Pharmacotherapy of small cell lung cancer: Current state-of-the-art

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Abstract

Introduction: Lung carcinoma is the leading cause of death in men and is closely related to smoking. The article focuses on the current statistics of this pathology in the world.

Materials and methods: The literature review was carried out using PubMed database and included articles published from 2006 to 2021. The current schemes of chemotherapy and diagnostic options of small cell lung cancer were analyzed. The mechanisms of drug action on tumor cells were considered. An analysis of the publication activity in PubMed database related to pharmacotherapy of small cell lung cancer allows reporting a twofold increase in the number of publications over the period from 2007 to 2017.

Results and discussion: A systematic review presenting staging of small cell lung cancer (SCLC) and its radiation diagnostics has been conducted. As demonstrated, there are no current methods with proven effectiveness to early detect this pathology. However, it has been found that annual low-dose CT screenings helped detect a significant number of lung cancer cases at the early stage, although, the proportion of small cell carcinoma is still very high. Analyses of clinical outcomes of small cell lung cancer have showed that cisplatin/etoposide (EP) or carboplatin/etoposide (EC) appear to be the key combinations with high treatment efficacy. The article also discusses chemotherapy for small cell lung cancer, namely and the principle of its effect on tumor cells. However, this chemotherapy remains very toxic and causes a number of life-threatening side effects. It is necessary to assess the effectiveness of chemotherapy immediately after the start of treatment in order to balance benefits and risks.

Conclusion: The search is currently under way for less toxic but effective compounds, this fact being a crucial issue of healthcare in providing high-quality medical and pharmaceutical care for cancer patients. Chemotherapy of the pathology under study requires high costs; therefore, a pharmacoeconomical assessment of the prescription of chemotherapy for small cell lung cancer is necessary to compare the costs of treatment and its effectiveness.
Introduction

Lung carcinoma occupies a leading position among all types of cancer (Mukhambetzhan et al. 2020). According to the Journal of the American Cancer Society statistics, there were 234,030 newly diagnosed cases of lung and bronchial cancer in the US in 2018 including 121,680 cases in men and 112,350 cases in women (Boloker et al. 2018). The trend in the incidence of lung cancer is increasing by 0.5% globally every year (Pronevich and Kovalchuk 2020). In recent years, the number of pharmacoeconomic studies in oncology has sharply increased, which is associated with high cost of treating patients with malignant neoplasms (Solodyankina and Eliseeva 2009; Avksentieva 2012; Yarovoy and Shikina 2020).

Globocan – the Global Cancer Observatory – estimates that 2.2 million new cases of lung cancer were registered in 2020, accounting for 11.4% of the total cancer cases; it is the second most frequently diagnosed cancer, slightly behind breast cancer, which is 11.7%. In addition, lung carcinoma remains the leading cause of death from cancer, accounting for 18.0% of the total number of cancer deaths. Lung cancer remains the leading cause of death in men. In women, it ranks the third in morbidity after breast and colorectal cancer and the second in mortality after breast cancer. Morbidity and mortality rates in men are about 2 times higher than in women (Sung et al. 2021).

The highest incidence rates of 51.6% in men and 22.9% in women are observed in Micronesia/Polyynesia, Eastern and Southern Europe, East Asia and West Asia, and the lowest rates are in West Africa – 2.8% in men and 1.8% in women, respectively (Sung et al. 2021). As reported, tobacco smoking is not the only risk factor contributing to the development of lung malignant neoplasms. In East Asia, smoking prevalence is low, but morbidity rates are high. This evidences that severe outdoor air pollution and exposure to other inhaled substances caused by household air pollution, such as burning solid fuels at home for heating and cooking, is one of the leading causes of lung cancer in these countries (Mu et al. 2013; Turner et al. 2020). The global share of lung cancer deaths attributable to air pollution from atmospheric PM 2.5 (known as fine particulate matter) was 14% in 2017, ranging from 4.7% in the US to 20.5% in China (Turner et al. 2020).

Global differences in lung cancer rates and trends largely reflect the maturity of the tobacco epidemic (Thun et al. 2012), with mortality rates close to morbidity rates due to the large number of deaths. Today, incidence rates among women are close to or equal to those among men in several European and North American countries (Lortet–Tieulent et al. 2015).

As can be seen nowadays, about two-thirds of lung cancer deaths worldwide are attributable to smoking, though the spread of the disease can be largely prevented through effective tobacco control policies and regulations. According to WHO, this pathology will kill more than eight million people annually by 2030, which is about 70% of the world’s population (World Health Organization (WHO 2008)).

The cohort of patients diagnosed with small cell lung cancer are commonly men over 50, although in the last...
decade the disease has tended to cover younger population. As stated, the percentage of patients under 45 years of age is 10%, patients aged 46-60 – 52%, 61 and older – 38%. The incidence rate of lung carcinoma in Russia is relatively stable; it ranks the 1st in the structure of malignant neoplasms in men, being 25%; the incidence of lung carcinoma in Russia among women is only 4.3% (Siegel et al. 2019).

In all oncological diseases, lung carcinoma results in the highest mortality rate, since it is very difficult to early detect this pathology. Most often, patients first see an oncologist for small cell lung cancer at advanced stages, specifically III or IV, when radical treatment is almost impossible, and the proportion of such cases is 72-76%. According to statistics, even regular checkups most often detect the disease at the advanced stages; neoplasms are detected at stage I or II in only 24-28% of cases (Siegel et al. 2019).

The major aspect of the pathogenesis of lung cancer is damage to the genome of the epithelial cell. This results in chromosomal aberrations and gene mutations, their accumulation in the genome; however, most of them are not strictly specific for lung cancer. Deletion of a small region 3p14-23 in the short arm of chromosome 3 is the most typical for small cell lung cancer. The studies demonstrated almost uniform damage to all major regions of chromosome 3p. Presumably, it is the chromosome that contains important tumor suppressors (Severgina et al. 2016). Although the most striking modifications were found as a result of mutations in the TP53 and RB1 genes. It has been investigated that the p53 tumor suppressor protein is usually activated when cells encounter DNA damage or hypoxia. This protein is crucial in maintaining the integrity of the genome by inhibiting the cell cycle or activating apoptosis; therefore, if the functional P53 protein is lost, then genomic instability occurs, which leads to the mutation accumulation (Casadei Gardini et al. 2016).

A recent study that sequenced 110 SCLC samples found previously unknown genomic rearrangements in another gene, TP73, a member of the TP53 family, in a significant proportion of cases (Zhu et al. 2020; Shivapriya et al. 2021). Specifically, these genomic rearrangements accounted for the deletion of exons 2 and 3 in TP735. The results of this study evidence that the p53 gene family is involved more in small cell lung cancer oncogenesis. It is gene mutations that are risk factors for the development of malignant neoplasms (Yuan et al. 2020).

**Materials and Methods**

The literature review was carried out using PubMed database and included articles published from 2006 to 2021 (Fig. 1). The current schemes of chemotherapy and diagnostic options of small cell lung cancer were analyzed. The mechanisms of drug action on tumor cells were considered. The following keywords were used for search: small cell lung cancer, oat cell lung cancer, small cell carcinoma, neoplasm, chemotherapy, carboplatin, cisplatin, irinotecan, doxorubicin, etoposide, chemotherapy of small cell lung cancer, and oncology diagnostics. All the authors independently selected articles, assessed the quality of the data, presented and interpreted the data in accordance with the main idea of the study, and compiled the final list of references. An analysis of the publication activity in PubMed database related to pharmacotherapy of small cell lung cancer allows reporting a twofold increase in the number of publications over the period from 2007 to 2017.

![Figure 1](image-url)

**Figure 1.** An analysis of the publication activity in PubMed database related to pharmacotherapy of small cell lung cancer allows reporting a twofold increase in the number of publications over the period from 2007 to 2017.
Results and Discussion

Staging and radiation diagnostics

Small cell lung cancer is a highly aggressive and rapidly developing form of all malignant neoplasms, which requires early diagnosis and effective pharmacotherapy.

There are many staging systems available for SCLC. One of them is the Veterans Administration Lung Study Group (VALG) system, which is based on clinical guidelines and is independent of the Tumor-Node-Metastasis (TNM) staging system. All conditions within the VALG system are divided into a limited stage of SCLC (LS-SCLC) and an extended stage of SCLC (ES-SCLC). The former is defined as lesions confined to one side of the thoracic cavity involving lesions of the contralateral mediastinum and bilateral supraclavicular lymph nodes with metastases, and lesions of the pleura on the same side, i.e. an area small enough to be included within a complete radiation portal. In contrast, those with extended stage of small cell lung cancer have clinical manifestations of cancer that spread beyond one hemithorax at the moment of initial diagnosis (Chen 2016; Thomas et al. 2018; Tsiouprou et al. 2019).

The prognosis of small cell cancer is highly dependent on the stage of a tumor. The new TNM staging system of the Union for International Cancer Control (UICC), the 7th edition, adopted for non-small cell lung cancer should also be used for small cell lung cancer (Lababede et al. 2011) (see Tables 1 and 2).

Table 1. (TNM staging of lung cancer: Definition of T, N and M) Classification of metastasis to tumor nodes*

<table>
<thead>
<tr>
<th>T category</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>≤ 3 cm</td>
</tr>
<tr>
<td>T1a</td>
<td>2 cm</td>
</tr>
<tr>
<td>T1b</td>
<td>&gt; 2-3 cm</td>
</tr>
<tr>
<td>T2</td>
<td>The main bronchus ≥ 2 cm from the keel bone affecting the visceral pleura, partial atelectasis</td>
</tr>
<tr>
<td>T2a</td>
<td>&gt; 3-5 cm</td>
</tr>
<tr>
<td>T2b</td>
<td>&gt; 5-7 cm</td>
</tr>
<tr>
<td>T3</td>
<td>&gt; 7 cm; the chest wall, the diaphragm, the pericardium, the mediastinal pleura, the main bronchus &lt; 2 cm from the keel bone, total atelectasis, sporadic nodules in the same lobe</td>
</tr>
<tr>
<td>T4</td>
<td>The mediastinum, the heart, large vessels, the keel bone, a trachea, the esophagus, a vertebra; sporadic tumor nodules in the other ipsilateral lobe</td>
</tr>
<tr>
<td>N1</td>
<td>Ipsilateral peribronchial, ipsilateral intrathoracic</td>
</tr>
<tr>
<td>N2</td>
<td>Subcarinal, ipsilateral mediastinum</td>
</tr>
<tr>
<td>N3</td>
<td>Contralateral mediastinum or hilar, scalene or supraclavicular</td>
</tr>
<tr>
<td>M1</td>
<td>Distant metastases</td>
</tr>
<tr>
<td>M1a</td>
<td>Separate tumor nodule in the contralateral lobe; pleural nodules or malignant pleural or pericardial effusion</td>
</tr>
<tr>
<td>M1b</td>
<td>Distant metastases</td>
</tr>
</tbody>
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The diagnosis and risks are initially assessed by past medical and social history, including smoking history, physical examination, CBC with differential counts, liver enzymes, levels of sodium, potassium, calcium, glucose, lactate dehydrogenase, kidney function tests, and, in case of the localized disorder, lung function tests. Computed tomography (CT) with contrast enhancement of the chest and abdomen is recommended initially. If metastases are detected, but the stage is not defined by CT imaging or the clinical findings suggest bone or brain involvement, further magnetic resonance imaging (MRI) of the brain and bone scintigraphy and CT are recommended. It is also possible to use positron emission tomography (PET) as an analogue of CT and bone scintigraphy. A recent review has demonstrated that PET-CT visualization revealed that 9% of patients had the advanced stage of the disease and 4% of patients had a disease at a lower stage; however, this analysis included studies that were non-randomized, retrospective, or small and often were not histologically confirmed. Thus, PET-CT findings that may influence the decision on treatment should be pathologically confirmed (Früh et al. 2013).

Early detection of small cell lung carcinoma is a challenging task, since there are no specific signs of the disorder and the tumor grows quite fast, which makes modern screening approaches ineffective in diagnosing patients at the early stages of the disease (Yang et al. 2019). The results of the National Lung Screening Trial evidence an aggressive nature of small cell lung cancer and its aptitude to specific early hematogenous spread (Aberle et al. 2013). This trial supported significance of low-dose computed tomography (CT) screening for early detection of lung cancer in patients at high risk of lung cancer development. However, 86% of 125 patients diagnosed with small cell lung cancer through this early detection program already had a disease at the advanced stage. As demonstrated, currently, there are no methods with proven effectiveness to early detect this pathology (Byers and Rudin 2014). However, American researchers conducted a study to assess the effectiveness of early diagnosis of small cell lung cancer which supported that annual low-dose CT screenings revealed
a significant number of cases with this pathology. In spite of this, the proportion of patients with small cell carcinoma at the late stage was very high. The results indicate that for the screening method to be successful in reducing lung cancer mortality, the pathology must be detected earlier than when it becomes visually accessible by low-dose CT imaging (Thomas et al. 2018).

**SCLC patients’ treatment: chemotherapy**

Small cell lung carcinoma is very sensitive to chemotherapy and ionizing radiation; however, the vast majority of patients can relapse, uncharged platinum ion surrounded by four ligands; while the amine ligands on the left form stronger interactions with the platinum ion, the chloride ligands or carboxylate compounds on the right form complexes leaving groups that allow the platinum ion to form bonds with DNA bases. Thus, it has the ability to cross-link DNA with platinum and inhibit mitosis, which subsequently leads to the destruction of cancer cells (Dasari and Tchounwou 2014). Etoposide, in turn, destroys the topoisomerase II catalytic cycle and stabilizes enzyme-related DNA strand breaks (Gibson et al. 2016; Qing Nian et al. 2019). Moreover, etoposide prevents the religation of DNA double-strand breaks, which leads to the accumulation of double-strand breaks in the genome (Pommier and Marchand 2012). Chromatin can also be the target of the drug, since etoposide exhibits a high affinity for chromatin and histones, especially H1 (Chamani et al. 2014; Montecucco et al. 2015). Importantly, etoposide inhibits mitosis and arrests cell division in S or G2 phase and triggers caspase-mediated apoptosis, which primarily occurs via cytochrome c/caspase 9 (Fujikawa-Yamamoto et al. 2012; Sinha 2020; Kluska and Woźniak 2021). In addition, etoposide treatment triggers the binding of the Fas ligand (FasL) to its receptor (FasR) on the cell membrane, resulting in the formation of a death-inducing signaling complex (DISC) (Gentry and Osheroff 2013). Furthermore, etoposide is metabolized by cytochrome P450, peroxidase, and tyrosinase to the etoposide phenoxy radical, o-quinoine etoposide. It was found that the presence of 4’-OH in etoposide is necessary for the formation of the radical of this drug, its metabolites, as well as antitumor activity (Pigatto et al. 2016; Sinha 2020). Moreover, the response rate to EP varies from 44% to 78%, indicating that many patients are very sensitive to treatment with EP or EC, and patients’ conditions are likely to improve after initial systemic therapy. Thus, cisplatin/etoposide is a favourable and reliable regimen to achieve clinical improvement in short terms, yet long term clinical outcome is still poor (Wang et al. 2020). Chemotherapy regimens use other drugs that have a different mechanism of action than those previously mentioned. For example, irinotecan is added to carboplatin in chemotherapy regimens. The ternary DNA complex irinotecan-topoisomerase I-nick prevents the release of topoisomerase (Kciuk et al. 2020). Collision of the resulting complex with advancing replication forks leads to the formation of a lethal double-strand break (DSB) (Yuan et al. 2021). This contributes to DNA checkpoint damage signaling, fork replication arrest, and cell death (Riera and Páez 2021; Yue et al. 2021). ATM-CHK2-TP53 is the main transduction signaling pathway activated in cells that accumulate DSB in response to irinotecan treatment. The uniqueness of topoisomerase I inhibitors is manifested in their dose-dependent increase in enzyme inhibition with increasing cellular topoisomerase concentration (Lee et al. 2019). Thus, the cell sensitivity to topoisomerase inhibitors mainly depends on the topoisomerase concentration inside the cell. Since cancer cells express higher yields of the enzyme, they are therefore more prone to topoisomerase poisons (Seto et al. 2020). Some regimens use doxorubicin + vincristine + cyclophosphamide combinations. The antitumor effect of doxorubicin is due to a combined effect of various mechanisms, such as the appearance of new structures within the DNA of the tumor cell and inhibition of topoisomerase II, which can lead to cell death or arrest of their growth (Minotti et al. 2004; Meredith and Dass 2016). As a leading chemotherapeutic agent, it is able to combat rapidly dividing cells and slow disease progression; its use is limited only by its toxicity to non-cancerous body cells, which is directly dependent on its concentration (Box 2006; Tacar and Dass 2013). Vincristine performs its antitumor function, as it is an inhibitor of continuous mitotic division due to the association with tubulin, which prevents the formation of microtubules and, consequently, the mitotic spindle (Liu et al. 2014; Su et al. 2020). Thus, cell division is blocked and the cell dies (Cormier et al. 2010). Once the formation of the mitotic spindle is blocked, the cell enters apoptosis with or without p53 activation (Lobert et al. 2000). Cyclophosphamide (CTX) is a nitrogen mustard alkylating agent from the oxazaphorins group (Emadi et al. 2009; Penel et al. 2012), which can suppress Treg, since its presence in the infiltrate around the tumor enhances cell resistance to antitumor therapy. However, in healthy individuals, Tregs promote self-tolerance and maintain immune homeostasis when stimulated by foreign antigens, and tumor cells take advantage of this (Guo et al. 2018). The disease progresses in almost all patients with metastatic small cell lung cancer and in about a third of patients with a localized condition. Survivors are acutely concerned about secondary malignancies, especially in cases when smoking continues; they require smoking cessation counseling. The main goal of regular follow-up is to detect relapse early while the patient is still in relatively good condition (Sugiyama et al. 2008).

**Complications of chemotherapy**

Complications of chemotherapy, which usually arise when using drug combinations, remain an unresolved issue nowadays. The most challenging aspect of drug
combinations involving DNA-damaging chemotherapy is acute and long-term toxicity to non-neoplastic tissues; this toxicity can affect almost every organ in the body (Thomas and Pommier 2016). Almost all drugs used in the treatment of malignant neoplasms can cause side effects, such as nausea, vomiting, and diarrhea. However, they are not as critical as other reactions that affect vital organs (Kosmas et al. 2001).

The drugs used as the first line of chemotherapy for small-cell lung cancer manifest a number of undesirable side effects, nephrotoxicity being one of the most specific and significant. Acute kidney injury, which occurs in 20-30% of patients, is the most severe and one of the most common manifestations of nephrotoxicity (Miller et al. 2010). Renal failure generally develops several days after the intake of cisplatin, and is manifested by an increased serum creatinine and blood urea nitrogen. Diuresis usually persists, and urine may contain glucose and small amounts of protein, suggesting proximal tubular dysfunction. Hypomagnesemia is also common, especially after repeated doses of cisplatin, even if there is no drop in glomerular filtration rate. Recovery of renal function usually occurs within 2–4 weeks, although longer courses and lack of recovery have been also reported (Taguchi et al. 2005). It is worth noting that cisplatin therapy can lead to severe kidney damage, having a very high mortality rate.

Efforts to develop chemotherapy less damaging to DNA were initially focused on the development of chemically modified analogs. This approach yielded some early successes, such as carboplatin, a less nephrotoxic derivative of cisplatin, yet drugs generally provided only modest progress in tolerability and efficacy. Current efforts are focused on achieving targeted drug delivery and retention while minimizing drug accumulation in the normal tissues (Thomas and Pommier 2016). Carboplatin is less nephrotoxic than cisplatin, yet it results in much worse blood count findings. Thus, the greatest risk of thrombocytopenia and anemia was recorded in a larger number of patients taking carboplatin (Griesinger et al. 2019). Etoposide, used to treat lung carcinoma, can cause leukopenia, thrombocytopenia, and hair loss, which is also an adverse effect of chemotherapy (Sinkule 1984).

Cyclophosphamide has high cardiotoxicity, but the pathophysiology of cardiac injury is poorly understood (Molinario et al. 2015), although it is believed that its metabolites can initiate toxic endothelial injury with subsequent extravasation of proteins, erythrocytes and toxic metabolites containing high levels of the anticancer drug (Ranchoux et al. 2014). Toxic metabolites, which result from the breakdown of endothelial cells, lead to direct myocardium and capillary vessel damage, which contributes to the appearance of edema, interstitial hemorrhage and the formation of microthrombosis (Ayza et al. 2020).

**Evaluation of the effectiveness of chemotherapy**

The goals of chemotherapy include: prolongation of life, improvement of the quality of life, elimination of signs of the disease with minimal side effects of treatment (Neville and Kuruvilla 2010). Therefore, assessment of the effectiveness of chemotherapy should be carried out almost immediately after the start of treatment. Depending on the type of tumor and goals of chemotherapy, a planned evaluation of therapeutic effectiveness should be performed every 6-12 weeks. However, an unscheduled assessment should be carried out according to indications, especially if the disease progression is suspected. There are several ways to assess the effectiveness of the therapy, for example, methods of planar radiography, ultrasound diagnostics, endoscopy, and physical examination. As the evidence from practice shows, it is necessary to use one and the same diagnostic method chosen before the start of the therapy in order to obtain reliable data on the dynamics of the process; this allows for a qualitative assessment of tumor foci with a detailed description of the revealed changes in the course of treatment (Tryakin et al. 2020). One of the criteria for tumor response to therapy is tumor foci, which, according to RECIST criteria, are divided into two types:

1) **Measurable foci** – foci identified, with the maximum diameter:
   - $\geq 10$ mm by helical CT, CT scan slice thickness no greater than 5 mm;
   - $\geq 20$ mm by step CT, CT scan slice thickness no greater than 10 mm;
   - $\geq 20$ mm by chest X-ray;
   - lymph nodes $> 15$ mm in a dimension perpendicular to the maximum diameter (i.e. along the short axis).

2) **Non-measurable foci** – foci identified, with the maximum diameter by step CT. Non-measurable foci include: small foci ($< 10$ mm), leptomeningeal metastases, pleurisy, ascites, pericarditis, cysts, lymphogenous carcinomatosis of the skin or lungs, bone metastases, inflammatory changes in the mammary glands, foci with cystic and necrotic transformation, enlargement of organs (hepatosplenomegaly), peritoneal implants.

First, the lesions are assessed quantitatively, then target lesions to be used for control in the course of therapy are selected. The targeted focus remains targeted throughout all repeated studies, even if the size of the focus decreases to the error limit of the research method. Target lesions should be as large as possible to make them more suitable for re-measurement. Non-targeting foci are all other foci, including those that are not measured and which are not classified as targeting ones. The criteria for assessment of the foci are the following:

1) **Partial Response (PR):** At least a 30% decrease in the sum of diameters of target lesions;
2) **Complete Response (CR):** Disappearance of all target lesions (target and non-target). Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to $< 10$ mm;
3) **Progressive Disease (PD):** At least a 20% increase in the sum of diameters of target lesions, the appearance
of one or more new lesions; absolute progression of non-target foci;
4) Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, no signs of the disease progression (Tryakin et al. 2020).

Conclusion

Therefore, the study results published in Russian and foreign literature demonstrate that chemotherapy for small cell lung cancer is performed through various schemes involving drugs with studied mechanisms of action. However, most regimens apply platinum-based drugs, such as cisplatin and carboplatin, and are considered among the most effective anticancer agents in the treatment of solid tumors. High toxicity and resistance of cancer cells are considered to be their major drawbacks. More cancer-selective drugs, such as etoposide, irinotecan, vincristine, and cyclophosphamide, are increasingly being used currently. Options for small cell lung cancer therapy are developing quite rapidly, various treatment regimens are being introduced, which, in turn, are optimized by a combination of drugs.

However, according to statistics, the average 5-year survival rate is quite low. At the same time, chemotherapy of the studied pathology is cost-demanding. Therefore, a pharmacoeconomic evaluation of the chemotherapy administration as a small cell lung cancer therapy option is required to compare costs of treatment and its effectiveness. In this regard, it is necessary to study the assortment, organizational and financial availability of drugs used to manage small cell lung cancer in the Russian pharmaceutical market; determine their competitive position, benefits and drawbacks.

Conflict of interest

The authors declare no conflict of interests.

References


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