Beneficial effect of additional treatment with widely available anticancer agents in advanced small lung cell carcinoma: A case report

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Abstract. Small-cell lung carcinoma is a type of lung cancer characterized by very poor prognosis, as the majority of the patients have already developed metastases at initial diagnosis. Small-cell lung cancer accounts for ~15% of all lung cancer cases. The present study reports the case of a female patient with advanced-stage small-cell lung cancer. The patient received the standard treatments (6 cycles of platinum and etoposide chemotherapy followed by Gamma Knife treatment of suspicious mediastinal lymphnodes); in addition, naturally derived agents (curcumin, parthenolide, betuline, sulforaphane, withanolides, lactoferrin, pomegranate fruit extract, flaxseed and dioscorea) were alternately administered at increased doses, while previously prescribed medications for other comorbidities (metformin and atorvastatin) were continued. Complete regression of the tumour was observed, and the patient remains in full remission and cancer-free for >7 years. Moreover, no treatment-related side effects and no drug interactions were observed.

Introduction

Lung cancer is the most common cause of cancer-related mortality worldwide. It was estimated that, in 2016, there were 158,080 deaths from lung cancer in the United States (1). In the latest statistical analysis, it is predicted that in 2018 the number of deaths may reach ~154,050 and the number of new cases 234,030, and the mortality from lung cancer is expected to be higher compared with that from other cancers combined (2). Small-cell lung cancer (SCLC) accounts for ~13-15% of all lung cancer cases (3) and is strongly associated with tobacco smoking. SCLC is very chemoradiosensitive, but patients often present with symptoms of metastatic disease at the time of SCLC diagnosis, and the prognosis remains poor. Unfortunately, in advanced-stage SCLC, the median survival with the currently available standard treatments is only 9-10 months from the time of diagnosis.

The treatment of SCLC mainly consists of chemotherapy, with a combination of platinum and etoposide or irinotecan. The use of prophylactic cranial irradiation (PCI) and sequential thoracic irradiation has been reported to improve survival in selected patients with extensive SCLC (4,5).

Unfortunately, almost all patients relapse with chemoresistant disease (6) and there has been almost no improvement in 1-year SCLC mortality rate over 10 years (7).

Case report

In February 2011, a 62-year-old woman was diagnosed with SCLC (Figs. 1 and 2). The patient was a retired teacher and a smoker (20 cigarettes/day for 45 years).A chest X-ray followed by computed tomography were performed to explain the cause of a persistent cough following a respiratory infection~1 month earlier. The diagnosis of SCLC was based on microscopic examination of the material obtained during bronchoscopy. The patient's overall health was good, but she reported previously taking metformin due to impaired fasting glucose and atorvastatin due to hypercholesterolemia. At 5 weeks after the initial diagnosis, chemotherapy with platinum (49.69 mg/day for 3 days) and etoposide (165.62 mg/day for 3 days) was administered. The patient received 6 cycles of this treatment, but the intervals between cycles had to be prolonged due to leukopenia (WBC <2,500/μl). Cancer remission was achieved after 6 cycles of standard therapy. After the 4th cycle, PCI (2.5 Gy/g; 10 cycles) was performed. In addition, long-term enoxaparin (40 mg/day) therapy lasting 2 years was prescribed.

In April 2012, a computed tomography-positron emission tomography scan was performed in order to exclude neoplastic changes in the lymphnodes and metastatic disease. Gamma Knife was then used to treat mediastinal lymphnodes suspected for neoplastic infiltration. Oncological treatment was completed in May 2012 (Figs. 3 and 4). The patient was advised to visit the oncological centre in case of tumour progression detected on annual follow-up examinations.

Simultaneously, an off-label therapy was administered. The individualized scheme included curcumin, parthenolide, betuline, sulforaphane, withanolides, lactoferrin, pomegranate

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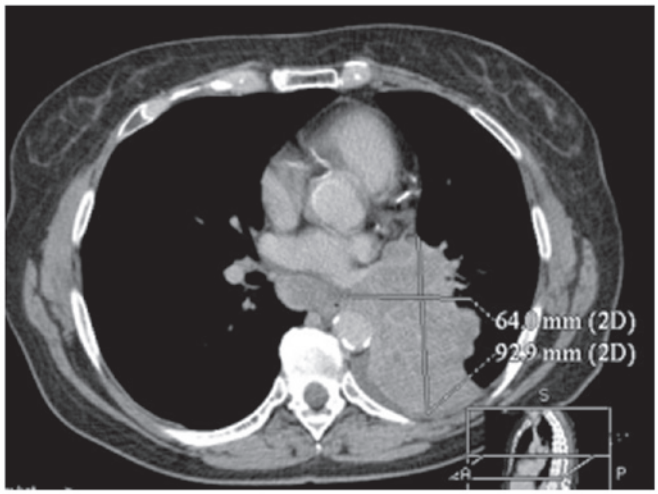

Figure 1. Computed tomography imaging showing the lung tumour at the time of diagnosis.

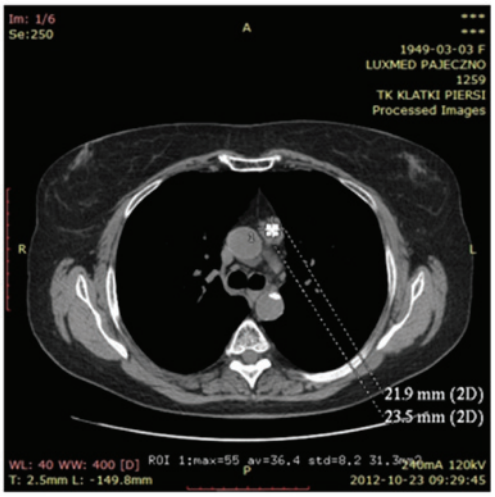

Figure 3. Computed tomography imaging showing a suspicious lymphnode in the anterior mediastinum after chemotherapy treatment.

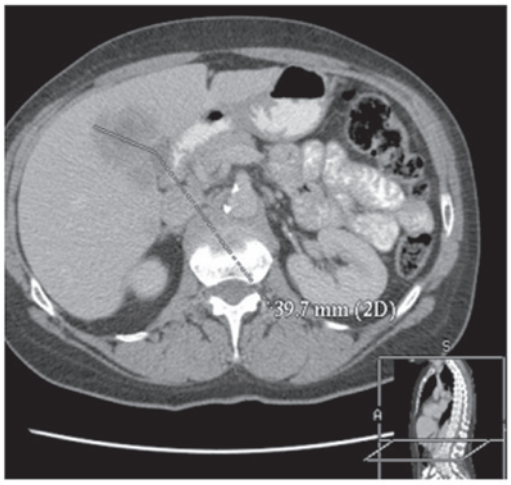

Figure 2. Computed tomography metastasis to the liver at the time of diagnosis.

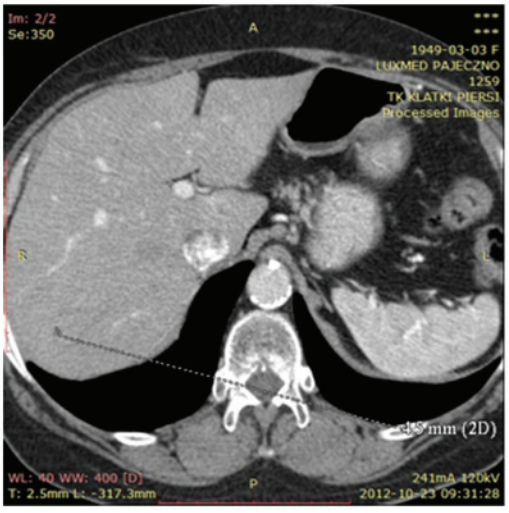

Figure 4. Computed tomography imaging showing regression of metastatic lesions in the liver after chemotherapy treatment.

fruit extract, flaxseed orally and dioscorea in inhalational form.

The treatment strategy was based on changing the agents every 5 days in order to avoid developing resistance to treatment. Compounds extracted from medicinal plants usually have low bioavailability; therefore, the pivotal role of appropriately higher doses of certain agents should be emphasised. In the majority of cases, double dosages were used, rather than what was recommended by the manufacturer. However, metformin, atorvastatin and enoxaparin were administered at doses of 850, 10 and 40 mg/day, respectively. The patient has been continuously taking curcumin (1,330 mg/day), betuline (10 ml 2% extract/day), withanolides (1,100 mg/day), parthenolide (0.624 mg/day), lactoferrin (200 mg/day), sulforaphane (100 mg/day) and pomegranate fruit extract (2,200 mg/day) to this day. Some of the active substances are administered on a daily basis (curcumin, sulforaphane, atorvastatin and metformin), whereas the others are changed every 5 days. All agents mentioned above were well-tolerated. Follow-up chest X-ray and abdominal ultrasound are performed annually and have not shown any progression or metastasis of the lung cancer. The results of the annual laboratory blood tests are also normal.

The patient is a member of the author's family and remains under his medical care. She remains alive and in good condition. The last examination took place in September 2018.

Discussion

The medications previously used by the patient due to comorbidities (metformin and atorvastatin) were continued during chemo- and radiotherapy. Atorvastatin may overcome the resistance to carboplatin in patients with lung cancer and, when used together with carboplatin, it inhibits the growth of lung cancer more effectively compared with either of these agents used alone (8). In addition, it has been previously reported that patients using rosuvastatin, simvastatin, atorvastatin and pravastatin had a significantly decreased lung cancer risk,

depending on statin doses (9). The beneficial role of metformin was observed by Chuang *et al* in patients with diabetes mellitus who had inoperable lung cancer. This patient group exhibited a significantly longer overall survival while using metformin (10). A number of previous studies indicated the anticancer activity of metformin, including cell cycle arrest, apoptosis of malignant cells and tumour growth suppression (11). In patients treated with cisplatin-based chemotherapy, an increased risk of arterial and venous thromboembolic events was confirmed (12). For example, in Asian patients with SCLC, the annual cumulative incidence of thromboembolic events is ~10% (13). Using primary thromboprophylaxis with low-molecular-weight heparin can significantly lower the risk of thromboembolic events in patients treated with chemotherapy (14). Enoxaparin may have a beneficial impact on overall survival in patients treated for lung cancer (15); however, in patients with SCLC, enoxaparin in supraprophylactic doses (1 mg/kg) increased the incidence of haemorrhagic events and had no beneficial effect on progression-free or overall survival (16).

Naturally occurring substances have known anticancer properties. Curcumin has been reported to regulate oncogenes (p53, egr-1, c-myc and Bcl-xL), transcription factors (NF-κB, STAT-3 and AP-1),protein kinases (MAPK)and enzymes (cyclooxygenase and lipoxygenase). The beneficial effects of curcumin have been observed in terms of sensitization to chemo- and radiotherapy, reduction of tumour invasion and metastasis (17).

Therefore, curcumin may be a potential candidate for augmenting response to adjunctive chemotherapies in lung cancer (17). However, due to its poor oral bioavailability and instability, new technologies are needed to achieve proper tissue concentration of this agent. For example, the level of serum curcumin following oral administration may be increased if combined with black pepper (18). Betulin [lup-20(29)-ene-3β, 28-diol]is a naturally occurring triterpene that has anticancer properties. Pentacyclic triterpene lupeol has also been reported to have anti-lung cancer activity. Both have a multifactorial mechanism of action in cancer tissues, including downregulation of isoenzyme cyclooxygenase 2 (COX-2), inhibition of malignant cell proliferation and inhibition of cell cycle (19,20), as well as induction of apoptosis, which is similar to cisplatin activity (21). Dioscorea japonica extract has been shown to suppress the expression of COX-2 and microsomal prostaglandin E synthase, which results in anti-inflammatory and anticancer activity (22). Suppression of COX-2 and reduction of prostaglandin E2 (PGE2) production are similar to the effects of sulforaphane. Sulforaphane inhibits the synthesis of PGE2 (23) and it has been reported that hypoxia in cancer tissues is related to increased production of PGE2, which is associated with cancer progression. Oral talactoferrin has been proven to be useful and was well-tolerated in patients with stage IIIB-IV non-small-cell lung cancer (NSCLC) in whom previous chemotherapies had failed (24). Withaferin A is a bioactive lactone, isolated from Withania somnifera. It has been shown that Withaferin A possesses anti-oxidative, anti-inflammatory, anti-proliferative and apoptosis-inducing properties (25). The combination of paclitaxel with Withaferin A effectively treated lung cancer in mice (26); additionally, it was demonstrated that Withaferin A induced inhibition of cancer growth and oxidative damage to NSCLC cells (27,28). Pomegranate fruit extract significantly inhibits the growth and progression of lung cancer in mice (29) due to the induction of apoptosis and modulation of cell signalling pathways. Moreover, the ingredients of pomegranates exert anti-inflammatory effects and inhibit angiogenic factors (30). Parthenolide, which is derived from the plant feverfew, induces apoptosis of NSCLC cells and selectively kills cancer stem cells (31). Flaxseed possesses antioxidant and hepatoprotective properties; in addition, in postmenopausal women, lignans from flaxseed may act as weak oestrogens. Its anti-inflammatory activity and influence on PGE2, leukotriene B4, TNF-α, interleukin and cytokines was confirmed (32). Furthermore, flaxseed may decrease the adverse effects of radiation in cancer patients (33).

The use of additional treatment in the form of medicinal substances with potential antitumor properties, provided that there are no side effects and no drug interactions, may be helpful in the treatment of certain types of cancer. Therefore, the long-term and alternate use of certain herbal and medicinal active substances may reduce the risk of recurrence or progression of certain types of cancer.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Not applicable.

Authors' contributions

PK prepared and approved the final manuscript.

Patient consent for publication

The patient provided written informed consent regarding the publication of the case details and associated images.

Competing interests

The author declares that he has no competing interests.

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