



Paul Hartel*

Sligo University Hospital, Sligo Ireland and West Virginia University School of Medicine, Morgantown WV, USA

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*Corresponding author: Paul Hartel, Sligo University Hospital, Sligo Ireland and West Virginia University School of Medicine, Morgantown WV, USA, Email: hartelp@davishealthsystem.org

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Mini Review

Lenalidomide as potential treatment in small cell neuroendocrine lung cancer with del 5q

Introduction

Lung cancer is a leading cause of cancer deaths world-wide, with the carcinogens in tobacco smoke playing a major etiologic role. Genetic changes responsible for carcinogenesis include activation of proto-oncogenes and inactivation of tumor suppressor genes. Tumor suppressor gene inactivation is contributed to, in part, by loss of chromosomal DNA. While cytogenetic findings in small cell neuroendocrine lung carcinoma are complex, 5q deletion is among the most frequently identified [1,2].

Very few studies have investigated the relationship between such cytogenetic alterations and clinical or pathologic factors in small cell neuroendocrine lung carcinoma [2-4]. Our recent investigation found that patients with small cell neuroendocrine carcinoma with del (5q) (Figure 1), had a greater quantity of spindle cells (Figure 2), and more tumour-associated mucin [5] (Figure 3), compared to patients with tumours without del (5q). Interestingly, when symptomatic, patients in this group more often reported cough as the most common presenting symptom. Patients with tumors having del (5q) were also older than patients without del (5q), and had greater pack-year smoking histories. While this may be explained by their older age, it potentially is the result of longer exposure to mutagenic influences, i.e. smoking, and that del (5q) in the genetic evolution of lung carcinogenesis occurs as a later "hit" in the tumorigenic pathway of small cell neuroendocrine lung carcinoma. Chromosomal losses have been shown to have meaningful clinical correlates, whether prognostically favorable or unfavorable, in oligodendroglioma (loss of 1p and 19q) [6], myelodysplastic syndromes (loss of 5q, 7q, and 20q) [7], acute myeloid leukemia (loss of 5q and 9q) [8], and chronic lymphocytic leukemia (loss of 13q) [9].

Lenalidomide, used conventionally to treat multiple myeloma and more recently myelodysplasia with del (5q), is undergoing clinical trial as a treatment for solid tumors, including carcinoma of the pancreas and non-small cell lung cancer [10-

12]. Lenalidomide has multiple mechanisms of action, and they can be simplified by organizing them as mechanisms of action in vitro and in vivo [13]. In vitro, lenalidomide has direct anti-tumor effect, inhibition of angiogenesis, and immunomodulation. In vivo, lenalidomide induces tumor cell apoptosis directly and indirectly by inhibition of bone marrow stromal cell support, by anti-angiogenic and anti-osteoclastogenic effects, and

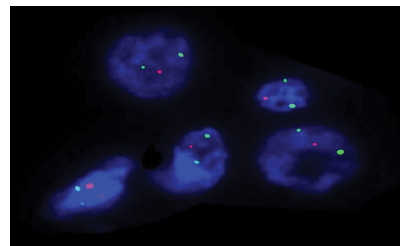


Figure 1: FISH showing small cell neuroendocrine lung carcinoma tumor cells with two green signals and only one red signal [del(5q)]. One tumor cell (lower left) shows two green and two red signals [(absent del(5q))].

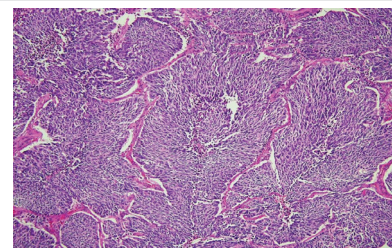


Figure 2: Small cell neuroendocrine lung carcinoma with del (5q) and spindle cell morphology. H&E, medium power.

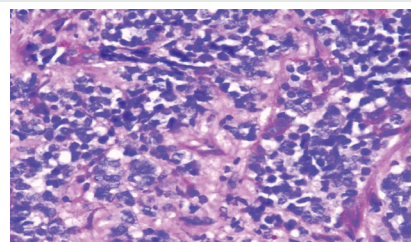


Figure 3: Small cell neuroendocrine lung carcinoma with del(5q) and increased mucin secretion. PAS, high power. (Author's picture).

by immunomodulatory activity. Lenalidomide has a broad range of activities that can be potentially exploited to treat many hematologic and solid cancers. Side effects, however, can be severe and include thrombosis, pulmonary embolus, and hepatotoxicity, as well as bone marrow toxicity resulting in neutropenia and thrombocytopenia. Yelo suppression is the major dose limiting toxicity [13].

Future studies are warranted to confirm the cytogenetic associations with clinical and histological variables in small cell neuroendocrine lung carcinoma utilizing larger sample sizes, larger tumor samples (i.e., wedge resections), and more extensive cytogenetic analyses. Lenalidomide, specifically targeting the del (5q) clone, may offer potential as an adjunct treatment in small cell lung cancer. We are eager to see more studies in this regard, as FISH offers an easy, economic means toward this end.

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