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Original article

Mediastinal radiotherapy after multidrug chemotherapy and prophylactic cranial irradiation in patients with SCLC – treatment results after long-term follow-up and literature overview

Radiothérapie médiastinale après chimiothérapie et irradiation prophylactique de l'encéphale chez des patients atteints d'un carcinome bronchique à petites cellules – Résultats et revue de la littérature

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ABSTRACT

Introduction. – Curative therapy for patients with small-cell lung cancer (SCLC) is based on multidrug chemotherapy combinations and radiotherapy. After a long time follow-up, the aim of the study was to evaluate the efficacy and toxicity of sequential chemo-radiotherapy and the effect of prophylactic cranial irradiation (PCI).
Methods. – From 1995–2005, 96 patients with SCLC (64 limited-disease [LD], 32 extensive-disease [ED]; median age 61 years [range 39–79]) were treated at our department with varying chemotherapy regimens and sequential mediastinal radiotherapy (50 Gy + 10 Gy boost in case of residual disease after chemotherapy). Afterwards, 15 patients with LD, good general condition and at least partial response after local treatment received PCI (30 Gy).
Results. – After a median follow-up of 78.6 months, 20 patients remained alive (20.8%, median survival time 18.2 months). The 2-/5-year overall survival rates were 33.8% and 12.6%, the 2-/5-year loco-regional control rates were 30.3% and 24.5%, respectively. Distant metastases occurred in 43 patients (24 cerebral). Cerebral metastasis occurred in 6.7% and 27.2% of the patients with PCI and without PCI respectively. Only tumor stage showed a statistically significant impact on overall survival and loco-regional control in multivariate analysis. Radiotherapy was well tolerated. Grade 3/4 toxicity occurred in seven patients. Prognosis of patients with SCLC remains poor. Administration of PCI in selected patients bears a decrease in the incidence of cerebral metastases. Alternative chemotherapy schemes as well as irradiation schemes and techniques should be the substance of future randomized trials.

Mots clés :
Cancer pulmonaire à petites cellules
Irradiation prophylactique de l'encéphale
Chimio-radiothérapie
Toxicité

RÉSUMÉ

Introduction. – Le traitement du cancer bronchopulmonaire à petites cellules repose sur l'association d'une polychimiothérapie et d'une radiothérapie. L'objectif de cette étude était d'évaluer l'efficacité et la toxicité de la séquence thérapeutique chimiothérapie–radiothérapie suivi d'une irradiation prophylactique de l'encéphale.
Patients et méthodes. – Entre 1995 et 2005, 96 patients atteints d'un cancer bronchopulmonaire à petites cellules, localisé pour 64, diffus pour 32, d'âge médian 61 ans [39–79 ans], ont été traités dans notre service avec différents protocoles de chimiothérapies puis par une irradiation externe médiastinale séquentielle de 50 Gy suivie d'un complément de 10 Gy en cas de maladie résiduelle après chimiothérapie.

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Une irradiation prophylactique de l'encéphale de 30 Gy a ensuite été délivrée aux 15 patients en bon état général atteints d'un cancer localisé qui a répondu au moins partiellement au traitement.
Résultats. – Après un suivi médian de 78,6 mois, 20 patients étaient en vie (médiane de survie à 18,2 mois : 20,8 %). Les taux de survie globale à deux et cinq ans était respectivement de 33,8% et 12,6%, les taux de contrôle local à deux et cinq ans respectivement de 30,3 % et 24,5 %. Quarante-trois patients ont été atteints de métastases dont 24 cérébrales. Les métastases cérébrales sont apparues respectivement chez 6,7 % des patients irradiés prophylactiquement dans l'encéphale et 27,2 % non irradiés. Seul le stade tumoral a montré un impact significatif sur la survie globale et le contrôle locorégionale en analyse multifactorielle. La radiothérapie a été bien tolérée. Des effets secondaires de grades 3 et 4 sont survenus chez sept patients.
Conclusion. – Le pronostic de patients avec des carcinomes bronchopulmonaires à petites cellules reste défavorable. L'administration d'une radiothérapie prophylactique cérébrale chez des patients sélectionnés apparaît diminuer l'incidence des métastases cérébrales. D'autres protocoles de chimiothérapies ainsi que des schémas et des techniques d'irradiation différentes doivent être testés dans les futurs essais randomisés.

1. Background

Lung cancer still represents the leading cause of death among all malignancies [12,17,38,39]. Approximately, 20% of these respiratory malignancies belong to the histological subgroup defined as small-cell lung cancer (SCLC) [7,10,49]. Among others, significant particularities of this tumor entity are rapid proliferation and distinctive tendency of systemic spread [10,14]. At time of diagnosis, approximately 60% of the patients have a progressed disease [51,53]. These characteristics are appreciated by interpreting SCLC as a systemic disease resulting in multimodal therapy regimens involving chemotherapy as central column of therapy [10,51].

According to the "Veterans Administration Lung Study Group" classification, two prognostic groups, "limited-disease (LD)" and "extensive-disease (ED)", are differentiated in SCLC [10,60]. LD is defined as disease limited to the ipsilateral hemithorax ± infiltration of the ipsi- or contralateral mediastinal or supraclavicular lymphnodes and ± ipsilateral pleural effusion, independent of its cytological status. ED is defined as any manifestation beyond LD [10,49,60]. Although SCLC holds a high intrinsic sensibility for chemotherapy and irradiation, treatment with curative intention is virtually exclusive for patients with LD, due to both high loco-regional and systemic relapse rates [10,14,37]. Remaining untreated, mean time of survival is 5 and 12 weeks for ED and LD, respectively [35,60].

Curative therapy involves multidrug chemo-radiotherapy regimens, whereas two treatment schemes are commonly applied: a sequential application of multidrug chemotherapy followed by mediastinal radiotherapy in case of tumor response, or a concomitant application of multidrug chemotherapy and radiotherapy [22,27,30,41,46,48,51,54,58]. Concomitant chemo-radiotherapy potentially increases hematological and somatic toxicities, e.g. lung and esophagus, possibly due to larger treatment portals, whereas combinations of cisplatin and etoposide have been proofed to be specifically feasible for the simultaneous application [27,42,52,54]. Furthermore, in selected patients with LD SCLC, studies showed a benefit for hyperfractionated radiotherapy in combination with chemotherapy on overall survival, whereas hematologic and somatic toxicities increased as well [6,55]. Due to the increased risk of hematological and somatic toxicities, the hyperfractionated concomitant chemo-irradiation treatment regimen should be restricted to selected patients with smaller tumor volumes and good general condition [8]. The current standard treatment of patients with LD SCLC is a chemotherapy containing etoposide and cisplatin plus chest radiation therapy beginning with the first or second cycle of chemotherapy [27,36].

Nowadays prophylactic cranial irradiation (PCI), initially recommended only for patients in complete remission after initial treatment, is recommended for patients with partial response and even more patients with extensive disease [3,25,29]. Therewith, the incidence of brain metastases can be reduced. In selected patients with early stage LD (T1-2, N0), surgical treatment may represent a further therapeutic option, whereas for treatment in curative intention chemo-radiotherapy has to be applied as well [10,25,37,46,51].

Despite this, prognosis of patients with SCLC still remains poor with long-term overall survival rates of 54–19% and 30–15%, after 2 and 5 years respectively for LD, and 5% and 3% after 2 and 5 years respectively for ED [2,14,18,19,21,54,55,59].

Therefore, ongoing research for further improvement of treatment concerns about optimal composition of the therapeutic options in the multimodal treatment, for example variations in chemotherapeutic doses, combinations or schedules, as well as altering fractionation and dose schemes in irradiation [18,21,54,55,59].

The aim of the present study was to analyze overall survival, and local control rates in patients with SCLC treated with multimodal treatment (chemo-radiotherapy, in selected patients subsequent PCI) at our department after long-term follow-up. The data are presented in the light of the current literature.

2. Methods

2.1. Patient characteristics

Between 1995–2005, 96 patients with histologically determined SCLC were treated at our department in curative intention. At the time of diagnosis, 64 patients (66.7%) were classified as LD and 32 patients (33.3%) as ED. In 26 (27.1%) patients, the primary tumor was located in the upper lobe, in 10 (10.4%) patients in the lower lobe and in 60 (62.5%) patients in the hili region. Sixty-seven patients were male and 29 patients female. Patients' age ranged from 39–79 years (median 61 years). Before the start of mediastinal radiotherapy, hemoglobin levels were determined in all patients. Considering a hemoglobin level of more or equal than 13 g/dL and 12 g/dL as normal for men and women, respectively, 64.2% of the male and 72.4% of the female patients had normal hemoglobin levels. The median hemoglobin level was 12.8 g/dL (range 8.9–17.4 g/dL).

2.2. Chemo- and radiotherapy

Prior to radiotherapy, all patients received at least one regimen of chemotherapy, whereas in 42 patients more than one regimen