

CD133 is indicative for a resistance phenotype but does not represent a prognostic marker for survival of non-small cell lung cancer patients

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Despite advances in anticancer treatment, lung cancer still has poor prognosis. Recently, a cancer stem cell (CSC) hypothesis has emerged describing a small subset of tumor cells with stem cell properties. CSCs found in many solid tumors express CD133 antigen on the cell surface. The presence of CSC is correlated with poor survival of patients with glioblastomas, colon or prostate cancers. In this study, we evaluated whether CD133 expression in non-small cell lung cancer (NSCLC) has a prognostic value in patients' survival. We also analyzed whether CD133 positivity of NSCLC correlates with the expression of resistance-related proteins, angiogenic factors, oncogenes, proliferative activity or apoptosis. CD133 expression was retrospectively examined in a total of 88 cases of previously untreated NSCLC by immunohistochemistry. We found no correlation between CD133 positivity or the amount of CD133⁺ cells with NSCLC patients' survival, expression of oncogenes c-myc, c-N-ras, c-jun, c-fos, c-erbB1, c-erbB2 or p53, angiogenic factors VEGF, VEGFR-1, FGF, FGFR-1, tissue factor and with proliferative activity or apoptosis in NSCLC tissues. However, there was a significant association between the expression of resistance-related proteins glutathione S-transferase, thymidylate synthase, catalase, O⁶-methylguanine-DNA methyltransferase and p170 and CD133. Because CD133 expression is linked to a resistant phenotype, detection of CD133⁺ cells may be useful to predict efficacy of cytotoxic therapy but CD133 is not a strong prognostic parameter for survival of patients with NSCLC.

The morbidity of lung cancer has increased considerably over the past 50 years, and lung carcinoma has become the leading cause of death by cancer in both men and women.^{1,2} The prognosis for patients with lung cancer is very poor: nearly 80% of patients die within 1 year of diagnosis. Despite major advances in surgical techniques, chemotherapy and radiotherapy of lung cancer, long-term survival is achieved in only 5–10% of patients.^{3,4} Although much is known about predisposing factors, natural history and the outcome of non-small cell lung cancer (NSCLC), our understanding of the disease is still incomplete. However, advances in molecular and cellular

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biology have opened new avenues for the characterization of these tumors.

Recent evidence suggested that there is a small subpopulation of cancer cells found within solid tumors, which possesses characteristics normally associated with stem cells (reviewed in Refs. 5 and 6). This subpopulation of tumor cells is currently described as cancer stem cells (CSCs) or tumor-initiating cells. CSCs are believed to be tumorigenic, have stem cell properties such as self-renewal and the ability to differentiate into various cell types. They are resistant to chemotherapy⁷ and often characterized by elevated expression of the stem cell surface marker CD133. CD133, also known as prominin-1, is a cell-surface glycoprotein comprising 5 transmembrane domains and 2 large glycosylated extracellular loops. The function of CD133 has not been established yet. Although an universal marker for cancer stem cells has not been identified, many tumors of different origin exhibit the membrane CD133 antigen, which expression is shared by normal stem cells of different lineages (reviewed in Ref. 8). Recent data revealed that CD133 antigen is expressed in tumors including glioblastomas,⁹ colon carcinomas,^{10–12} pancreatic carcinomas,^{13,14} hepatocellular carcinomas,^{15,16} ovarian carcinomas¹⁷ and tumors of the prostate.¹⁸

Increased numbers of CD133⁺ cancer cells have been found in NSCLC^{19,20}; however, the role/significance of these CD133⁺ cells is still not known. Also, little is known about