

Medication for the treatment of lung cancer: Emphasis on aerosolized chemotherapy

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Key words:

- lung cancer
- aerosolized chemotherapy
- dry powder aerosols

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SUMMARY. Lung cancer is fast becoming the leading cause of death from malignant disease, not only in men but also in women. The prevention of lung cancer entails abstaining from cigarette smoking, which is the main risk factor. The low survival rate of patients suffering from lung cancer, along with the adverse side-effects of chemotherapy in current use, creates a fundamental need for the development of new therapeutic agents and new methods of administration. This review focuses on the anatomical and clinical pathology of lung cancer and the medications currently prescribed in clinical practice for its treatment. Emphasis is given to the administration of anticancer drugs using dry powder inhalers. Aerosolized chemotherapy is described and its advantages and disadvantages are delineated. Research programmes and clinical studies aiming at the formulation of the known anticancer drugs in dry powder aerosols are highlighted. *Pneumon 2012, 25(3):298-304.*

INTRODUCTION

Lung cancer has become the most common type of cancer worldwide, accounting for over 20% of all malignancies. In Greece, more than 5,000 new cases of lung cancer are reported every year.

Cigarette smoking is the leading risk factor for lung cancer and is implicated in over 80% of all cases. The extent of the risk is correlated with the number of cigarettes consumed daily, the age of the individual and the duration of smoking. Passive smoking and exposure to various other carcinogens, including asbestos, chrome, arsenic, nickel, silica, cadmium, tars, oils, increase the risk of development of lung cancer. Heavy atmospheric pollution, dietary factors (such as deficiency of vitamin A) and several pathological conditions (pulmonary fibrosis, tuberculosis) compound this high risk. A synergistic effect has been observed between cigarette smoking and exposure to asbestos, arsenic and ionizing radiation, increasing the risk of disease. It appears, therefore, that lung cancer could be prevented by avoiding smoking and exposure to other risk factors¹⁻³.

It has also been shown that genetic predisposition contributes to de-

velopment of the disease. Gene polymorphisms codify significant proteins involved in the immune response to environmental factors and the control of cell proliferation. This genetic variation is the main reason why some smokers do not develop lung cancer while non-smokers may suffer from this disease. Gene polymorphisms also explain the high rates of lung cancer in certain families^{3,4}.

PATHOPHYSIOLOGY

According to the histological classification submitted by the World Health Organization (W.H.O.), 95% of all primary lung cancers belong to the following 4 types: epidermoid carcinoma (30%), adenocarcinoma (25%), large-cell undifferentiated carcinoma (10-15%) and small-cell carcinoma (20%). The first three categories are treated collectively as the so-called non-small cell lung carcinoma (NSCLC). The classification of lung cancer as "small-cell" and "non-small cell" carcinoma reflects their different response to chemotherapy and radiotherapy, small cell carcinoma being more sensitive^{2,3}.

CLINICAL SYMPTOMS

Lung cancer is usually diagnosed between the ages of 50 and 60 years (over 75% of patients) and rarely under the age of 35 years. The initial symptoms vary and depend on the tumour localization, the histological type, the tumour growth rate, the presence of metastasis, the ectopic production of peptides and hormones and the pre-existence of underlying lung injury. Symptoms can be either general (fever, anorexia, weight loss, fatigue) or specific (cough, expectoration, haemoptysis, dyspnoea, wheezing, pain)^{3,5,6}.

GENERAL TREATMENT

Prevention is the best way to avoid lung cancer, and this can be achieved by not smoking or by giving up smoking. The risk of developing lung cancer is gradually reduced in former smokers; 16 years after smoking cessation, an ex-smoker has almost the same likelihood as a non-smoker of the same age of developing the disease⁷.

When lung cancer has been diagnosed, its treatment is a matter of emergency. Treatment is based on the histological type of the cancer (small cell or non-small cell), on its spread and on the patient's medical history and condition. The distinction between the histopathological types of bronchial cancer is necessary not only because of

their different clinical symptoms but for the determination of treatment, as different types respond to different therapeutic agents⁸. For example, the chemotherapeutic agent pemetrexed (Alimta®) as monotherapy or in combination with platinum is indicated as the first-line treatment of patients suffering from NSCLC, except for cases where squamous cells are predominant⁹.

The current most common modes of treatment include surgery, radiotherapy and chemotherapy.

LUNG CANCER CHEMOTHERAPY

Chemotherapy is traditionally applied with the anti-cancer drugs being infused intravenously or administered orally¹⁰. These drugs enter the systemic blood circulation and spread throughout the whole body, penetrating even into distant tissues, rendering this form of administration particularly useful for the treatment of metastasized cancer.

Depending on the stage of lung cancer, chemotherapy (in combination with radiotherapy) may be applied in the following cases:

- 1) For tumour shrinkage before surgery. This kind of chemotherapy is known as "neoadjuvant therapy".
- 2) For the elimination of remaining cancer cells after surgery, known as "adjuvant therapy".
- 3) As the main treatment for patients with advanced cancer or patients in poor physical condition.

Chemotherapy is given in *cycles*, where every administration period is followed by a wash-out period. Generally, each chemotherapy cycle lasts about 3 to 4 weeks and a typical chemotherapeutic regimen consists of 4 to 6 cycles. Chemotherapy is not recommended for patients who are in poor physical condition, but fit elderly patients can be treated with chemotherapy and may tolerate it well.

In most cases, lung cancer chemotherapy includes a combination of two chemotherapeutic agents. According to recent research, the addition of a third chemotherapeutic agent does not benefit patients and increases the possibility of inducing more serious adverse effects. Single-drug chemotherapy can be applied to patients who cannot tolerate combined chemotherapy (for example, patients in generally poor physical condition). Table 1 shows the chemotherapeutic agents most commonly used for the treatment of lung cancer.

The most common combinations in current use are either cisplatin or carboplatin with another agent, even though it has been shown that other combinations, such as gemcitabine with vinorelbine or paclitaxel can be equally effective and safe.

TABLE 1. Chemotherapy of lung cancer: Anticancer agents, routes and means of administration and adverse effects^{11,12}

ANTICANCER AGENT	ROUTE OF ADMINISTRATION	COMMON ADVERSE EFFECTS
Cisplatin	Intravenous infusion in saline	Vomiting, nephrotoxicity, neurotoxicity
Carboplatin	Intravenous infusion in saline	Nausea, vomiting, myelosuppression
Paclitaxel	Intravenous infusion in saline	Neutropenia, peripheral neuropathy, bradyrhythmia, alopecia
Docetaxel	Intravenous infusion in saline	Neutropenia, peripheral neuropathy, bradyrhythmia, alopecia
Gemcitabine	Intravenous infusion in saline	Myelosuppression, nausea, vomiting, alopecia
Vinorelbine	Intravenous infusion in saline	Granulocytopenia
Irinotecan	Intravenous infusion in saline	Myelosuppression, neutropenia, alopecia, thrombopenia
Etoposide	Intravenous infusion in saline or oral administration	Myelosuppression, leukaemia, alopecia
Vinblastine	Intravenous infusion in saline	Myelosuppression, alopecia, phlebitis, cellulitis
Topotecan	Intravenous infusion in saline	Myelosuppression, diarrhoea, thrombopenia, immunodeficiency
Pemetrexed	Intravenous infusion in saline	Neutropenia, GI disorders, fatigue

GENE THERAPY AND THERAPY OF GENE MUTATIONS

“Gene therapy” refers to the transfer of genetic material into a cell for therapeutic purposes. This can be achieved via the integration into an organism of the appropriate gene, which can then either suppress the activity of cancer cells or increase the tolerance of the healthy cells. This latter modification allows the subsequent administration of higher dosages of chemotherapy. The p53 gene, dysfunction of which is related to drug resistance, is a very potent agent, which can reverse malignant activity through its integration into cancer cells using retroviruses. “Suicide gene therapy” is a second type of gene therapy, which acts through the integration of genes that can increase cancer cell sensitivity to certain anticancer drugs. These genes are known as “deaminase system of cytosine/5FU” and “thymidine kinase system/ganciclovir”¹⁰.

A recent study the results of which were presented at the American Society of Clinical Oncology (ASCO) annual conference, showed the activity of the [PF-02341066] or [PF-1066] agents (selective antagonists of ATP) to be an inhibitor of tyrosine kinase (TK) receptors found in the [ALK] and [MET/HGF] oncogens¹³. [EML4] and [ALK] genes are usually identified in 4% of patients with NSCLC. For this reason a clinical study was made of patients with NSCLC carrying the [ALK] gene, to whom [PF-1066] monotherapy was administered. To date 76 patients have been completely cured and 50 others have shown a remarkable response to the treatment. The mean duration of treatment was approximately 25.5 weeks. The most common adverse effects were those involving the gastrointestinal (GI) system, including nausea (55 %) and vomiting (39 %).

The authors concluded that in patients carrying the [ALK] oncogen [PF-1066] administered orally demonstrated a high response rate and was generally safe. A phase III clinical trial is now in progress that aims at the application of individualized therapy in patients with NSCLC¹³.

A recent publication suggests that crizotinib (Xalkori®, Pfizer), an [EML4] and [ALK] inhibitor, is an equally potent agent¹⁴. Crizotinib can shrink tumours in patients with NSCLC who carry a specific mutation on the [EML4] and [ALK] genes. In a clinical trial with 82 patients carrying this mutation, crizotinib therapy was associated with tumour shrinkage or stasis at a rate of 87 %. In August 2011, crizotinib was approved by the Food and Drug Administration in the US (F.D.A.) for administration to patients with terminal lung cancer.

The recognition and identification of the ERB family [EGFR (Erb1), HER2/neu (Erb2), HER3 (Erb3) and HER4 (Erb4)] has also proved to be of great significance, as it consists of a group of cell receptors relevant to cell proliferation. These receptors activate a chain of intracellular reactions leading to the regulation of specific significant cell functions, such as proliferation and apoptosis. Over expression of the epidermal growth factor receptors (EGFR) is predominant in squamous carcinoma (84%), observed less often in non-small cell carcinoma (>65%) and adenocarcinoma and totally absent in small cell carcinoma.

A number of newly identified antibody-molecules are under investigation for their possible role in inhibition of EGFR function and their efficacy in the prevention and treatment of lung cancer. Some examples are the monoclonal antibody C225 (cetuximab) and small molecules

such as ZD1839 (gefitinib, Iressa), OSI-774 and erlotinib (Tarceva[®]) which selectively inhibit the activation of TK, an intracellular portion of the EGFR function¹⁶⁻¹⁸.

Finally, excision repair cross-complementing group 1 (ERCC1) and Ribonucleotide reductase subunit 1 (RRM1) are strongly associated with chemotherapy response and therapeutic benefit from gemcitabine and platinum. Both genes are critical components of the DNA synthesis and DNA damage repair pathways¹⁹⁻²⁵. High levels of tumour expression of these agents had been found in retrospective analyses to be associated with poor survival of patients with NSCLC treated with gemcitabine/platinum-based chemotherapy. The level of RRM1 expression and, to a lesser degree, the level of ERCC1 expression are inversely correlated with tumour response to gemcitabine and carboplatin in patients with NSCLC^{19,20,26}.

INHALED CHEMOTHERAPY

Introduction

Drugs administered via inhalation have been used for many years in the therapy of respiratory diseases²⁷. Even though this method of administration is very common in the treatment of asthma, there is an increasing interest in the application of this form of administration for other bronchial and pulmonary diseases, including lung cancer²⁸⁻³⁰.

Up to the present, anticancer therapy administered intravenously or orally has been insufficient, due to the inability of the drugs given by this route to reach affected regions in adequate concentrations. This is the main reason why lung cancer remains the most lethal type of malignancy, without the accomplishment of any significant progress in its treatment^{31,32}.

The development of new pharmaceutical devices and drug formulations with enhanced pharmacokinetic properties has become a necessity. A number of preclinical studies concerning thoracic oncology have shown that administration of drugs via inhalation leads to the transfer of large amounts of the chemotherapeutic agents directly to the lower respiratory tract and into the lung tissue, with only a minor degree of peripheral distribution^{29,33}. The administration of low doses of anticancer drugs directly into the region of malignancy provides greater response with less adverse effects^{29,34}.

Advantages

Inhaled chemotherapy has a significant number of advantages when used for the treatment of systemic

diseases. This route of administration, unlike oral administration, enhances drug absorption and excludes both the gastrointestinal metabolism and the first-pass effect in the liver. Compared with the intravenous method of administration, inhaled therapy is not painful, leading to increased patient compliance and better therapeutic effect²⁷. In addition, the large alveolar surface provides rapid systemic absorption of water-soluble drugs. Finally, regional chemotherapy transferred via inhalation to lung tumours can increase the exposure of the tumour to the drug while minimizing adverse side effects³⁰.

Disadvantages

Even though inhaled chemotherapy has been available since 1968^{30,35} the development of inhaled anticancer agents has been limited^{30,33}. One of the main reasons is the possibility of lung toxicity, because many chemotherapeutic molecules, such as irinotecan, gemcitabine, paclitaxel and docetaxel, can cause severe toxic reactions in the lung during or even after treatment^{30,36,37}. In addition, a large number of patients with lung cancer already show severe lung dysfunction due to smoking^{30,38}, and in these individuals inhaled treatment could lead to a worsening of their pulmonary condition. The lung toxicity risk should be evaluated for every new drug intended to be administered via inhalation³⁹.

Limitations

Inhaled chemotherapeutic agents need to be transferred to the target region in adequate concentrations in order to be effective^{30,32}. One of the most important factors for dose determination and lung distribution is the size of the inhaled particles^{32,40}, which must have a diameter range between 1-5 μm , so that the drug can reach the peripheral airways and the alveolar region of the lung. Particles greater than 5 μm in size are usually retained in the oral cavity and those smaller than 0.5 μm can be easily exhaled^{32,41}. Another important limitation is the paucity of information concerning the metabolism of inhaled drugs in the lungs, which can modify their pharmacokinetic profile and their efficacy^{30,42}. Finally, the exposure of healthcare professionals to the drug nebula is also a significant safety issue. Inhaled anticancer treatment should be applied in a well ventilated room, equipped with an air filter system^{30,43}.

Recent research results in dry powder aerosols

Drug administration in the form of inhaled powders

(dry powder inhalers, DPI) offers many benefits in the use of medications as preventive and therapeutic agents for several respiratory and lung diseases, including lung cancer⁴⁴. In the last decade, new therapeutic molecules, – such as doxorubicin, cisplatin, celecoxib, paclitaxel and temozolomide, have been tested in preclinical and clinical trials⁴⁵. In addition to these anticancer agents, the application of gene therapy via inhalation for the treatment of lung cancer is also under investigation (specifically,

the p53 gene). Table 2 shows the results of the most important *in vitro* and *in vivo* studies and clinical trials examining inhaled formulations of already approved anticancer agents.

Paclitaxel is one of the most potent molecules used for lung cancer treatment, but its low hydrophilicity makes the use of organic solvents as excipients (e.g. Cremophor EL) a necessity, leading to additional toxicity and hypersensitivity reactions. Because of this, efforts have

TABLE 2. Results of preclinical and clinical trials of inhaled chemotherapy for lung cancer.

Active molecule/ Formulation	Cancer type	Dosage	Subjects or type of study	Results
Inhaled Doxorubicin ⁴⁶	Metastatic lung cancer	0.4- 9.4 mg/m ² every 3 weeks	53 patients	Safe and effective dose: 7.5 mg/m ²
Aerosolized SLIT-Cisplatin ³⁸	Lung carcinoma	Escalated doses twice daily	18 patients (Clinical study phase I)	Well tolerated No significant toxicity. Stabilization of the disease
Aerosolized Docetaxel + Celecoxib ^{47,48}	Non-small cell lung cancer (NSCLC)	DOC (0.01 µg mL ⁻¹) and CXB (10 µg mL ⁻¹)	<i>In vitro</i> cancer cell lines A549 and H460 from human lung	High rates of cancer cell necrosis
Gemcitabine Aerosol ^{49,50}	Lung cancer	1mg/kg for 9 weeks	a. <i>In vitro</i> cancer cell lines A549 and NCI-H460 b. 3 baboons	Safe and efficacious molecule for inhaled chemotherapy. Cytotoxic characteristics of drug maintained.
Nebulized Farnesol ^{51,52}	Lung cancer	52.74 mg/5 mL	<i>In vitro</i> cancer cell lines A549 and H460 from human lung	Up to 100% cytotoxicity
Inhaled 5-fluorouridine (5-FU) ⁵³	Lung cancer and cancer of the trachea and regional lymph nodes	1.50 mg/kg 2.250 mg/5mL	a. 18 mongrel dogs b. 10 patients	60% response, intense anticancer activity. Absence of severe adverse effects
Inhaled Temozolomide ⁵⁴⁻⁵⁸	B16F10 model of static lung cancer	0.4% TMZ (m/v)	27 mice	Almost complete eradication of tumours in 11% of the animals. Well tolerated and active. (Clinical trial phase I in progress)
Inhaled Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) ⁵⁹	Lung cancer	60 µg, 120 µg, 240 µg 2 times per day x 7 days	7 patients	Stabilization or amelioration of the disease. Inhaled administration is feasible, safe and efficacious
Inhaled 9-Nitrocarnitocin Dilayroylphosphatidylcholine (9NC-DLPC) ^{60,61}	Primary or metastatic lung cancer	6.7 µg/kg for 60 min daily x 5 days	12 patients	Tumour stabilization . Low toxicity in general. 3 patients had deterioration of the tumour
Inhaled AND-p53 gene (polylysine/protamine combination-AND) ^{60,62}	Non-small cell lung cancer (NSCLC)	8 µg DNA/mouse x 4 days	Mice carrying human NSCLC cells	Extension of life expectancy Absence of systematic toxicity

been made to encapsulate paclitaxel into liposomes for inhaled administration. Many preclinical and *in vivo* studies in animals have shown promising results and thus the formulation of paclitaxel into lipid nanocapsules (LNCs), which are dispersed in aqueous droplets, could become a new method of chemotherapy via inhalation²⁹.

CONCLUSION

Lung cancer is fast becoming the leading cause of death from malignant disease among both men and women. Prevention of lung cancer means abstention from smoking, the main risk factor. The low survival rate of patients suffering from lung cancer along with the adverse effects of the chemotherapy in current use creates a fundamental need for the development of new therapeutic agents and new methods of administration. The discovery and design of new anticancer agents is laborious and time-consuming, which has led to the alternative development of new methods of administration of chemotherapy. These new formulations are intended to have a targeted action in the lung and as a result to reduce adverse effects.

Inhaled chemotherapy is a very promising method of anticancer treatment for lung tumours, as evidenced by the great number of clinical studies still in progress or already completed. Tested chemotherapeutic agents, such as paclitaxel, cisplatin, gemcitabine, and doxorubicin, administered via inhalation, appeared in several clinical studies to be very potent. These results have raised the interest of the scientific community and the hopes that lung cancer will no longer constitute one of the main causes of death globally.

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