Concurrent hyperfractionated radiotherapy and chemotherapy for patients with limited small-cell lung cancer. Results from a single institution

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SUMMARY

BACKGROUND: Concurrent use of chemotherapy and twice-a-day hyperfractionated radiotherapy is an efficacious scheme to control limited disease (LD) small-cell lung cancer (SCLC).

AIM: Our main objective was to estimate initial results in overall survival for patients with LD-SCLC treated with concomitant chemotherapy and hyperfractionated thoracic radiotherapy in routine practice. Response to treatment and toxicity were also assessed.

MATERIAL AND METHODS: Forty-nine patients with confirmed LD-SCLC were treated at the Department of Radiotherapy of the Hospital General de Catalonia (Spain) from December 1999 to February 2007. The chemotherapy regimen was cisplatin (80 mg/m^2) on day 1 and etoposide (100 mg/m^2) on days 1, 2, and 3, every 21 day. The target dose to the tumor volume was 45 Gy. Prophylactic cranial irradiation (PCI), consisting of 30 Gy delivered in 15 fractions, was prescribed for all patients with a response rate >75% (23 of 30 patients).

RESULTS: Median follow-up was 12 months (range, 6-58 months) and median overall survival was 28.9 months. Two-year and 4-year survival rates were 56.4% and 30.1%, respectively. At 2 years, specific survival, local control, and systemic control were 64.2%, 88.8%, and 46.8%, respectively. Myelotoxicity and oesophagitis were the most severe toxicities.

CONCLUSIONS: The combined schedule – hyperfractionated irradiation plus concurrent chemotherapy – can be applied in routine practice in the context of early radiotherapy, which is considered standard treatment, with acceptable toxicity and similar results to those described in the literature.

KEY WORDS: small-cell lung cancer, radiotherapy

BACKGROUND

Small-cell lung cancer (SCLC) accounts for approximately 15% of the total lung cancers diagnosed around the world [1]. Nearly 33% of these are categorized as limited disease (LD-SCLC) based on their clinical confinement to a single hemithorax, regional lymph nodes, which can be treated in a reasonable radiation field [2]. Meta-analyses by Pignon et al. [3] and Warde and Payne [4] found that combined chemoradiotherapy produces a modest but significant increase in survival and also achieves better local control compared to chemotherapy alone.

External beam radiation is accepted as an integral part of the treatment of LD-SCLC but controversies remain regarding dose, tim-

ing, and fractionation. These controversies have been extensively discussed in recent reviews by Fried et al. [5] and De Ruysscher et al. [6], both of whom conclude that available evidence indicates that 2- and 5-year survival rates of patients with LD-SCLC favour the use of early chest radiotherapy, with a significant difference in survival if the overall treatment time of the chest radiation is less than 30 days and when hyperfractionated radiotherapy and platinum-based chemotherapy are used.

Twice daily fractionation is theoretically advantageous for malignancies such as SCLC, which are characterized by rapid cell proliferation. The effect of hyperfractionation in LD-SCLC has been evaluated in two trials. Turrissi et al. [7] carried out a randomized trial of concurrent chemoradiotherapy with 45 Gy radiation delivered either once or twice daily during the first cycle of cisplatin and etoposide. The authors reported a significant increase in 2- and 5-year overall survival rates for the hyperfractionated arm. In a trial carried out by Bonner et al. [8], radiotherapy was delayed until the start of the fourth cycle of cisplatin and etoposide and patients randomized to the hyperfractionated arm were given a midcourse break of 2.5 weeks (split-course radiotherapy). However, the authors found no benefit in overall survival with the use of twice-daily radiation.

AIM

The main objective was to estimate initial results in overall survival of patients with LD-SCLC treated with concomitant chemotherapy and hyperfractionated thoracic radiotherapy in daily practice at a single institution (Hospital General de Catalunya, Spain). Response to treatment and toxicity were also assessed.

MATERIAL AND METHODS

After the results of the Turrissi et al. study were published in October 1999, we began treating patients with the same chemoradiotherapy regimen in our clinical practice. Between December 1999 and February 2007, 49 patients with LD-SCLC were treated at the Department of Radiotherapy of the Hospital General de Catalunya. In the present article we present the results of the first 30 patients, treated up to March 2005.

Pretreatment diagnostic and staging procedures included complete history and physical examination, full blood count, blood chemistry, chest X-ray, fibreoptic bronchoscopy, radionuclide bone scanning, and computed tomographic scan of the thorax including the upper abdomen and central nervous system. No positron emission tomography (PET) was performed. Patients with contralateral hilum or supraclavicular nodal disease were excluded from hyperfractionation regimen treatment.

Histological diagnosis of SCLC was based on criteria from the World Health Organization (WHO) [9] and stage classification was based on the recommendation of the Veterans Administration Lung Group (VALG), including supraclavicular nodes and pleural effusions [10]. General inclusion requirements were as follows: adequate organ function, including leucocyte count >3000/mL, absolute granulocyte counts >1500/mL, platelets >100,000, and creatinine <1.5 mg/dL. Additional inclusion criteria were hepatic parameters (especially transaminases) within normal limits and forced expiratory volume in one second > 1500 mL.

The chemotherapy regimen consisted of cisplatin (80 mg/m^2) given on day 1 and etoposide (100 mg/m^2) on days 1, 2 and 3. This regimen was then repeated every 21 days for a total of 4 to 6 cycles depending on performance status.

Radiotherapy, given concomitantly to chemotherapy, commenced as soon as it was feasible: 22 patients received radiotherapy during the third cycle, 7 during the second, and 1 during the first cycle. Patients were given 2 fractions/day of 1.5 Gy each, separated by an interval of 6 hours, 5 days per week for 3 weeks. The aim was to deliver a dose of 45 Gy to the tumour volume. Two patients received 50.5 Gy and one 54.5 Gy to compensate for interruptions in the radiotherapy delivery. The planning target volume (PTV) included all of the tumour area defined by the CT scan as well as the bilateral mediastinal nodes–including one lymph echelon beyond the involved nodal area, and homolateral hilum. The contralateral hilum and supraclavicular nodes were excluded from the PTV. Anteroposterior/posteroanterior fields were used in the two fractions given during the first week. In the second and third weeks of administration, the second fraction

was given through oblique fields so as to preclude irradiation of the spinal cord to avoid exceeding 36 Gy to that risk organ.

Response assessment took place approximately 4–6 weeks after completion of the final chemotherapy cycle and included complete history and physical exam, full blood analysis, and chest CT scan. PCI, consisting of 30 Gy delivered in 15 fractions, was prescribed for all patients who achieved a response >75% and was administered 6 weeks after the last chemotherapy cycle. Toxicity was scored using the CTCAE scale (version 3.0) [18].

RESULTS

Patient Characteristics:

Table 1 shows patient characteristics. Males were clearly predominant (28:2), with a median age of 57.8 years (range: 35–75). Most patients (20 patients; 67%) had a Karnofsky index in the range 90%–100%, while the remaining patients (10 cases; 33%) had a Karnofsky index in the range 70%–80%.

Table 1. Patient characteristics (N=30)

Age:	
Range (years)	35–75
Median (years)	57.8
Sex:	
Male:	28 patients
Female:	2 patients
Karnofsky status	**# of patients**
100%	1
90%	19
80%	9
70%	1

Compliance with radiochemotherapy treatment:

For logistical reasons, most patients began radiotherapy treatment during the second and the third cycle of chemotherapy. This delay was attributable, in most cases, to waiting lists in the radiotherapy department. As a result, 22 patients received radiotherapy during the third cycle, 7 patients during the second, and only 1 patient during the first cycle. Treatment was delivered with a linear accelerator in nearly all cases (29 patients) with only one exception: 1 patient received mixed treatment (linear accelerator and cobalt unit).

The total dose was 45 Gy in 27 patients. However, 3 patients received a higher dose (in 2 cases, 50.5 Gy and in 1 case 54.5 Gy) to compensate for interrupted radiotherapy secondary to machine breakdowns. The median overall treatment time was 21.2 days (range, 18–27 days).

Most patients (28 of 30) underwent cisplatin-based chemotherapy, although carboplatin was used in 2 cases.

Acute Toxicity:

Myelotoxicity and oesophagitis were the most severe toxicities (Table 2).

Severe anaemia requiring blood transfusion was present in 3 patients (10% G3–G4).

Table 2. Acute Toxicity:

Anaemia	**# of patients**
G0	13
G1	12
G2	2
G3	2
G4	1
Leucopenia	**# of patients**
G0	15
G1	4
G2	5
G3	3
G4	3
Neutropenia	**# of patients**
G0	16
G1	3
G2	2
G3	4
G4	5
Thrombocytopenia	**# of patients**
G0	22
G1	0
G2	4
G3	1
G4	3
Oesophagitis	**# of patients**
G0	2
G1	11
G2	14
G3	3
G4	0

G3 leucopenia occurred in 3 patients, while 3 others experienced G4 leucopenia (20% of patients with severe leucopenia). G3 neutropenia was detected in 4 patients, and 5 others had G4 (30% severe neutropenia). Concomitant infection was documented in 7 patients, all of whom responded satisfactorily to intravenous antibiotic therapy and haematopoietic growth factors. G3 thrombocytopenia occurred in 1 patient and G4 in 3 patients (13.3% severe leucopenia). No toxic deaths occurred.

During chemoirradiation, the most common grade of oesophagitis was G2, which occurred in 14 patients (48%). Only 3 patients presented G3 oesophagitis, treated with an endoscopic gastric tube and major analgesia. No G4 oesophagitis occurred.

Several different factors–including length of oesophagus irradiated, overall treatment time, and total number of neoadjuvant chemotherapy cycles–were studied to determine if there was any association with acute oesophagitis. None of these variables were found to be significant except for the use of 2 or more neoadjuvant chemotherapy cycles, in which patients seemed to develop less acute oesophagitis. Five patients developed G2 weight loss, while most experienced G1 (14 patients). Three patients had G1 acute pneumonitis at the end of radiotherapy.

Response

All 30 patients completed the recommended treatment. Of these, 7 showed a partial response of less than 75%. The remaining patients (23 cases; 76.6%) achieved a partial (> 75%) or complete response and all of these underwent PCI. No cases of disease progression occurred after radiochemotherapy was applied. The total PCI dose was as follows: 19 patients received 30 Gy in 15 fractions, 2 were given 32 Gy, and 2 underwent 36 Gy to compensate for the delay (> 6 months) between diagnosis and PCI.

Chronic toxicity

Nine patients developed G1 clinical oesophagitis that was well controlled with symptomatic management. Lung toxicity was present in different grades: G1 in 5 patients, G2 in 5 patients, G3 in 1 patient, and G4 in 2 patients. Additionally, chronic encephalitis–confirmed by clinical examination and cerebral MRI changes–was diagnosed in 2 patients.

Patterns of recurrence

The site of first recurrence was documented in 18 patients. Recurrences were local alone (in-field) in 3 patients, local alone (out-of-field) in 1 patient, systemic failure alone in 13 patients, and systemic and local out-of-field in 1 patient. Brain metastases occurred in 7 patients as a first recurrence, 4 of whom had previously undergone PCI.

Survival

With a median follow-up of 12 months (range, 6-58), the median survival was 28.9 months. Overall survival at 2 and 4 years was 56.4% and 30.1%, respectively (Figure 1). At 2 years, specific survival was 64.2% (Figure 2), local control was 88.8% (Figure 3), and systemic control was 46.8% (Figure 4)

DISCUSSION

Our treatment schedule, based on the randomised trial by Turrissi et al. [7], was applied as part of routine practice in the year 2000, in an attempt to reproduce the most effective arm of that study.

We encountered several difficulties in applying a regimen identical to that described by Turrissi. First, due to waiting lists, most patients began radiotherapy concomitant with the second (7/30 patients) or third chemotherapy cycle (22/30 patients). As a result, treatment began on day +21 and day +42. In addition, the definition of early and late radiotherapy is a subject of intense debate. Fried et al. [5] found that chest radiotherapy delivered within the first 9 weeks after starting chemotherapy conferred a survival benefit at 2 years. In contrast, De Ruysscher and colleagues [6], who defined early radiotherapy as beginning within 30 days after the start of chemotherapy, found early treatment to be associated with a better 5-year survival rate, especially if the overall treatment time of chest radiotherapy is less than 30 days. A review carried out by Stuschke et al. [11] showed that scheduling of radiotherapy and chemotherapy is important in the treatment of a fast proliferating tumour such as SCLC and prolonged overall treatment with sequential radiochemotherapy should be

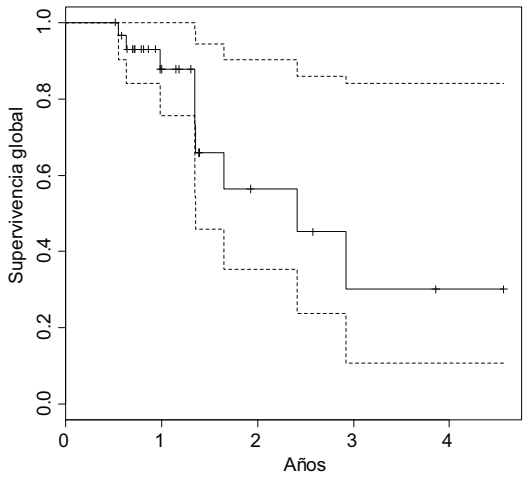

Fig. 1. Overall survival

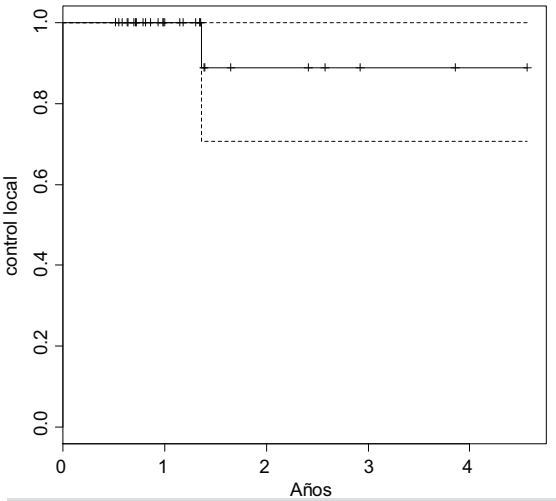

Fig. 3. Local control

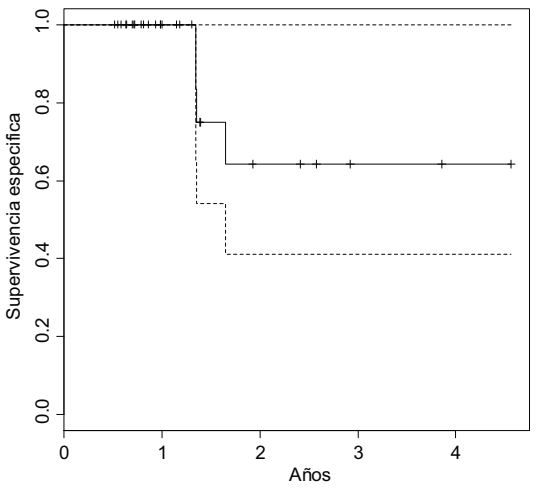

Fig. 2. Specific survival

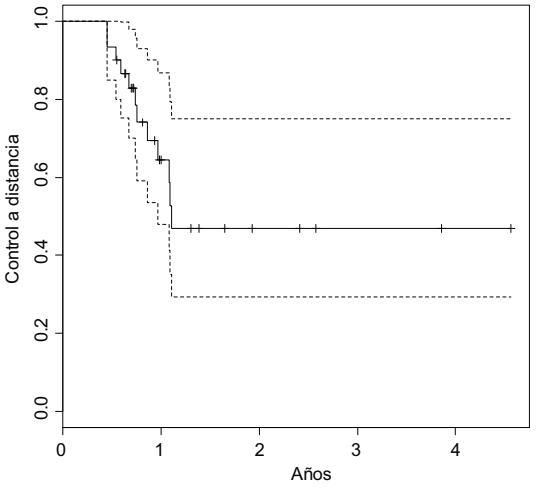

Fig. 4. Systemic control

avoided. In our case, radiotherapy was delivered concomitantly either with the second or third cycle, unlike the study by Turrissi, in which radiotherapy treatment was concurrent with the first cycle.

The second difficulty was related to the fact that, in contrast to Turrissi, we routinely excluded contralateral disease and supraclavicular nodes because 2.5D radiotherapy (2 dimensions in different slices) was delivered to the PTV and it was extremely difficult to ensure perfect coverage in these cases. Given the rapid shrinkage of the tumour during the course of chemotherapy, the GTV became considerably smaller at the beginning of the second or third chemotherapy cycle. As a result, a smaller lung volume and shorter length of oesophagus was irradiated than in Turrissi et al. A study from the Southwest Oncology Group (SWOG) [12] showed no difference in recurrence rates between patients randomized to receive wide-field radiation (pre-chemotherapy target volume) and those who received reduced field (post-chemotherapy target volume) radiation.

Despite the limited number of patients (30) in our study, median survival was 28.9 months, similar to the results (23 months) reported by Turrissi. The survival rate was good: 56.4% at 2 years and 30.1% at 4 years, similar to rates reported by Turrissi (41% at 2 years and 26% at 5 years).

Our series showed modest toxicity. Haematological toxicity included G3–G4 anaemia in 3 patients (10%), G3–G4 leucopenia in 6 patients (20%), G3–G4 neutropenia in 9 patients (30%), and G3–G4 thrombocytopenia in 4 patients (13%). In general, patients in our series showed less haematological toxicity than that reported by Turrissi, probably due to the different doses of etoposide used (100 mg/m^2 versus 120 mg/m^2) and smaller radiotherapy fields that included fewer vertebrae. This may also explain the limited number of severe oesophageal toxicities: no patients developed G4 oesophagitis, while only 3 developed G3 oesophagitis, in contrast to Turrissi, where 5% and 27%, respectively, of patients developed G4 or G3 oesophagitis. Finally, only 3 patients experienced either G3 (1 patient) or G4 (2 patients) chronic pneumonitis, the most debilitating toxicity. Other authors [13, 14] have reported similar toxicities using hyperfractionated radiotherapy and concomitant chemotherapy in daily practice.

A meta-analysis [15] found that PCI was associated with a 5.4% increase in overall survival at 3 years in patients who achieved a complete response. In our series, patients who achieved a partial (> 75%) or complete response (23/30 patients) underwent PCI. After PCI, only 4 of these 23 patients experienced a relapse in the brain. Although PCI is delivered after completion of chemotherapy and ideally no longer than 6 months after diagnosis, the optimal dose has not yet been clearly established. The standard seems to be 25 Gy in 10 fractions, although 36 Gy delivered in 18 fractions has been shown to have a lower brain relapse rate [19]. We used 30 Gy in 10 fractions, a schedule with a biologically equivalent dose (using an alpha/beta ratio of 3 for neuronal tissue) to the accepted standard in place at the beginning of 2000. Evidence from trials with up to 2 years of follow-up data shows that PCI does not cause significant late neurotoxicity or other adverse effects such as emotional distress and deteriorated physical condition. Chemotherapy can contribute to neurological dysfunction in some SCLC patients, and nearly 40% of these patients have neurological impairment prior to PCI [16, 17]. Chronic encephalitis – confirmed by clinical examination and changes on the brain MRI – was diagnosed in 2 patients in our practice. Neurotoxicity was not evaluated by neuropsychometric testing.

Excellent local control is another advantage of hyperfractionated treatment. In our series, local control was 88.8% at 2 years and the main pattern of first recurrence was systemic (14 patients; 46.6%). New approaches in staging, such as PET CT scans, can help to define more clearly those patients that have only limited disease. In this way, we may influence and improve systemic control.

CONCLUSIONS

The Turrissi schedule can be applied in routine practice in the context of early radiotherapy concomitant to chemotherapy, which is considered standard treatment, and similar results can be achieved. Longer follow-up needs to be done, especially considering the number of patients treated at our institution (49 by February 2007). The optimal dose is already being explored in a current phase III (Convert) trial comparing accelerated twice-daily radiotherapy (45 Gy) to once-daily radiotherapy up to 66 Gy concurrently with cisplatin-etoposide during the second cycle.

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