CASE REPORT

Battling regional (stage III) lung cancer: bumpy road of a cancer survivor in the immunotherapy age

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SUMMARY

A 58-year-old woman, a heavy smoker, was diagnosed with stage III squamous cell lung cancer. She was treated with concurrent chemotherapy and radiotherapy, with partial response. 2 months later, she had haemoptysis caused by brisk bleeding from the radiated right upper lobe. Fortunately, her bleed was self-limited. 4 months later, a rapidly enlarging renal mass was discovered and turned out to be metastatic from the lung primary. Second-line chemotherapy with docetaxel and ramucirumab did not have effects on the renal mass after 2 cycles. Despite not being eligible for a durvalumab trial because of lack of PD-L1 expression, she had a meaningful response to nivolumab. Once every 2 weeks, infusion of nivolumab resulted in rapid tumour shrinkage in multiple areas. In the next few months, she experienced a variety of side effects, some of which were potentially life-threatening. She had disease progression 9 months into treatment.

BACKGROUND

Lung cancer was ranked as the number one cause of cancer death in men and women in developed countries, and number one and two in men and women, respectively, in developing countries (American Cancer Society Global Cancer Facts & Figures, 3rd edition). Most lung cancers are diagnosed in regional and advanced stage (III and IV), at which point cure is uncommon (stage III 20%, stage IV is considered incurable).^{1 2}

Concurrent chemoradiation is used for stage III patients especially for those tumours that are not resectable but are otherwise performing well.³ However, local and distant failures are very common despite intensive multimodality treatments. Current research efforts are focused on adjuvant systemic treatment to decrease the odds of local or distant failure in these patients and to improve cure rate.

Generally, metastatic disease that has progressed from local regional cancer following concurrent chemoradiation therapy is treated with systemic chemotherapy unless the cancers are driven by one of the known driver mutations (epidermal growth factor receptor (EGFR),^{4 5} anaplastic lymphoma kinase (ALK),⁶ ROS1⁷). However, chemotherapies are often not effective, frequently have dose-limiting toxicities and are not for patients with poor performance status (ECOG3 or above). Options for the squamous cell subtype are even more limited since pemetrexed and bevacizumab are not approved for this situation. Docetaxel and erlotinib are the most popular choices.²

Unfortunately, due to limited treatment efficacy and, often, quick decline in performance, most patients soon succumb to the disease after recurrence.

Immune checkpoint inhibitor nivolumab was first approved by the US Food and Drug Administration (FDA) for squamous cell lung cancers in March 2015.⁸ The approval was further expanded to include adenocarcinoma of the lung in November 2015, following reports in a phase III trial that nivolumab was superior to docetaxel in second-line settings.⁹ In October 2015, another anti-PD-1 antibody was approved for the treatment of non-small cell lung cancer (NSCLC) after failing platinum-based doublet if tumours expressed PD-L1.¹⁰ With the use of these drugs, responses have been seen in ~20% of all cases of heavily treated patients. Responses are often durable, and it is much less demanding in terms of performance. Autoimmune-related side effects are characteristic and can sometimes be fatal. Although generally perceived to have fewer and less serious side effects, they do happen and can be serious,¹¹ therefore careful monitoring is advised.

We report a case of advanced squamous cell lung cancer treated with immunotherapy after progression from treated stage III disease. We present this case to highlight the need for finding more effective treatment for patients with stage III lung cancer by enrolling them onto clinical trials. We want to stress that nivolumab, an antibody directed against PD-L1, can be life-saving even for those with poor performance, tumours stained negative for PD-L1 and aggressive disease. These patients have been only treated with supportive care in the past. Generally benign, adverse effects associated with immunotherapy are not uncommon.

CASE PRESENTATION

A 58-year-old woman, a bank executive and former smoker with a 30-pack-year history, presented to her primary care physician, with cough, wheezing and shortness of breath. She was prescribed an inhaler and antibiotics, without relief. Imaging work up revealed a right upper lobe lung mass and she was eventually diagnosed with squamous cell cancer at stage IIIa (T3N2M0) in May 2014 (figure 1A). The primary tumour was 9.3×8.0 cm in the right upper lobe. The patient was enrolled into the RTOG1106 protocol (<https://clinicaltrials.gov/ct2/results?term=RTOG1106>), a randomised phase II clinical trial testing whether positron emission tomography (PET)/CT guidance of radiation therapy would lead to improved survival in stage

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Figure 1 Histology of lung cancer and PD-L1 staining. Shown are H&E staining of squamous cell cancer from the lung biopsy on 5 May 2014 (A×200), renal biopsy 7 February 2015 (B×200) and immunostaining for PD-L1 (C, negative).

IIIa and IIIb NSCLC. She received a total of 66 Gy in 31 treatments spanning more than 6 weeks. She was removed from the protocol before the boost due to significant volume loss in the right lung, which would make the boost unsafe by exposing the normal tissue to excess amounts of radiation. Along with radiation, she had a total of six weekly chemotherapy infusions with carboplatin and paclitaxel, as specified in the protocol ending 25 July 2014. After treatment, she was found to have reached a partial response per RECIST 1.1. She received no consolidation chemotherapy following chemoradiation, and was monitored.

Late September 2014, she developed haemoptysis and was evaluated by her pulmonologist, using bronchoscopy. The patient was found to have a brisk bleed from the right upper lobe, which was radiated. A code blue was called and she was intubated and treated in the intensive care unit. Fortunately, the bleed was self-limited and she was able to be extubated, eventually recovering.

Four months after the haemoptysis episode, a restaging CT scan showed appearance of a new large renal mass measuring 7.5×8.2×8.1 cm, with para-aortic lymphadenopathy and renal vein tumour thrombosis. Although the radiated tumour was stable, there were several enlarging pulmonary nodules including a lingular lobe nodule measuring 1.1×0.6 cm. Distant failure with cancer progression from the known NSCLC was suspected. Biopsy of the left kidney mass proved it was of the same morphology found in the lung at first diagnosis (figure 1B). The patient received two cycles of docetaxel plus ramucirumab with growth factor support until April 2015.

A restaging scan showed disease progression. The tumours continued to enlarge in the bilateral kidneys, with right retroperitoneal and retrocrural lymphadenopathy. The patient's performance now declined to an ECOG3 with palpable left flank mass causing pain and constipation. While we were considering an immunotherapy trial on durvalumab versus nivolumab, recently

approved for squamous cell lung cancer, the patient received palliative radiation to her kidney mass (30 Gy in 10 fractions) with effective palliation to her abdominal pain. Her tumour stained negative for PD-L1 (figure 1C) and she did not qualify for the durvalumab trial due to her condition. Fortunately, nivolumab became available and she started receiving nivolumab. Over the next 9 months, her tumour burden decreased by 30% (partial response per RECIST1.1, figure 2A–D). The individual tumours waxed and waned. Her performance improved 8 weeks into the treatment to the point where she could resume her work (ECOG1). Her quality of life was very good.

The treatment was not without side effects. The patient had a large pleural effusion, accumulated on the left chest after 12 cycles. The effusion had to be drained and managed with pleurodesis. Analysis of the pleural fluid revealed an exudate with neither malignant cells nor infection but with a high concentration of triglycerides (508 mg/dL), however, the patient had no trauma, no damage to the thoracic duct and no superior vena cava syndrome. She had abdominal pain and constipation attributable to the use of nivolumab, with work up showing no other apparent aetiologies. In addition, she developed autoimmune nephritis with elevation of creatinine (grade 2, creatinine 2.19) after 16 cycles, and received prednisone with resolution of renal insufficiency. Later, she had to be treated for grade 2 hypercalcaemia (Ca 12.2 mg/dL) with bisphosphonate (pamidronate 90 mg intravenous) after 18 cycles, which exacerbated the constipation. This occurred at almost the same time the hypercalcaemia had developed, and she started having increased abdominal pain, nausea and vomiting, along with abdominal distention that could not be controlled. Work up eventually diagnosed her with paralytic abdominal ileus (bowel rest, no TPN, G2); the nivolumab was withheld and she was treated with nasogastric (NG) tube and bowel rest. MRI of the abdomen showed no bowel obstruction but progressive increase in the bulk of metastatic

Figure 2 Response of lung cancer to nivolumab. Shown are non-contrast CT images taken on 6 May 2015 (B) and 27 August 2015 (A and C). Arrows point to remarkable shrinkage in tumor sizes in both the pleural based mass (A and B) and renal mass (C).

lymphadenopathy within the central mesentery, porta hepatis, lesser sac and abdominal retroperitoneum, and worsening renal, liver and pleural metastases. The mass was also compressing on the splenic vein and invading the back of the pancreas, causing increase in pancreas size. The patient was taken off nivolumab due to treatment failure and serious side effects.

The patient unfortunately passed away just before her 60th birthday, 20 months after diagnosis. Immediate cause of death was pneumonia and/or pulmonary embolism.

INVESTIGATIONS

- ▶ CT-guided renal mass biopsy
- ▶ Tumour tissue PD-L1 immunohistochemistry staining
- ▶ Thoracentesis and pleural fluid cytology
- ▶ Abdominal ultrasound and X-ray to help differentiate drug aetiologies for the abdominal pain
- ▶ Bilateral low extremity compression ultrasound to search for venous thrombosis
- ▶ MRI of the abdomen without and with contrast

DIFFERENTIAL DIAGNOSIS

- ▶ Small cell lung cancer
- ▶ Lung adenocarcinoma
- ▶ Large cell carcinoma of the lung
- ▶ Renal cell carcinoma
- ▶ Other causes of exudate/chylothorax
- ▶ Acute kidney injury
- ▶ Hypercalcaemia of malignancies

TREATMENT

Our patient was initially treated with concurrent chemoradiation therapy. External beam radiation was given fractionated, daily, 5 days/week, for a total of 66 Gy in 31 fractions; chemotherapy was six weekly infusions of carboplatin at AUC of 2 in 30 min, paclitaxel of 45 mg/m² in 1 hour with standard

premedication with dexamethasone, zofran, pepcid and benadryl. On recurrence, docetaxel was given intravenously once every 3 weeks in half an hour, 75 mg/m² in 30 min together with ramucirumab (10 mg/kg) on day 1 with growth factor support, and pegfilgrastim 6 mg subcutaneously 24 hours after chemotherapy. Premedication included dexamethasone, given 1 day before, on the day of infusion and 1 day after. Nivolumab was given once every 2 weeks at 3 mg/kg as infusion in 1 hour. CT scan of the thorax and abdomen without contrast (the patient was allergic to intravenous contrast, displaying wheezing and labile blood pressure) was used for restaging once every 8 weeks. The pleural effusion was drained with a chest tube. The autoimmune nephritis was treated with prednisone 40 mg daily taper in 6 weeks. The hypercalcaemia was treated with pamidronate 90 mg intravenous infusion. The paralytic ileus was treated with NG tube and bowel rest.

OUTCOME AND FOLLOW-UP

The patient received nivolumab once every 2 weeks for 18 consecutive cycles. The final CT scan without contrast showed a subtle increase of lymphadenopathy and an enlarging pancreas in the abdomen. MRI of the abdomen with contrast revealed progressive increase in the bulk of metastatic lymphadenopathy within the central mesentery, porta hepatis, lesser sac and abdominal retroperitoneum, and worsening renal, liver and pleural metastasis. The patient was taken off nivolumab and considered for a clinical trial or alternate chemotherapy. She passed away shortly after.

DISCUSSION

Most patients with lung cancer do not develop symptoms until their cancers are in the late stage. Before implementation of lung cancer screening, only about a quarter of patients were diagnosed in the early stages (stage I and II). Local regional diseases are found in 22% of all patients and 57% at stage IV.¹²

This is likely partially due to the fact that our lungs have ample reserves. In socioeconomically disadvantaged areas/populations, diagnosis is skewed towards an even later stage. This is likely going to change somewhat since major organisations such as the National Comprehensive Cancer Network (NCCN)¹³ and USPTF¹⁴ are recommending lung cancer screening and the Center for Medicare and Medicaid Services (CMC) has started to cover the cost of such screening. However, severe cost burden and the false-positive rate during screening still need to be properly addressed before the situation completely turns around.

Regional diseases are often unresectable, leaving chemoradiation therapy as the treatment of choice. Unfortunately, local or distant failure rate are high after chemoradiation therapy, therefore clinical trials designed to improve the situation is an area of hot research. RTOG1106, a randomised phase II study of unresectable stage III NSCLC treated with concurrent chemoradiation therapy is testing the hypothesis that PET scan-guided adaptive radiotherapy given concurrent with chemotherapy improves survival. Other trials for stage III patients include the ALCHEMIST and the PACIFIC study. The ALCHEMIST study (<https://clinicaltrials.gov/ct2/results?term=ALCHEMIST&Search>) accrual surgically resected including stage IIIa patients whose tumours are positive for EGFR, ALK or other mutations. The PACIFIC study (<https://clinicaltrials.gov/ct2/show/NCT02125461?term=PACIFIC&rank>) is an international, multicentre, randomised and placebo controlled phase III study of durvalumab versus placebo in patients who have been treated with concurrent chemoradiation therapy. The primary end point is progression survival. Our patient was able to enrol into the RTOG1106. Unfortunately, she came off the study due to severe volume contraction in the radiated right upper lobe, which made continued execution of the protocol dangerous due to excessive exposure of normal tissue to the radiation field. She did not receive consolidation chemotherapy since it is believed that consolidation chemotherapy adds little to decrease recurrence.³ Her disease recurred with distant metastasis shortly (6 months) after she finished treatment.

In the current management of NSCLC, histology dictates the choice of chemotherapy agents. Squamous cell lung cancer has fewer options compared with adenocarcinoma, since bevacizumab and pemetrexed are not effective.¹⁵ After failure of platinum-based chemotherapy doublet, a commonly used second-line chemotherapy regimen was docetaxel before ramucirumab and immune checkpoint inhibitors were approved. In the trial, ramucirumab was shown to improve survival compared with docetaxel alone.¹⁶ However, even this combination was not effective in our patient.

Immune checkpoint inhibitors are now approved for use in patients with lung cancer after failure of platinum-based chemotherapy. These inhibitors work by blocking the lethal interaction between cancer cells and the CT8(+) T cells cell, which triggers T-cell anergy and death of the host T-cells. This effectively activates the CT8(+) T cells cells in the tumour microenvironment and controls the tumours in patients responding to such agent. Since this mechanism is normally used by our body to downregulate the immune system, blocking such mechanism can trigger an autoimmune state manifesting as colitis, thyroiditis, hepatitis, nephritis, hypophysitis, pneumonitis, myasthenia gravis, etc. Sometimes it can be lethal.¹⁷ The treatment, should any of these conditions develop, is steroid equivalent to 1 mg/kg or 40 mg a day of prednisone, tapered down slowly over 4–6 weeks. Most patients will do fine without evidence of compromise in anti-neoplastic activity. However, nivolumab works by blocking the PD-1 expressed on tumour cells, which expresses PD-L1 as the

ligand. Low levels of PD-L1 or sometimes ‘no expression’ do not preclude response to nivolumab, as was the case in our patient. The reason for this is not entirely clear, but PD-L1 expression can be dynamic, among other features.¹⁸

In addition to the known, clearly autoimmune-related side effects, patients treated with immunotherapy can have serious side effects. Therefore, they need to be closely monitored in order to avoid hospitalisation and mortality due to serious side effects. Our patient had pleural effusion, with more than 2 L of chylorous fluid being drained. Her renal failure did not improve until prednisone was started. Owing to the undetected progressive lymphadenopathy, she had abdominal pain that had her chronically using opioids. Unfortunately, opioids exacerbate constipation, requiring laxatives such as miralax and sorbitol, etc. Laxative use sometimes worsens abdominal pain. She also had hypercalcaemia during treatment, which was controlled only with intravenous pamidronate infusion. Paralytic ileus related to the use of nivolumab (G2) caused another hospitalisation. Although patients on immunotherapy typically have autoimmune colitis manifested by abdominal pain, diarrhoea, fever and, sometimes, bowel perforation, this patient had paralytic ileus, which has only been seen in one other case report.

In patients treated with immunotherapy, the judgement of disease progression is often not readily made. Restaging follows RECIST1.1 criteria, however, it is managed by immune-related RECIST criteria.¹⁹ Disease progression needs to be confirmed in subsequent scans before taking patients off treatment. Commonly, imaging shows up and down changes, including new lesions, while the patients are doing well clinically. Under such conditions, patients are often kept on the drug as they are thought to still derive benefit from the treatment. Unless their condition keeps worsening with increasing tumour size, which is confirmed in subsequent scans, treatments continue.

Learning points

- ▶ Locally advanced/local regional lung cancers frequently relapse after ‘definitive’ treatment. Clinical trials designed to improve cure rate comprise an area of hot research.
- ▶ Immune checkpoint inhibitors such as nivolumab and pembrolizumab provide a viable option for patients with recurrent and metastatic disease, even if it is rapidly progressing, with poor performance. Nivolumab does not need a positive PD-L1 staining to begin with.
- ▶ Although generally perceived to be benign, immune checkpoint inhibitors often cause morbidity. Some of them are serious and need to be watched closely. Good supportive care is essential for prolonging life.²⁰ Despite all these, immunotherapy can lead to response not seen with chemotherapy, with a better toxicity profile.
- ▶ Immune-related side effects may include renal insufficiency, which needs to be treated with cortical steroids.

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Competing interests None declared.

Patient consent Obtained.

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