Case Report

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Selpercatinib plus cemiplimab in *RET* positive medullary thyroid cancer patient with skin cancers

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Abstract

Background: Remarkable advancements in the therapeutic armamentarium for medullary thyroid cancer (MTC) have been observed in the last 10 years. The current understanding of driver mutations, such as RET and RAS, has enabled the development of new therapies for advanced and metastatic disease, demonstrating improved efficacy.

Patient Findings: A patient with RET-positive hereditary MTC developed multiple skin cancers (basal cell and squamous cell carcinomas) along with progression of MTC after 12 years of treatment with vandetanib. Once surgery to manage skin cancers has been excluded, the patient received a combination of selpercatinib and cemiplimab, and has been on this treatment at the full dose for 15 months, with ongoing therapy.

Summary: The combination of selpercatinib and cemiplimab was possible, with no new safety signals observed.

Keywords

selpercatinib, medullary thyroid cancer, RET, skin cancer, vandetanib

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Introduction

Medullary thyroid cancer (MTC) is a rare tumor, representing less than 15% of thyroid cancers.[1] Sporadic MTC is diagnosed in about 75% of the cases, while 25% of MTCs are hereditary. *RET* gene alterations have a pathogenetic role in MTC. Germinal *RET* gene mutations are present in about 98% of hereditary MTC, while *RET* somatic mutations are reported at least in 50% of patients with sporadic MTC at diagnosis. The standard of care in case of locally advanced disease is a total thyroidectomy plus central neck dissection associated to lateral neck dissection if needed. In the past, patients with metastatic, progressive disease and/or symptomatic disease were candidates for systemic therapy with multi-tyrosine kinase inhibitors (MTKIs), such as cabozantinib 140 mg and vandetanib 300 mg, according to pivotal EXAM and ZETA trials and regardless of the tumor's genomic profile.[2,3] Both cabozantinib and vandetanib inhibit the Vascular Endothelial Growth Factor 2 (VEGFR2) and the Rearranged During Transfection Gene (RET), while the Epidermal Growth Factor Receptor (EGFR) and the Mesenchymal-Epithelial Transition Gene (MET) are selectively inhibited by vandetanib and cabozantinib, respectively. MTKIs are antiangiogenic agents characterized by a broad spectrum of activity with high rate of toxicities, conditioning frequent treatment interruption and discontinuation. However, patients may remain under therapy even for several years and late side effects may occur. The most common late toxicities reported with vandetanib are cardiovascular (hypertension, 26.7%; QTc prolongation, 23.8%), followed by skin rash and nausea/vomiting.[4,5] A case of basal cell carcinoma of the skin (BCC) has been also reported.[5]

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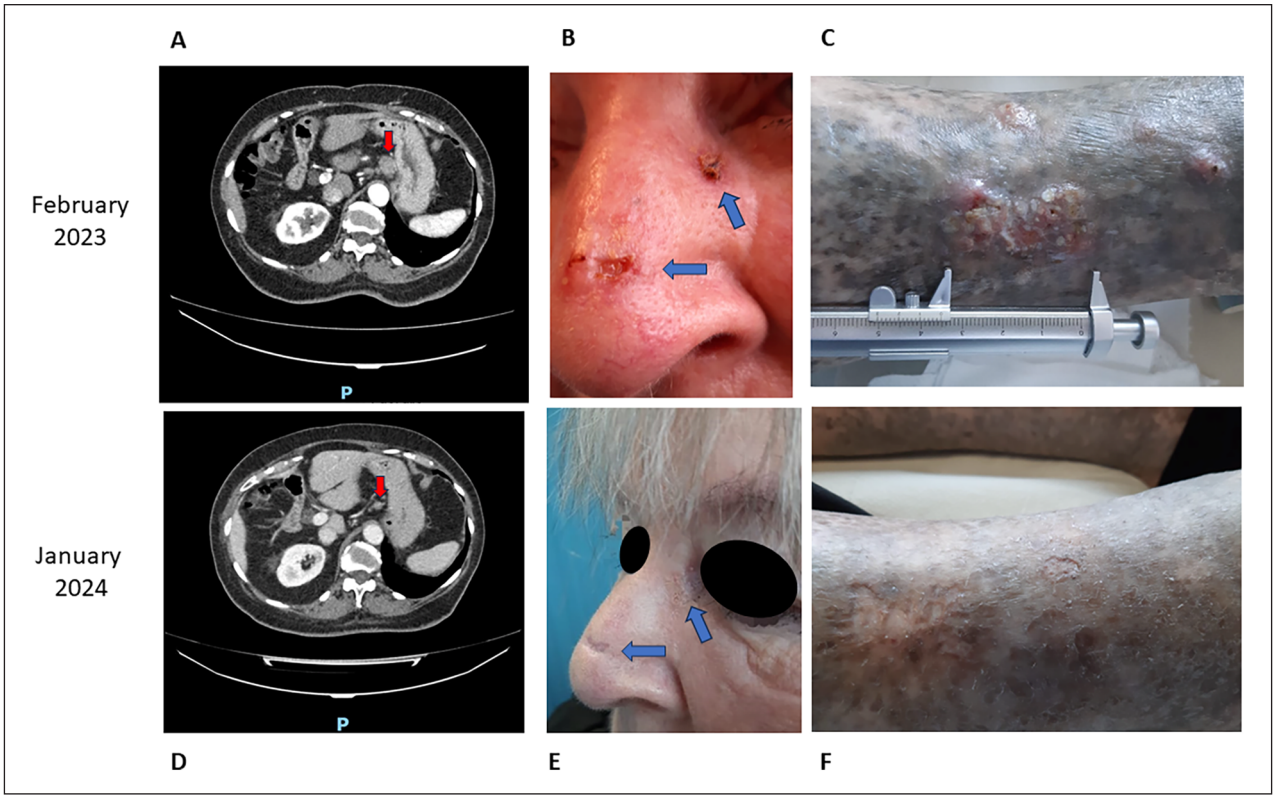

Figure 1. (A) CT scan demonstrating pathologic perigastric lymph node with 23 mm short axis (red arrow). (B) BCC of the nose (blue arrow). (C) One SCC of the leg at diagnosis. (D) CT scan after 15 months of treatment, showing a lymph node partial response (9 mm short axis) (red arrow). (E) Clinical complete remission of BCC of the nose after 13 months of cemiplimab (blue arrow). (F) Clinical complete remission of the leg SCC after 13 months of cemiplimab.

Since 2020, selpercatinib, a new selective RET inhibitor has been approved as monotherapy for the treatment of adults and adolescents (12 years older) with advanced *RET*-mutant MTC and advanced *RET* fusion-positive differentiated thyroid cancer already treated with a prior MTKIs. Recently, EMA granted selpercatinib for the first line treatment for both indications.[6]

A randomized phase III trial (Libretto 531) in patients with *RET* mutated MTC with progressive disease, demonstrated the reduction by 72% of the probability of disease progression of selpercatinib over cabozantinib/vandetanib in first line, paving the way to selpercatinib as the new standard of care for *RET* mutated MTC.[7]

Herein, we report a challenging case of a patient who developed multiple skin cancers (BCC and squamous cell carcinoma [SCC]) concomitant to MTC progression after 12 years of vandetanib. On February 2023, the patient started selpercatinb in combination with cemiplimab to manage both cancers.

Case description

A 75 years old patient with hereditary medullary thyroid cancer (hMTC), *RET* germline mutation in exon 15, Ser 891Ala, stage IV for bone and hepatic lesions, started vandetanib 300 mg in July 2011 when she was 62 years old. No further clinical manifestations associated with Multiple Endocrine Neoplasia (MEN) were found.

The dosage was reduced to 200 mg after one month due to hypertension grade 3. She obtained a partial remission as best response according to RECIST v1.1 after six months and continued with vandetanib 200 mg up to January 2023, when an ^{18}FDG PET/CT scan showed disease progression in multiple bone sites, such as left iliac crest, sacrum, and in lymph nodes of the small gastric curvature (Figure 1A); bone lesions were confirmed by pelvic magnetic resonance. In addition, small (< 1 cm), multiple, nodular and ulcerated lesions on both legs (at least 10), at the nose, and on the inner side of the left eye, suspicious for cancer appeared (Figures 1B and 1C). On the legs, diffuse blue-grey pigmented skin lesions appeared during vandetanib use and progressively increased over the years. Pathological diagnosis of skin lesions was well-differentiated invasive SCC in the legs and BCC in the face.

Selpercatinib 160 mg twice a day (BID) was started in February 2023 once vandetanib was withdrawn. At that time, Calcitonin (CT) and Carcinoembryonic

Antigen (CEA) levels were 1510 pg/mL and 90 ng/mL, respectively. Skin SCCs were not amenable to radical resection due to their number and characteristics (fixed at superficial skin) while BCCs were on the H areas of the face and, despite apparently being easy to treat, were at high risk of recurrence.[8] Hence, the patient started cemiplimab 350 mg (every three weeks) in April 2023, in combination with selpercatinib. The latest radiological evaluation in January 2025, showed a partial response according to RECIST v1.1 of target lesions correlated to MTC (Figure 1D), with SCC and BCC almost having disappeared (Figures 1E and 1F). After 24 months, selpercatinib plus cemiplimab are still ongoing at full dosage; CT and CEA were 11 pg/mL and 8 ng/mL, respectively. Combined treatment was well tolerated, without observing any significant toxicity. After six months of cemiplimab, we observed an increase in ACTH levels (from 79 pg/ml at baseline to 194 pg/ml, grade 1), with circulating cortisol at the upper limit of the normal range. There were no further changes over time, and no signs of hypercortisolism. The case was discussed and approved by the Comitato Etico Territoriale Lombardia 6, N° 0054213/24.

Discussion

We present, to our knowledge, the first reported case of combining selpercatinib with a PD-1 inhibitor in a *RET*-positive hMTC patient. Skin toxicity such as rash, acne, blue-grey hyperpigmentation is a known side effect of vandetanib, while skin cancer has been anecdotally reported as late side effect.[3,5,9] Vandetanib inhibits several tyrosine kinase receptors, including VEGFR2, RET and EGFR, the latter playing a role in the progression of skin SCC and BCC. Indeed, EGFR activation regulates the downstream signaling pathways (Ras-Raf-MEK-ERK, PI3K), which influence keratinocyte proliferation, differentiation and survival. The overall effect promotes the development of skin tumors.[10]

Management of skin cancers raised several concerns. Surgery was not considered for the leg SCC due to their clinical presentation, while the location of BCC on the H-zone of the face would have required an invasive procedure. Following multidisciplinary discussion, cemiplimab was chosen for both SCC and BCC treatment.

Cemiplimab is a PD-1 monoclonal antibody approved as first-line therapy for locally advanced or metastatic cutaneous SCC, and for patients with locally advanced or metastatic BCC who experienced adverse effects with a hedgehog pathway inhibitor (HHI) or had disease progression following HHI treatment. Treatment-emergent adverse events (TEAEs) of any grade were reported in approximately 90-100% of patients treated with cemiplimab, with fatigue, constipation, diarrhea and pruritus being the most common.[11,12]

Selpercatinib is a potent and highly selective RET inhibitor approved for RET-altered NSCLC, differentiated thyroid cancer, and MTC. In the phase I-II trial LIBRETTO-001 trial, selpercatinib demonstrated durable efficacy with a more favorable toxicity profile compared to prior therapies, such as cabozantinib and/or vandetanib. The ORR was high: 82.5% in treatment naïve patients and 77.6% in those previously treated with cabozantinb or vandetanib. One-year progression-free survival was 91.1% (CI 95% 84.8 to 94.8) in naïve patients and 79.5% (CI 95% 71.8 to 85.3) in pre-treated MTC patients.[12]

To date, immunotherapy has not been used in combination with selpercatinib. A recent retrospective study of 329 patients with RET fusion-positive, non-small cell lung cancer (NSCLC) compared hypersensitivity reactions in those patients previously treated with immunotherapy versus immunotherapy-naive counterparts. Hypersensitivity reactions to selpercatinib (grade 1-3) were more frequent in patients with prior immunotherapy exposure (77%) compared to immunotherapy naïve patients (23%). However, no significant differences were observed in the overall TEAEs rates, suggesting that selpercatinib can be safely administered regardless of prior immunotherapy status.[12] Although an increase in TEAEs was anticipated with the combination therapy, cemiplimab plus selpercatinib proved effective and well-tolerated, with no significant toxicity observed, apart from elevated ACTH levels (an effect already reported with selpercatinib).[13] The patient has continued full-dose treatment with both drugs over two years without major side effects.

Furthermore, selpercatinib demonstrated efficacy across all *RET* mutations, including the rare Ser 891Ala variant. Indeed, this patient harbored a rare *RET* germline mutation in exon 15 (Ser891Ala). The phenotypic heterogeneity of hMTC is largely driven by the specific *RET* mutation. Substitutions at cysteine 634 are usually associated with classical MEN2A, while mutations in non-cysteine codons such as Ser 891Ala, are more commonly associated to familial MTC.[14] The differing biological behavior of these mutations influences both latency and tumor aggressiveness.

Conclusions

The combination of selpercatinib plus cemiplimab was safe and well-tolerated, with no major TRAEs. Notably, we observed no hypersensitivity reactions associated with sequential use of immunotherapy followed by selpercatinib.

Author contributions

F.P., V.A. and L.D.L.: conceptualization, writing. A.B. and F.S.: review and editing.

Declaration of conflicting interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or

publication of this article: F.P.: nothing to declare. V.A.: Conference honoraria: Novartis, AstraZeneca. F.S.: Conference honoraria: Eli Lilly. A.B.: Advisory Board and Public Speeches: HRA Pharma, Novartis AAA, Bayer, AMGEN. L.D.L.: Conference honoraria/Advisory Board: EISAI, MSD, Merck Serono, Eli Lilly, Sanofi, Sunpharma, IPSEN, Bayer, Roche, Istituto Gentili Srl; New Bridge; Seagen; Novartis; Travel grant: Gilead

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