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Case Report

Combination of Osimertinib with Concurrent Chemotherapy and Hormonal Therapy for Synchronous NSCLC, Hormone Receptor-Positive Breast Cancer, and Triple-Negative Breast Cancer: Case Report

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Keywords
Multiple primary malignancy · Osimertinib · Chemotherapy · Epidermal growth factor receptor · Non-small cell lung cancer · Breast cancer

Abstract
Patients presenting with multiple primary malignancies remain a growing challenge for physicians due to a lack of data for generalizable guidelines. Identification of driver mutations in carcinogenesis leads to the development of targeted treatment of many different cancer types, but its combination with other anti-cancer therapy is not well understood. We report a case of a 66-year-old woman who presented with triple-negative breast cancer, multifocal hormone receptor-positive breast cancer, primary epidermal growth factor receptor-mutated lung adenocarcinoma, possible primary lung adenocarcinoma of unspecified mutational status in the contralateral lung, and a solitary metastatic lesion in the brain from one of her primary cancers. She was treated with stereotactic radiosurgery and osimertinib in combination with carboplatin/nab-paclitaxel, doxorubicin/cyclophosphamide, and letrozole, with excellent clinical and radiographical response. We did not observe synergistic toxicity or unexpected adverse events from the treatment. To the best of our knowledge, this is the first report of concurrent osimertinib with these chemotherapy and hormonal therapy agents. As large-scale studies are difficult to conduct for these rare cases requiring exceptional treatment, it is

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important for physicians to build on the community's shared experience via case reports to better predict efficacy and safety of combining targeted agents with other conventional systemic treatments.

Introduction

Multiple synchronous primary malignancies largely refer to the co-occurrence of two or more unrelated primary cancers. These patients represent a unique challenge in oncology. However, the criteria for multiple primary malignancies are not universal and remain a hurdle in cataloguing incidence, prognosis, and treatments pursued [1]. As such, the reported incidence of multiple primary malignancies harbours a large variance from 1.7%–18.4% across multiple studies [1–3]. Nevertheless, retrospective analysis of large databases suggests that the incidence of multiple primary malignancies is increasing, but these patients remain in a black box in oncology where individualized treatment is paramount due to a lack of strong evidence for generalizable guidelines [1].

Identification of driver mutations in carcinogenesis leads to the development of targeted treatment of many different cancer types. On this frontier, treatment of non-small cell lung cancer (NSCLC) has been revolutionized by next-generation sequencing, which allows for patient-specific treatment [4]. Osimertinib is a third-generation tyrosine kinase inhibitor (TKI) that has dramatically improved outcomes for patients with advanced NSCLC with an activating mutation in the epidermal growth factor receptor (EGFR) gene [5]. However, there is only limited evidence for the combination of osimertinib with other targeted treatment or cytotoxic chemotherapy, especially for patients with multiple primary malignancies. Therefore, further data are required to assess safety and efficacy for these combination treatments.

We aimed to contribute to addressing this gap in the literature through this case report of biopsy-proven synchronous EGFR-mutated NSCLC, triple-negative breast cancer (TNBC), and hormone receptor-positive breast cancer treated successfully with osimertinib in combination with cytotoxic chemotherapy and hormonal therapy without synergistic side effects.

Case Presentation

A 66-year-old woman was found to have an incidentally elevated CEA level on her routine blood tests performed by her family physician. She had a past medical history significant for hypertension, primary hyperparathyroidism, and nephrolithiasis. There were no focal or systemic symptoms of malignancy. Her ECOG performance score was 0. The patient denied alcohol use, endorsed a 25-pack per year history of tobacco use having quit 20 years ago, and occasional marijuana use. Family history was significant for colon cancer in the father, colon cancer in her maternal uncle, breast cancer in her paternal grandmother, and breast cancer in her paternal aunt. The patient underwent a screening colonoscopy and esophagogastroduodenoscopy, which were negative for malignancy. A screening CT of the chest showed scattered bilateral pulmonary nodules with mediastinal lymphadenopathy and bilateral breast densities. The patient was referred to medical oncology for further workup.

A PET scan was performed, revealing FDG-avid lesions in the left lower lobe of the lung (LLL), right middle lobe of the lung (RML), right paratracheal lymph node (LN), subcarinal LN, right supraclavicular LN right breast, and multiple lesions on the left breast (Fig. 1).

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Imaging-guided biopsy of the suspicious lesions revealed the following: (1) LLL mass, 3.4 × 2.4 cm, adenocarcinoma of the lung, PD-L1 0%, EGFR mutation in exon 20 S768I, ALK, and ROS1 negative; (2) RML nodule, 1.4 × 2.3 cm, nondiagnostic biopsy; (3) right supraclavicular LN, positive for metastatic carcinoma from lung primary. A mammogram was performed, showing bilateral multifocal breast masses highly suggestive of malignancy (BI-RADS 5). Ultrasound of the breasts and targeted biopsies revealed the following: (1) right breast with 2.7 × 1.4 × 1.4 cm spiculated lesion, biopsy revealing invasive ductal carcinoma with apocrine features, Nottingham grade 2, ER 0%, PR 0%, and HER2 2+, FISH negative; (2) left breast 1.7 × 1.4 × 1.7 cm mass, biopsy revealing invasive ductal carcinoma, Nottingham grade 1–2, ER >95%, PR >95%, HER2 1 +; 3), left breast 1.1 × 1.1 × 1 cm mass, biopsy revealing invasive carcinoma with mixed lobular and ductal features, Nottingham grade 2, ER >90%, PR >90%, HER2 1 + 3 right axillary LN positive for metastatic adenocarcinoma. Finally, an MRI of the brain revealed a solitary left inferior temporal lobe lesion measuring 1.5 × 1.2 × 0.9 cm. In summary, the patient was found to have right primary TNBC, left multifocal hormone receptor-positive breast cancer, left primary EGFR-mutated lung adenocarcinoma, possible right primary lung adenocarcinoma of unspecified mutational status, and a solitary metastatic lesion in the brain from one of her primary cancers (Fig. 1).

The case was discussed at multi-disciplinary tumour boards. She was treated with 20 Gy in 1 fraction stereotactic radiosurgery for her oligometastatic brain lesion. Systemic treatment was initiated with osimertinib 80 mg, weekly carboplatin AUC 2, and weekly nab-paclitaxel 100 mg/m^2. Restaging CT after 12 weeks of systemic treatment revealed complete radiographical response of her LLL lesion and regression of her RML lesion and mediastinal lymphadenopathy. She was transitioned to doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 every 3 weeks. Osimertinib was continued. She experienced increasing fatigue despite serial dose reductions of doxorubicin and cyclophosphamide to 85% and 75% of conventional doses, respectively, and was able to complete 3 cycles. The patient's breast masses had complete clinical and radiographical response post-chemotherapy. The patient underwent a right mastectomy, and histologic analysis revealed a complete pathological response in the right breast and sampled LNs. The patient was initiated on maintenance letrozole with osimertinib without significant side effects. PET scan 16 months post diagnosis redemonstrated a metabolically active RML nodule, but a complete metabolic and radiographical response to all other previously noted lesions (Fig. 2). This raised the suspicion for this being a non-EGFR-mutated lung cancer given the discrepancy in response to treatment. Local consolidative therapy with radiation or surgery to the RML nodule and a left mastectomy was declined by the patient. Serial brain MRI was significant for radiation-related changes without recurrent lesions. The patient remains clinically well without side effects from previous or current treatments 20 months post diagnosis. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000533783).

Discussion

The expanding horizon of translational medicine introduces exciting novel therapies in oncology. However, clinical trials routinely exclude patients with multiple concurrent cancers, and there is not sufficient evidence for generalizable guidelines in these patients. As personalized precision medicine evolves, physicians will be challenged with combining targeted agents and other systemic treatments without adequate data to support efficacy or safety for patients with multiple primary malignancies. In our patient, osimertinib combined with carboplatin/nab-paclitaxel, doxorubicin/cyclophosphamide, and letrozole

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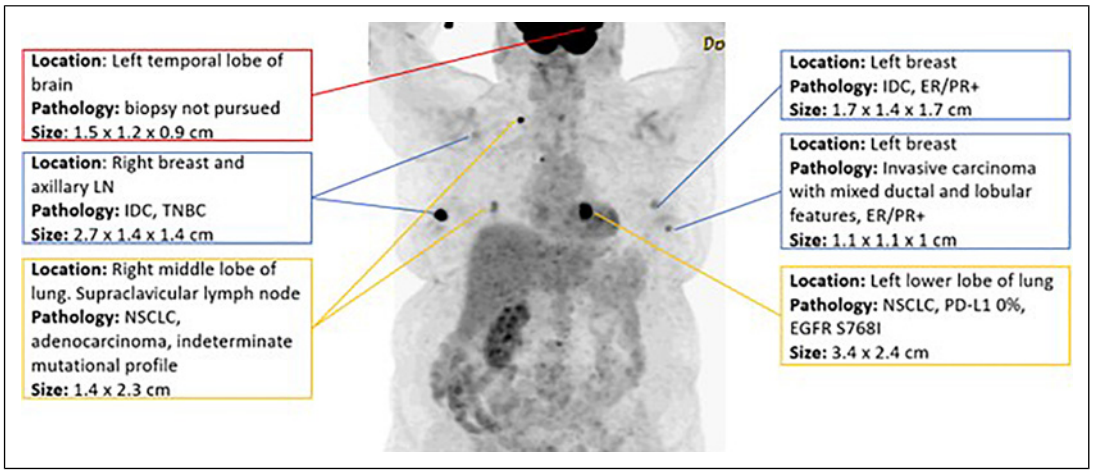

Fig. 1. PET scan displaying metabolically active lesions with corresponding pathology. LN, lymph node; IDC, invasive ductal carcinoma; TNBC, triple-negative breast cancer; NSCLC, non-small cell lung cancer; ER, oestrogen receptor; PR, progesterone receptor; PD-L1, programmed death ligand 1; EGFR, epidermal growth factor receptor.

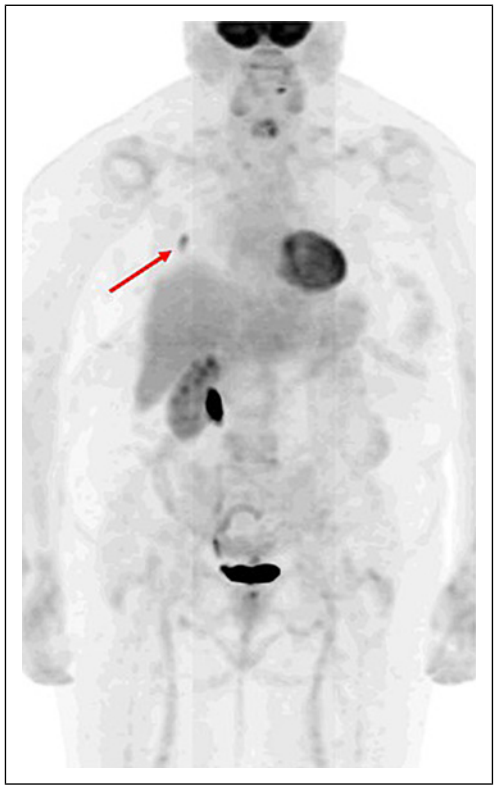

Fig. 2. Restaging PET scan 16 months post-diagnosis showing residual metabolic activity in the previously biopsy-proven RML NSCLC and complete metabolic response at all other sites of previous activity.

yielded an excellent clinical and radiographical response without synergistic side effects or significant adverse events. To the best of our knowledge, this is the first report of concurrent osimertinib with these chemotherapy and hormonal therapy agents. As large-scale studies are difficult to conduct for these rare cases requiring exceptional treatment, it is important for physicians to build on the community's shared experience via case reports.

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Treatment of multiple concurrent primary malignancies is often a therapeutic challenge which requires an individualized approach through shared decision-making with the patient and the multi-disciplinary team [6]. Oftentimes, a common denominator for the best first-line treatment does not exist across multiple tumour types, and systemic treatments in this setting may need to be altered from their conventional components to maximize overall efficacy and minimize drug interactions. One strategy is to prioritize the cancer that is likely to be symptomatic or prognosis-limiting [7]. In our patient, this was the solitary brain metastasis. As a biopsy was not pursued, it is difficult to ascertain the primary as the prevalence of brain metastasis in EGFR-mutated NSCLC is reported to be as high as 70% versus 46% for TNBC [8, 9]. As such, definitive treatment with radiation was completed alongside osimertinib to cover both scenarios. Combination of carboplatin and paclitaxel is a common chemotherapy regimen used in operable TNBC and advanced NSCLC [10, 11]. Doxorubicin and cyclophosphamide is used in the neoadjuvant setting for both TNBC and hormone receptor-positive breast cancer [12]. These cytotoxic chemotherapy regimens share certain similar adverse events to osimertinib including bone marrow suppression, rash, diarrhoea, alopecia, nausea, and fatigue. These side effects were deemed observable/manageable and thus optimal treatment was pursued. Neoadjuvant pembrolizumab was considered for TNBC but given reports of increased pneumonitis from the combination of osimertinib with immunotherapy, this was withheld [13–15]. The addition of oestrogen receptor-modulating agents to osimertinib has not been well described in the literature including potential drug-drug interactions. Nevertheless, the risk versus benefit of letrozole and osimertinib was discussed and a collective decision was pursued for combination treatment.

Combining targeted therapies such as TKIs with cytotoxic chemotherapy is not a novel concept. Several clinical trials are evaluating the safety and efficacy of osimertinib in combination with platinum-based chemotherapy for the treatment of advanced EGFR-mutated NSCLC. The FLAURA2 study is a phase 3 randomized control study evaluating osimertinib monotherapy versus osimertinib in combination with platinum-pemetrexed chemotherapy for first-line treatment (NCT04035486). Similar to our case, results of the pre-randomization safety run-in study of 30 patients showed no unexpected adverse events of the combination treatment [16]. Furthermore, in a randomized control study involving 44 patients whose cancer progressed on osimertinib, continuation of osimertinib with chemotherapy appeared safe and efficacious [17]. A similar study showed that continuing gefitinib, which is a first-generation EGFR TKI, in combination with chemotherapy at the time of progression did not yield synergistic adverse events, although this combination did not provide additional clinical benefit [18].

Conclusion

This case report describes a rare presentation of multiple concurrent primary cancers treated with combination chemotherapy, targeted oral therapy, hormonal therapy, radiation, and surgery with excellent clinical and radiographical response. As we discover novel targetable mutations in various cancers, combination treatment with other targeted agents and/or chemotherapy will become more common, especially for patients with multiple synchronous primary cancers. Therefore, further studies are required to better characterize the efficacy and safety of combining targeted treatments with conventional chemotherapy.

Statement of Ethics

Ethical approval is not required for this study in accordance with local or national guidelines. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

C.L.P. wrote the main body of the manuscript. F.M. wrote the body of the manuscript. R.R.S. supervised the scientific and clinical direction of the manuscript. All authors reviewed the final manuscript for publication.

Data Availability Statement

All data generated or analysed during this study are included in this article and its online supplementary material files. Further enquiries can be directed to the corresponding author.

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