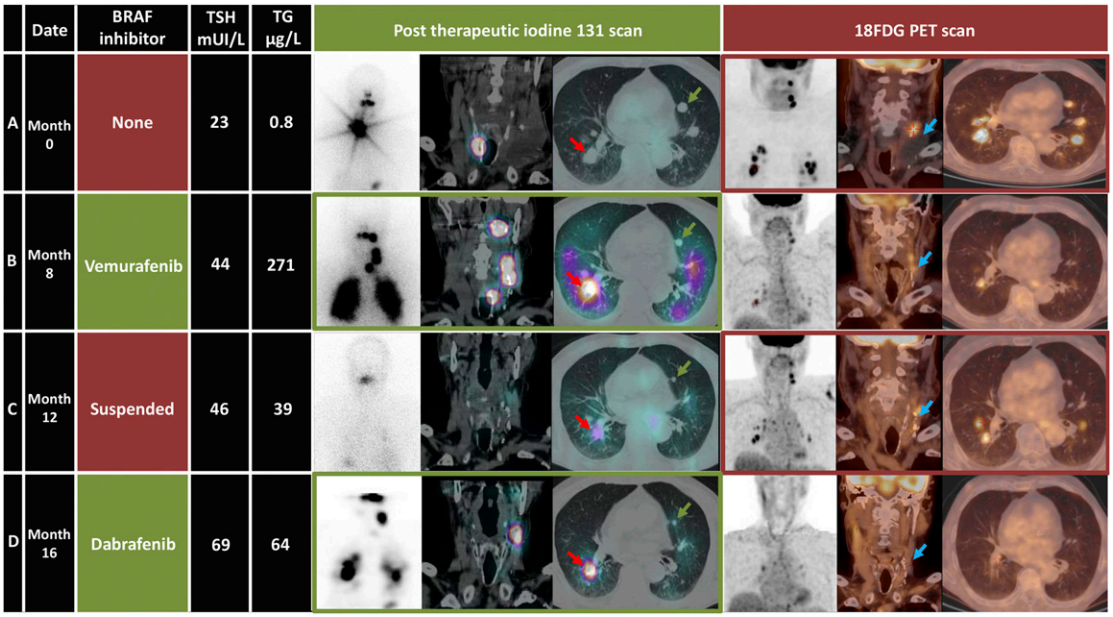

Figure 1. Imaging and biology during the treatment course.

exposure. PET/CT showed stable lesions associated with an increase in 18F-FDG uptake (SUVmax: cervical lymphadenopathies, 8.3; right pulmonary macrometastasis, 8.7).

Fig. 1(D): After treatment with dabrafenib for 3 months, a new post-^{131}I therapy scan (5.5 GBq) showed restored uptake in lymphadenopathies and pulmonary lesions (^{131}I uptake was 1.66% in the left cervical nodes and 1.26% in the lungs) but no lung miliary. PET/CT showed shrinkage of the lesions and a decrease in 18F-FDG avidity (SUVmax: cervical lymphadenopathies, 1.8; right pulmonary macrometastasis, 2.7).

Tumor responses were compared after three lines of radioiodine therapy (one at diagnosis, one under vemurafenib, one in the absence of BRAF inhibition; cumulative dose, 14.7 GBq) and 10 months of BRAF inhibition (7 months of vemurafenib and 3 months of dabrafenib). The red arrow signals a pulmonary macrometastasis with ^{131}I restored uptake showing a partial response (60% shrinkage), the green arrow signals a pulmonary macrometastasis without ^{131}I restored uptake showing a partial response (67% shrinkage), and the blue arrow signals a cervical lymphadenopathy with ^{131}I restored uptake showing a complete response (short axis from 36 to 5 mm).

This image illustrates a multimodal therapeutic strategy for an iodine-refractory *BRAF*-mutated metastatic PTC. Three lessons can be highlighted. First, both BRAF inhibitors can restore RAI uptake and may help characterize or visualize lesions, such as the pulmonary miliary here. Second, the redifferentiation process appears to be limited to the period of the inhibitor pharmacologic effect, indicating that the treatment should be continued during the RAI therapy. Moreover, plasma drug monitoring should be considered to prevent erroneous conclusions. Third, imaging must be used to assess efficacy because a rise in thyroglobulin can represent disease progression, disease redifferentiation, or tumor cell lysis.

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