Chemotherapy advances in small cell lung cancer

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Small cell lung cancer accounts for 13–15% of all lung cancer worldwide. There has been a decrease in the number of cases, with no clear explanation, except probably to changing in smoking habits in the last two decades. In the early 1980s, it became clear that SCLC was an extremely sensitive tumour to radiation as it was to chemotherapeutic agents. With cisplatin/etoposide combinations or cyclophosphamide, anthracycline and vincristine/etoposide regimens responses were observed in 50–70%, with 20–30% complete remissions in extensive disease. For limited-stage patients chemotherapy associated with thoracic radiation was able to produce a cure rate of 10–20%. The addition of prophylactic brain irradation to limited stage cases has reduced mortality by a factor of nearly 5%. But despite these early good results no breakthrough came later on, and in the last decade or so, we are still facing this plateau. New agents have recently been included in the therapeutic armamentarium, such as gemcitabine, irinotecan, paclitaxel and more recently pemetrexed. This fact has allowed many patients to receive a relatively active second line therapy, but the overall survival remains unchanged. Targeted therapies are undergoing some evaluations, but the data are too premature and, so far, quite discouraging. At the present time there is an urgent need to improve clinical research in this somehow forgotten disease.

Key words: small cell lung cancer, chemotherapy, targeted therapy

introduction (where do we come from?)

Small cell lung cancer (SCLC) accounts for only 13–15% [1] of all new cases of lung cancers, but anyway it still affects nearly 3500 patients in Italy every year, with a death rate of over 90%. Worldwide mortality due to this disease overtakes 200 000 patients/year. Despite this fact, the interest among clinical oncologists for such a tremendous disease seems to have reduced, if we take into consideration the declining numbers of papers presented in the last decade at big international events or studies performed.

In the early and mid-1980s a take-off in terms of interest and clinical resources employed was observed, and it was speculated that the solution of the problem was just round the corner or close to that. Response rate was comparable to germ cell tumours which in the same years have proved to be the first curable neoplastic disorder. The vast majority of SCLC patients treated with chemotherapy for extensive disease did obtain a response with four-six courses of standard therapy, with nearly a fourth of them achieving a clinical complete remission. After two decades, SCLC remains a highly incurable disease, probably the most incurable among the sensitive ones. Major advances came from active drugs, mainly cisplatin and etoposide combination, or the triplet of anthracycline, cyclophosphamide and vincristine/etoposide. A further improvement came from the addition of thoracic radiation in patients in complete remission [2, 3]; survival was improved by 5% at three years, even if the assumption is valid only for patients <65 years of age, and also local relapses were significantly reduced. Since those times, the addition of radiation to chemotherapy has become the standard of treatment for patients with limited stage disease. Nevertheless two meta-analyses were not able to answer questions such as: when deliver radiation, or how much radiation, or timing of radiation. In order to improve local control and possibly survival, several attempts have been made of delivering radiation (timing, scheduling, fractionating). A pivotal trial conducted in the late 1990s [4] compared a new technique of twice-daily versus once-daily with cisplatin/etoposide chemotherapy. The results of this randomized trial clearly favoured the experimental arm, which was superior for overall and disease-free survival. Nevertheless this modality has never become the standard option, but the research is continuing and a very recent, but rather small phase two study has employed irinotecan plus cisplatin followed by concurrent twice-daily radiation with cisplatin and etoposide. Objective response rate was 100% [5] and 2-year progression-free survival was in excess of 35%. Radiation treatment should possibly be delivered early in conjunction with chemotherapy as a practical guideline for the treatment of small cell lung cancer, even if the real advantage of early concurrent radiation is a question of debate as the most recent systematic review shows just a trend (P = 0.07) in favour of early concomitant therapy [6]. The last small, but significant improvement came from a relatively large meta-analysis regarding the use of prophylactic radiation in patients in complete remission [7] with a 5% improvement in overall survival. So far this is the best we can do.
**standard chemotherapy**

As mentioned before, cisplatin and etoposide has become the standard of treatment option for patients with limited and extensive disease. Even if it is not superior to CAV or CAV-like regimes, it allows concomitant radiation to the chest avoiding major toxicities (such as heart damage above all) [8]. Results of SECSG and Japanese studies have demonstrated a similar effect of PE and CAV or the alternation of the two schedules [9, 10]; the Japanese trial however [10] has shown a trend favouring CAV/PE alternations, but only in limited disease patients. In a more recent study conducted in Norway, PE was statistically superior to CEV, but only in LD patients [11]. The role of carbolated, a less toxic and more expensive platinum derivative, has been proven to be active in SCLC; direct comparisons between cisplatin/etoposide and carboplatin/etoposide (as in LD as in ED patients) have shown similar antitumour activity, but the carboplatin based schedule was less toxic [12]. All these combinations may be considered equally effective in the treatment of this disease with response rate in ED in the range of 50% to 60% and median survival times of 7 to 11 months. For LD patients responses are higher and 2-year survival is in excess of 20%, but these figures have unfortunately come to a plateau and no breakthrough has appeared on the clinical scenario.

**new drugs and new combinations (where do we go from here?)**

Such a plateau has generated a pessimistic wave and it seems that the interest of thoracic oncologists has moved from SCLC towards NSCLC in a sort of changing the Cinderella role 20 years apart. Nevertheless new drugs have undergone clinical evaluation as in second line and as in first line.

Irinotecan, a topoisomerase I inhibitor, has shown to have activity in SCLC in phase II studies and it has been added to cisplatin and compared to the standard PE combination in a Japanese trial [13]. The planned size of the study population was 230 patients, but enrollment was terminated early because an interim analysis found a statistically significant difference in survival favouring the irinotecan/cisplatin combination (12.8 months versus 9.4 months). Such a treatment has become a standard in Japan, but nowhere else, and the study has recently been replicated in the USA in a confirmatory trial with different results [14]. The schedule was in fact slightly different with irinotecan delivered weekly at the dose of 65 mg/m² (in the Japanese trial it was given every 3 weeks), but the overall survival was equal in both arms. Possible interpretations of this discrepancy are not totally understood, and one explanation might be ethnicity. Topotecan, another topoisomerase I inhibitor, has extensively been studied in relapsed patients with a clear difference regarding the previous sensibility. In patients treated within three months from previous chemotherapy (refractory) response rate was very low, in the range of 5%, while if delivered in chemosensitive patients the response rate was in the range of 14% to 37% [15]. When compared to CAV regimen in relapsed patients, topotecan monotherapy was over imposable to the triplet with 14% one year survival rate [16]. In the first line setting topotecan and paclitaxel or cisplatin or etoposide has shown to be a possible therapeutic option with a response range in extensive disease around 50% to 70% range; unfortunately all these phase II studies have not shown that a topotecan containing combination may be the way to overcome the wall. A doublet based on this agent and etoposide or paclitaxel, may be considered as an alternative option for patients not fit for platinum chemotherapy [17]. Gemcitabine has been shown to be an active agent in untreated and recurrent SCLC [18]; a recent multicenter, randomized, phase II trial conducted in Italy [19] has compared cisplatin, etoposide, and gemcitabine or cisplatin plus gemcitabine as first line treatment in patients with poor-prognosis SCLC. Seventy patients per arm were randomized; higher complete response rate was obtained in the triplet containing arm (18.6% versus 4.3%), while survival and time to progression was equal in both arms. Anyway haematologic toxicity was greater for the three drugs schedule. Cisplatin plus gemcitabine seems to be reasonable options for poor-prognosis LD and for ED patients.

Recently Pemetrexed has been tested in a randomized phase II trial [20] with either cisplatin or carboplatin in 78 extensive disease patients. The efficacy of both regimens was equal with nearly 45% response rate and haematologic toxicity grade 3–4 on 16–20% of the patients and one year survival not inferior to the known published data with newer agents. Pemetrexed is therefore another potential candidate to enter the increasing list of active agents in SCLC armamentarium.

Anyway none of these treatments has been compared in randomized phase III trials with the standard PE regimen, which therefore remains the cornerstone of SCLC therapy. In conclusion, in the last few years several new doublets and triplets have been generated, which may be considered as possible therapeutic alternatives. But the wall is still there.

**targeted therapy**

The majority of SCLC express the c-KIT oncoprotein which is a member of the type III receptor tyrosine kinase family [21]. Anyway a careful study performed in the Netherlands has shown that there is a lack of c-kit exon 11 activating mutations in c-kit/Cd117 positive sample. This may be the reason why imatinib is ineffective in this disease. A study performed on 26 patients (untreated or sensitive to prior chemotherapy) has shown no activity, with only one patient achieving stabilization [23]. This study anyway was conducted mainly in patients not showing expression of the imatinib target. In a recent study performed on twelve patients [24] expressing c-kit no responses were observed. A study conducted in a xenograft model [25] in NCr nude immunodeficient mice showed that therapeutic concentrations of imatinib were achieved in plasma and tumours xenografts, but not in the brain. Moreover imatinib blocked the constitutive activation of c-kit in SCLC tumour cell lines in vitro, with had a negligible effect on SCLC xenograft growth in vitro. At the present time is it not suggested to embark in expensive, time consuming and potentially ineffective clinical studies on imatinib in SCLC patients [26]. Temsirolimus (CCI-779) an ester of sirolimus is a potent inhibitor of mTOR interacting with FKBP-12 binding protein. The ECOG has conducted a randomized phase II study of two
dose levels of temsirolimus: 25 or 250 mg in 87 patients [27]
after induction chemotherapy (progressive disease patients
excluded). Median progression-free survival was 2.2 months
after randomization, with a slight increase in overall survival
for the higher dose arm. Further studies with such drug may not
be planned in the future.

Thalidomide was extensively studied by the FNCLCC
Group in France. Ninety-two extensive disease patients with
PS up to 2, age < 70 years were randomized to placebo or
thalidomide 400 mg/daily at the time or response after
induction therapy [28]. Overall survival was 8.7 months for
the placebo arm and 11.7 for Thalidomide (P = 0.02). This study
is a clue in favour of angiogenesis process as a therapeutic
window in SCLC therapy, nevertheless the drug proved to be
poorly tolerated at the planned dose of 400 mg, and was reduced
to 200 mg/daily in half of the patients.

Hu 901-DM 1 (or BB 10901) is an immunoconjugate created
by the conjugation of the maytansinoid drug DM 1 to
a humanized version of the murine monoclonal antibody N901.
BB10901 binds with high affinity to CD56 which is expressed
in SCLC. At the dose of 60 mg/m²/weekly BB 10901 was tested
in 10 patients with relapsed SCLC [29] and two obtained
a partial remission and another one a minor response. This study is on going up to 35 patients.

The story of the inhibition of matrix metalloproteinases
(MMP) seems to have come to an end after the phase II
randomized study of marimastat which is a synthetic inhibitor
of MMP [30]. Fifty hundred and thirty two patients (LD and
ED) were randomized to placebo or 10 mg bid orally of
marimastat. Median time to progression was 4.4 and 4.3 months
respectively. No role for MMP in lung cancer has been
observed with two other compound BAY 12-9566 and
AG3344 (prinomastat) showing poor results.

Another approach tempted is the use of bortezomib (PS-341)
which targets the ubiquitin-proteasome pathway interfering
with the p21 and p27, p53, cyclins D, E and A, Nuclear Factor
k-B, and members of the Bax family [31]. A phase II trial was
conducted at the SWOG in 57 ED evaluable patients either
responsive or refractory after a platinum combination [32]
employing bortezomib at the dose of 1.3 mg/m² on days 1, 4, 8,
11 q 21 days. Only one partial response was obtained. The
SWOG next step with this compound will be the association
of bortezomib with topotecan in second line.

conclusions
SCLC may be well represented as a wall, against which all the
efforts seem to have been unable to overtake the hurdle, after
the first enthusiastic age over twenty-years ago. Nevertheless at
the present time we are in a position of offering our patients
a standard, well defined, validated approach consisting of
standard chemotherapy (possibly PE) and early thoracic
radiation for LD patients, and four-six courses of PE (or
equi-active schedules). CNS prophylaxis is mandatory in all
patients in complete remission. These suggestions are found in
all the recommendations from different agencies or scientific
societies, and should constitute the standard approach for every
patient. Among the several options for second line, no one may
be recommended as the best and many drugs have shown
interesting activity (gemcitabine, paclitaxel, topotecan). Elderly
patients with good geriatric assessment have to receive the
standard therapy and not an a priori ‘dedicated’ dose. This has
clearly been shown in an elegant study [33]. Concurrent
radiotherapy is not a standard in elderly patients, because
we are lacking definitive data. Much work has to be done in the
field of targeted therapies in SCLC. Very few data, the
majority of which are negative, have been produced. The only
way to keep on tracking the path of research is to maintain
alive the interest of clinical oncologists towards this peculiar
and unique disease. We know the past, future is ahead.

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