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Editorial

Small cell lung cancer: What are the treatment results in routine management?

In the present issue of *Lung Cancer*, a 20-year experience in the routine management of small cell lung cancer (SCLC) is reported by the team of the Medical University of Innsbruck and affiliated hospitals. The records of 484 consecutive patients diagnosed between 1991 and 2011 were reviewed, in the context of the comprehensive lung cancer project "Twenty-Year Retrospective of Lung Cancer (TYROL study)". A total of 443 patients (91.5%) received adequate antitumoral therapy: 26 had radical surgery, 112 with limited disease (LD) curative radiochemotherapy (RT-CT), 311 a first line palliative therapy (mainly chemotherapy). In addition, 209 patients received at least a second line of palliative anticancer treatment. In term of survival, 56 were still alive at time of last update. The overall median survival after first diagnosis was 11.3 months. It was 90.8 months after radical surgery, 21.8 months after radical RT-CT, 9.7 months after palliative chemotherapy. Factors independently associated with favourable survival were response to therapy and prophylactic brain irradiation in patients treated by RT-CT, and response, age <70 years and absence of LDH elevation in those receiving palliative therapy. There was no significant difference in the survival results according to the decade of treatment (1991–2001 vs. 2002–2011).

The originality of the TYROL study is to report on a series of patients with SCLC managed in a specific setting over 20 years. As pointed by the authors, data in the literature are usually reported from clinical prospective studies, implementation studies, registries, cohorts collected from a specific problem [1]. Very few analyses are available from unselected population whose extensive data have been collected on patients and diseases characteristics, treatments administered, outcome and long follow-up. Those studies are important because they are the best for describing the routine management and allow determining how thoracic oncology is practiced in specific settings or countries without selection of the patients according to trials criteria. Registries, such as the SEER (for Surveillance, Epidemiology and End Results) for LD SCLC [2] or the Netherlands Cancer Registry [3], provide limited data on very large populations; they have the advantage to report on the whole population of the area but do not allow careful analyses as performed in the present report.

The presently reported study might be called unselected patients cohorts, with data collected in order to assess the care management of a specific disease by a given setting (institution, organisation, etc.). To the best of our knowledge, it is the first dealing with SCLC. Similar data have been published for lung cancer with any histological type, in France by the Collège des Pneumologues des Hôpitaux Généraux (CPHG) [4–7] and more recently in Portugal for the Northern part of the country by a consortium of hospitals [8]. It should be noted that the publication of such studies in the international press is difficult because journal editors prefer prospective therapeutic trials or meta-analyses. They have to be searched in national medical literature.

The TYROL study failed to show survival improvement over the two decades patients were selected. This is not very surprising because few progresses have been performed in the treatment of SCLC since the early nineties. Nevertheless the treatment policy is not described, probably because the concept of multidisciplinary conferences for cancer management is too recent [9]. These conferences should be based upon a treatment programme based on guidelines. For instance, in our own institution, the programme is based on the European Lung Cancer Working Party (ELCWP) guidelines [10,11] which have been updated in 2014. They are summarised in Table 1. We recently reviewed the experience of

Table 1
ELCWP guidelines for the management of small cell lung cancer: main recommandations.

Limited disease
- Chest radiotherapy should be part of the treatment and given early (during the first 30 days) and given concomitantly to chemotherapy.
- A dosage of at least 45 Gy by conventional delivery or biologically equivalent should be administered.
- In case the patient condition or the tumour volume does not allow that dosage, chest irradiation might be delayed until the third course of chemotherapy.
- The recommended chemotherapy regimen is the combination of cisplatin and etoposide for 4–6 courses.
- Prophylactic brain irradiation (25 Gy in ten fractions) might be administered as soon as complete response is achieved according to the modalities of the trials supporting its efficacy.
- Surgery might be considered in some very limited tumours (stage I or II) in association with adjuvant chemotherapy
Extensive disease
- Chemotherapy with active drugs has to be administered. The recommended regimen is the combination of cisplatin and etoposide.
- Four to six cycles should be at least administered.
- There is no routine indication for intensive, maintenance, alternate or sequential chemotherapy.
- Second-line chemotherapy should be considered in case of cancer progression, without recommendation for a specific regimen, except the first-line regimen if relapse occurs more than three months after the end of the initial treatment with a good response to that chemotherapy.

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our own centre in the application of that approach. Between 2009 and 2012, 50 consecutive cases of SCLC were discussed in our multidisciplinary weekly conference, including 1, 9 and 40 with respectively stages I, III and IV diseases. One patient was not treated, 9 received concomitant chemoradiotherapy, 39 chemotherapy and 1 presenting with brain metastases was treated by concomitant chemoradiotherapy and brain stereotaxic irradiation. The majority received the cisplatin + etoposide regimen (33), some were treated in a clinical trial without cisplatin (5) or by carboplatine + etoposide (7) or other regimens (4) mainly for unfitness. The programme has thus been very well applied and this type of information has to be reported in unselected patients cohorts analysis.

The authors have reported survival rates in accordance with those usually obtained in the studies and registries, better than those reported in the IASLC (International Association for the Study of Lung Cancer) data basis [12] but similar to those obtained in our own trials [13,14]. This suggests that the patients of the TYROL study have been managed according to the best guidelines. For the prognostic factor analysis, a word of caution is necessary because the authors have used as parameters some treatment effects such as response or administration of radiochemotherapy. This should be avoided because treatment choice might be based on the own prognosis perception of the physician, biasing the parameter. Otherwise, the authors found data in according with IASLC study [15].

The last aspect of the study that we would like to discuss is the level of evidence in unselected patients cohorts. In evidence-based medicine, randomised clinical trials are considered as the best level of evidence [16,17], followed by prospective studies with a control group, comparative studies with historical controls, prospective cohorts without control group, retrospective studies and case reports. As we have pointed in a recent editorial [1], "this is true from a scientific point of view (internal validity) because randomisation minimises the risk of bias. It is less true for external validity. Indeed, the patients selected for trials are often a small part of the whole group of patients which we have to treat. Patients which are compromised by conditions such as poor performance status, organ failures, other severe diseases, or old age, are often excluded for trials but not for routine treatment. In fact, results of clinical trials should be confirmed by studies conducted in the context of the daily practice where patients do not receive the recommended therapy only in case of medical contra-indication to its administration. Those studies of which methodology should be better defined are the best level evidence for generalizability (external validation). A similar approach should be recommended for practice guidelines. Indeed, a lot of guidelines are today published but none have been so far validated by implementation studies".

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