Published in final edited form as:
Clin Lung Cancer. 2014 March ; 15(2): 93–95. doi:10.1016/j.cllc.2013.12.010.

Left Behind? Drug Discovery in Extensive Stage Small Cell Lung Cancer

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Abstract

Systemic therapy and subsequent survival for patients with extensive stage small cell lung cancer (SCLC) are poor and have remained unchanged in the last quarter century. To improve outcomes in these patients, a new drug development paradigm must be adopted that moves away from empiricism and instead focuses on tumor biology and heterogeneity as a means to increase target and drug class diversity. By incorporating tools that have led to new diagnostic and treatment options in non-small cell lung cancer, there could be hope yet for the future of SCLC therapeutics.

In this issue of *Clinical Lung Cancer*, Sekine *et al* report the results of a randomized trial of single agent amrubicin versus carboplatin/etoposide as frontline therapy in an elderly population of Japanese patients with extensive stage small cell lung cancer (ES-SCLC). (Sekine et al, Clinical Lung Cancer 2014). Amrubicin is a next-generation anthracycline without the cardiac toxicity of other anthracyclines. Since high response rates are often observed with platinum/etoposide in first line SCLC treatment, it would be difficult to show superiority with single agent amrubicin; thus the authors designed the trial as a non-inferiority study. Additionally, the investigators logically hypothesized that a single cytotoxic agent would have less toxicity than a doublet regimen in this patient context. Unfortunately, this was not the case: the trial was terminated prematurely due to intolerable toxicity. Rates of pneumonitis and grade 4 neutropenia were high. Of the 21 patients treated with amrubicin, three died (2 from sepsis in the setting of febrile neutropenia and one from amrubicin-induced pneumonitis). Clearly, amrubicin was not well tolerated in this population despite being used as a single agent and with appropriate dose modifications. Previous attempts to de-escalate first-line ES-SCLC therapy to single agents have been met with similarly poor results. For example, trials comparing oral etoposide to multidrug therapy were stopped early due to inferior survival outcomes in patients receiving oral etoposide[1, 2].

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In the modern era, SCLC represents about 15% of all lung cancer diagnoses and has been decreasing in incidence in the United States–attributed to decreasing tobacco consumption[3, 4]. Long-term survival in extensive stage disease remains dismal; in fact, little has changed in the front-line systemic treatment of extensive stage SCLC since the 1970s. In contrast, new diagnostic and therapeutic options have emerged during the same period (accelerated in the last decade) for adenocarcinoma of the lung, where molecular phenotyping and therapies against actionable targets are now considered standard-of-care[5].

To-date, platinum and etoposide remains the preferred first line regimen to treat ES-SCLC[6]. Following such therapy, high response rates can be achieved; however, relapse is universal and virtually all patients will succumb to the disease. Several randomized trials and meta-analyses have shown that platinum/irinotecan combinations are essentially comparable (but not superior) to platinum/etoposide[6, 7]. The only caveat is that irinotecan-based regimens may be incrementally more active in select Asian populations, possibly due to pharmacogenomic differences between patient groups[7, 8]. Clearly there has been a dearth of new agent development in ES- SCLC. Empirically designed trials of other cytotoxics – some of which were not even supported by any meaningful preclinical data – have failed to improve outcomes[9–12]. In the second line setting, systemic SCLC therapies have focused on single-agent treatment rather than combination therapy[6]. Topotecan is the only FDA-approved agent in this setting, based on a trial that showed its comparable efficacy to an older regimen of cyclophosphamide, adriamycin and vincristine (CAV), but with less toxicity[13]. Amrubicin was subsequently tested against topotecan in a large phase III trial in SCLC patients with progressive disease after first-line chemotherapy. Unfortunately, that trial was negative: no benefit for overall survival (the primary endpoint) was observed for amrubicin over topotecan (HR 0.88, p=0.17). In a hypothesis-generating subset analysis, overall survival appeared to be modestly improved with amrubicin in platinum refractory patients[14].

These sobering results force one to reflect on potential strategies to increase the success rate of SCLC drug development. Strategies should include attempts to 1) define SCLC biology to identify new actionable molecular targets; 2) increase the diversity of agents; and 3) abandon empiricism in favor of molecularly-based clinical trial design. Identifying new actionable targets is a formidable challenge. A weakness in discovering targeted treatments is that treatment of SCLC is not typically a surgical disease. Surgery only has a role only in those uncommon patients with very early stage SCLC, and early stage tumors may even be biologically different from extensive stage disease. This limits the availability of primary tumor tissue available for appropriate molecular phenotyping studies necessary for precision medicine. Lack of tissue cripples discovery of the molecular underpinnings that lead to new targeted agents and investigations into mechanisms of resistance to treatment.

Recent whole exome and transcriptome sequencing results highlight high mutation rates in SCLC with several potentially actionable somatic driver mutations and amplifications[15]. In addition to universal TP53 and Rb inactivation, mutations in histone modifying genes, FGFR1 amplifications (6%), MYC family amplifications (16%) and PTEN deletions (11%) were noted. Drugs targeting some of these pathways such as FGFR inhibitors are in clinical development. The keys to successful targeted therapy in SCLC are: 1) identifying subsets of

patients with potentially actionable molecular aberrations, 2) proving oncogenic addiction in preclinical models and 3) matching identified patients whose SCLC harbors the actionable molecular aberration to a potent targeted therapy.

A concerted effort to obtain adequate amounts of tumor tissue for research from patients at the time of diagnosis cannot be over-emphasized, even in extensive stage disease. Fortunately, technologies are sufficiently evolving to allow molecular characterization using smaller and smaller amounts of available tissue. Use of patient derived xenografts may also facilitate cultivation of scant amounts of SCLC tumor cells into sufficient quantities through serial passaging[16]. A recent study demonstrated high numbers of circulating tumor cells and tumor cell clusters in patients with extensive SCLC[17]. These circulating cells can potentially serve as clinical material for molecular phenotying and tumor heterogeneity studies.

Identification of the molecular underpinnings of SCLC biology and matching these to effective targeted agents is a key approach, similar to recent experience in lung adenocarcinoma drug development. This will certainly help diversify the number of new agents being developed beyond that of traditional cytotoxics. Multiple classes of molecular therapeutics including: anti-apoptotic agents, hedgehog inhibitors, and insulin-growth factor-receptor antibodies have been examined in extensive stage SCLC, but have not shown robust activity with the caveat that these trials were all performed in unselected SCLC populations[18]. A concerted approach to identify subsets of SCLC patients who may particularly benefit from specific targeted treatments has been lacking. At least in preclinical studies in SCLC, this approach is currently yielding some promising results. For example, preclinical studies highlight subsets of SCLC cell lines with MYC amplification and PIK3CA inactivation that preferentially respond to aurora kinase inhibition[19]. It is therefore not a surprise that aurora kinase inhibitors (alone or in combination with camphothecins or other agents) are currently in early phase clinical trials. Recent novel strategies to treat SCLC include a bioinformatics drug repositioning approach that identified tricyclic anti-depressants as having promising preclinical activity in SCLC. The proposed mechanism of action is through inhibition of G-protein coupled receptors and PK-A; a phase II clinical trial testing the tricyclic desipramine in extensive stage small cell lung cancer is currently enrolling patients[11].

It is time to abandon empiricism in SCLC drug development. The identification of predictive markers should be pursued not just in the preclinical phase, but constantly throughout the trajectory of drug development, including clinical trials. By adopting established strategies and tools that have led to success in NSCLC and by fostering a culture that encourages the collection of adequate amounts of tumor tissue at the time of diagnosis, there is a real chance for diversification of targets and therapies in this long neglected disease.

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