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Invited Review

Targeting DNA damage in SCLC

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ABSTRACT

SCLC accounts for 15% of lung cancer worldwide. Characterised by early dissemination and rapid development of chemo-resistant disease, less than 5% of patients survive 5 years. Despite 3 decades of clinical trials there has been no change to the standard platinum and etoposide regimen for first line treatment developed in the 1970's.

The exceptionally high number of genomic aberrations observed in SCLC combined with the characteristic rapid cellular proliferation results in accumulation of DNA damage and genomic instability. To flourish in this precarious genomic context, SCLC cells are reliant on functional DNA damage repair pathways and cell cycle checkpoints.

Current cytotoxic drugs and radiotherapy treatments for SCLC have long been known to act by induction of DNA damage and the response of cancer cells to such damage determines treatment efficacy. Recent years have witnessed improved understanding of strategies to exploit DNA damage and repair mechanisms in order to increase treatment efficacy.

This review will summarise the rationale to target DNA damage response in SCLC, the progress made in evaluating novel DDR inhibitors and highlight various ongoing challenges for their clinical development in this disease.

1. Introduction

The incidence of lung cancer continues to rise, with small cell lung cancer (SCLC) currently accounting for ~15% of cases. The highest incidence is in Central and Eastern Europe [1] reflecting the direct link between SCLC and cigarette smoking [2]. Biologically, SCLC is characterised by a rapid cancer cell doubling time and early metastatic dissemination; two thirds of patients present with metastatic (extensive) disease (ED) [3]. Drug treatment has changed little in the past 30 years and very few patients survive beyond 5 years [4]. A platinum drug and etoposide (PE), with or without the addition of thoracic and prophylactic cranial radiation, is the universal frontline standard of care [4]. The aggressive nature of the disease leads to extremely rapid deterioration and median survival of only 3–4 months without chemotherapy [5] yet long term survival and cure can occasionally be achieved in patients with limited stage disease (LD) [6]. In patients with ED treatment is palliative with typical response rates of approximately 70%, median progression free survival (PFS) and overall survival (OS) of approximately 6 and 9 months, respectively and 1 year survival rate of approximately 30% [7]. Unfortunately SCLC recurs in the vast majority of patients. The only drug approved by the United States Food and Drug Administration for treatment of relapsed SCLC in the second line setting is topotecan [5] for which response rates are low between 7 and 24%, progression free survival approximately 3–4 months and overall survival approximately 6–8 months [8]. Agents such as irinotecan, temozolomide (TMZ), amrubicin and anthracycline based regimens have also shown similar activity to topotecan in the second line setting [9,10].

SCLC is hallmarked by rapid development of acquired chemoresistance despite initial chemo and radiosensitivity (Fig. 1), with recurrence after initial therapy almost inevitable, usually within one year of treatment. Around 30% of patients have primary chemoresistant or refractory tumours and the probability of response to second-line chemotherapy can be predicted according to response to first-line

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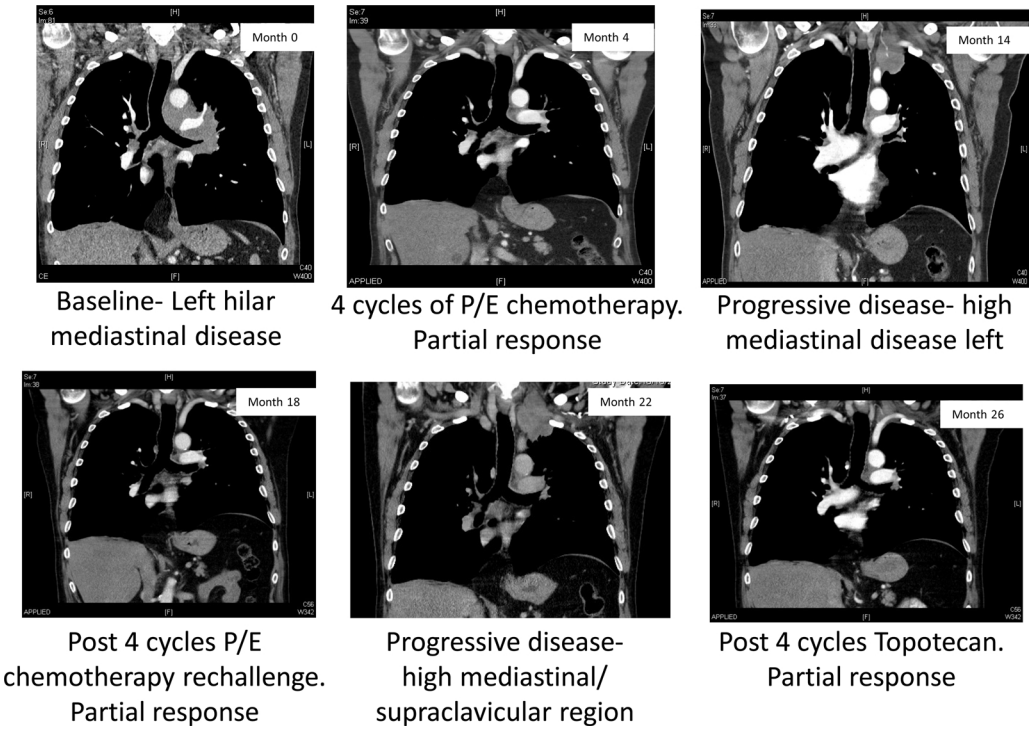

Fig. 1. CT images of disease during treatment for SCLC.

treatment and the time to progression after completing it [11–14]. Patients with SCLC that relapse during first line platinum combination therapy or who have a treatment free interval of 60–90 days or less after the end of first-line therapy (resistant/refractory disease) have a worse outcome compared to those relapsing more than 90 days after completion of first-line therapy (sensitive disease) [11,13,15]. Due to the increasing tumour resistance to second line treatment and often rapid clinical deterioration during or following second line treatment, very few patients receive a third line of therapy. For these reasons earlier study enrolment into trials of maintenance or first line combination studies have become more common.

Current cytotoxic drugs and radiotherapy treatments for SCLC have long been known to act by induction of DNA damage and the response of cancer cells to such damage determines treatment efficacy [16]. Recent years have witnessed improved understanding of strategies to exploit DNA damage and repair (DDR) mechanisms in order to enhance sensitivity and/or overcome resistance to conventional DNA damaging treatments [2]. The DDR network is highly complex and dynamic with at least 450 proteins integral to DNA repair [17]. Different DDR proteins and pathways have the ability to compensate in the absence of integrity of the optimal pathway [16]. Five major DNA repair pathways are known: base excision repair (BER) to repair single-strand breaks (SSBs); homologous recombination repair (HRR) and non-homologous end-joining (NHEJ) to repair double-strand breaks (DSBs); mismatch repair (MMR) to repair replication errors, and nucleotide excision repair (NER) to repair bulky adducts caused by platinum salts and UV radiation, for example [16]. An armamentarium of novel DDR inhibitors, designed to inhibit distinct proteins critical for the integrity of these pathways are in various stages of preclinical and clinical development (see [16] for comprehensive review). Here we focus on the rationale to target DDR in SCLC, the progress made in evaluating novel DDR inhibitors and highlight various ongoing challenges for their clinical development in this disease.

2. Rationale to evaluate DDR inhibitors in SCLC

In the setting of tobacco-related carcinogenesis the SCLC genome is highly damaged as evidenced by an exceptionally high mutation burden, with approximately 8.88 mutations per megabyte [3,18]. The tumour suppressor genes *TP53* and *RB1* are the most commonly mutated, with TP53 virtually universally mutated in SCLC. The oncogenic transcription factors *MYC* and *SOX2* are amplified in 27% of cases, and histone modifiers such as *CREBBP1* and *EP300* are mutated in 15% and 13% of cases, respectively [3,19–21] (Table 1). The majority of mutations have little significance for the SCLC pathogenesis and are described as passenger mutations. The challenge is to find driver mutations in a heterogeneous disease between patients and then being able to use them as actionable targets for treatments. Performing whole genome sequencing to identify therapeutically targetable oncogenic driver mutations, George et al. detected *BRAF, KIT*, and *PIK3CA* mutations in 4 out of 110 tumours analysed [3,19–21]. Although discrete, druggable subsets akin to those observed for non-small cell lung cancer (NSCLC) have not been identified, these results indicate that some patients might benefit from genotyping and subsequent targeted therapy [3,19–21]. The net consequence of the genomic aberrations in SCLC is rapid cellular proliferation in the context of accumulating DNA damage due to replication stress [22] and genomic instability. Replicative stress is the accumulation of errors during endogenous DNA replication. DNA repair pathways can maintain genomic integrity in times of replicative stress but defects in regulators, checkpoints or DNA repair pathways can result in genomic instability [23]. For instance, aberrant activation of the oncogene *MYC* in an *RB1* and *TP53* mutant background results in rapid proliferation and ultimately replication stress in SCLC [2]. To flourish in this precarious genomic context, SCLC cells are reliant on functional DDR pathways and cell cycle checkpoints. However, defects in the DDR mechanisms can be present and be compatible with tumour survival. These aberrations create potential ‘Achilles heels’ and opportunities to selectively increase the therapeutic effect of DNA-damaging agents on cancer cells by inhibition of the remaining intact DDR. Aberrations in DDR proteins or pathways have also been implicated in resistance to conventional DNA damaging agents [24].

Although little is known about the molecular mechanisms in SCLC that confer resistance to chemotherapy, three main mechanisms of platinum resistance have been described. The first two concern drug handling; reduced intracellular drug accumulation and increased inactivation of the drug, the third concerns increased capability for repair