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Review

Therapy of small cell lung cancer with emphasis on oral topotecan

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ABSTRACT

Systemic chemotherapy plays the major role in the management of patients with small cell lung cancer. Cisplatin plus etoposide is the most widely used regimen and is considered as standard in patients with limited disease. Cisplatin plus irinotecan improved survival compared to cisplatin plus etoposide in a Japanese trial but failed to do so in two trials in Caucasians. Cisplatin plus topotecan had similar efficacy compared to cisplatin plus etoposide in patients with extensive disease. In the second-line setting, topotecan showed similar efficacy but better tolerability compared to cyclophosphamide, doxorubin plus vincristine. Oral topotecan was as efficacious as its intravenous formulation and was shown to improve survival compared to best supportive care alone in patients previously treated with chemotherapy. Thus topotecan is considered as the standard second-line chemotherapy in patients with small cell lung cancer.

1. Introduction

Lung cancer is among the most common cancers [1,2]. In 2008 in Europe, 390,900 patients were newly diagnosed with lung cancer and 342,100 lung cancer deaths occurred which accounted for 19.9% of all cancer deaths [1]. Unless smoking prevalence decreases, lung cancer will remain common but avoidable [3].

Small cell lung cancer (SCLC) represents approximately 15–25% of all lung cancers [4] with a varying incidence in different countries [2,4,5]. Without treatment, SCLC is the most aggressive one of all lung cancer types. Patients with SCLC have a high propensity for early regional and distant metastases. Thus systemic chemotherapy is the cornerstone of treatment, while local treatments such as surgery or radiotherapy alone rarely result in long-term survival [6].

SCLC should be staged according to the TNM staging system but is often still staged according to the Veteran's Administration Lung Cancer Study Group as limited disease or extensive disease [7,8]. Hematogenous metastases usually involve the contralateral lung, liver, adrenal glands, brain, bones, and bone marrow. Limited disease SCLC carries a median survival of approximately 18–24 months [4,9] but is potentially curable with combined modality therapy which results in long-term disease-free survival in approximately 20–25% of patients [10,11]. Extensive disease SCLC is considered incurable. Median survival time is approximately 9–12 months and the 5-year survival rate is less than 3% [4,12].

Although SCLC is regarded as highly sensitive to both chemotherapy and radiotherapy, only modest improvement in survival has been achieved during the last 20 years [13].

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Table 1
Chemotherapy protocols for the treatment of SCLC.

Cisplatin and etoposide (PE)
Carboplatin and etoposide (CE)
Cyclophosphamide, doxorubicin, and vincristine (CAV)
Cyclophosphamide, doxorubicin, and etoposide (CAE)
Cyclophosphamide, doxorubicin, vincristine, and etoposide (CAVE)
Ifosfamide, carboplatin, and etoposide (ICE)
Etoposide, ifosfamide, and cisplatin (VIP)

2. Prognostic factors

Pre-treatment prognostic factors for prolonged survival are good performance status, female gender and limited disease [14–17]. Extensive disease, performance status >2, and metastatic lesions of certain organs (liver, bone marrow, central nervous system) at the time of diagnosis are associated with worse outcome [14–17].

Several laboratory parameters including serum lactate dehydrogenase, serum sodium, alkaline phosphatase, serum bicarbonate, white blood cell count, platelet count, hemoglobin level and neurone-specific enolase were also shown to be important prognostic factors [15–20]. However, the prognostic values of these parameters depend on whether all or subsets of patients with SCLC are analyzed [15].

Patients who are confined to bed have increased morbidity and poorly tolerate aggressive therapy. Nevertheless, patients with poor performance status can still derive symptom relief and prolongation of survival from treatment.

3. General treatment principles

First-line chemotherapy has to be aggressive and, therefore, consists of combination chemotherapy [21]. The protocols, which are used with different frequencies, are summarized in Table 1. These protocols result in response rates of 50–80% [22] and are superior to single-agent therapy with regard to symptom relief, quality of life, and survival [23,24]. In two meta-analyses, cisplatin-containing regimens have been shown to be more active than non-cisplatin-containing regimens [25,26]. Protocols containing either etoposide or etoposide combined with cisplatin were also found to result in a survival benefit [26]. Thus cisplatin plus etoposide is the most widely used protocol and is considered as the standard first-line chemotherapy in limited disease where it can be combined at full dose with thoracic radiotherapy [27].

Prophylactic cranial irradiation (PCI) has been established as standard treatment for patients who respond to initial treatment independent of tumour stage [28,29]. Fractions of 1.8–2.5 Gy are delivered up to a total dose of 25 Gy [30]. Higher-dose PCI (36 Gy) did not improve outcome in patients with limited-stage SCLC in complete remission after chemotherapy and thoracic radiotherapy [30]. In elderly patients, the absolute benefit of PCI, life expectancy and the presence of neurocognitive co-morbidities should be considered and discussed with the patients.

Despite high response rates to first-line treatment, the majority of patients will progress and succumb to their disease. In patients with progressive disease, the focus has been on single-agent chemotherapy due to the better tolerance compared to combination chemotherapy. The drugs studied in these patients include topotecan, irinotecan, paclitaxel, docetaxel, gemcitabine and vinorelbine, with topotecan being the best-characterized drug [31].

Despite improvements in both diagnosis and therapy during the past decades, the prognosis for patients with SCLC remains unsatisfactory. In order to improve outcome, new treatment strategies are urgently needed and should be evaluated in clinical trials. Patients should be enrolled into these trials whenever possible.

3.1. Treatment in patients with limited disease

For patients with limited disease SCLC, chemoradiotherapy remains the standard of care [4,32]. Cisplatin plus etoposide (PE) is the regimen of choice because it can be combined at full dose with thoracic radiotherapy and also has slightly superior activity compared with doxorubicin- or cyclophosphamide-containing regimens [4]. Patients usually receive 4–6 cycles of chemotherapy.

Thoracic radiotherapy is given at a total dose of 45–60 Gy. Thoracic radiotherapy appears to be more effective when given early in the course of chemotherapy [32] and when given twice daily for 3 weeks versus once daily for 5 weeks [27]. Chemotherapy combined with radiotherapy twice daily resulted in 2-year and 5-year survival rates of 47% and 25% but was associated with a higher rate of grade 3 esophagitis (27% versus 11%) [27].

In patients treated with chemoradiotherapy and prophylactic cranial irradiation, clinical complete response rates of up to 50–60% of patients and 2-year survival rates up to nearly 50% can be achieved [27,33].

3.2. Treatment in patients with extensive disease

In patients with extensive disease SCLC, combination chemotherapy remains the cornerstone of treatment. Several protocols are used with varying frequencies in daily practice (Table 1). The currently accepted first-line therapy is a platinum-based therapy containing etoposide [25,26,34]. These protocols achieve objective responses in about 60–80% of patients and median survival times of 8–13 months [35].

Carboplatin plus etoposide seems to be as effective but less toxic (except for increased myelosuppression) than cisplatin plus etoposide [36–38]. Three-drug combinations did not improve survival, with the exception of the VIP protocol. The VIP protocol slightly improved survival compared to cisplatin plus etoposide in a randomized trial [39], but due to its greater toxicity has not been widely used in clinical practice.

4. New drugs

In order to improve outcome of systemic chemotherapy in patients with extensive SCLC, several new drugs with a focus on topoisomerase-I- and topoisomerase-II-inhibitors have been investigated.

4.1. Irinotecan

Irinotecan, a topoisomerase-I-inhibitor, has been studied in several randomized phase III trials. Cisplatin plus irinotecan was shown to be superior to cisplatin/etoposide in a Japanese phase III study with median survival times of 12.8 and 9.4 months, respectively, and 2-year survival rates of 19.5% and 5.2%, respectively [40]. Gastrointestinal toxicity was worse in patients treated with cisplatin/irinotecan, while hematotoxicity was more severe in patients treated with cisplatin/etoposide.

In contrast to the Japanese trial, however, a North American/Australian study failed to show any improvement with a modified weekly regimen of cisplatin/irinotecan compared to cisplatin/etoposide in 331 patients with extensive disease SCLC [41]. The modified weekly irinotecan/cisplatin regimen resulted in less myelosuppression but more diarrhoea and vomiting. Another North American phase III trial, which included 620 patients and used the same regimen of cisplatin/irinotecan as the original Japanese study, also failed to demonstrate a survival benefit for