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L1CAM expression associates with poor outcome in endometrioid, but not in clear cell ovarian carcinoma

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HIGHLIGHTS

- L1CAM predicts poor outcome in endometrioid, but not in clear cell ovarian carcinoma.
- Our findings are similar to those previously observed in endometrial carcinoma.
- L1CAM associates with poor outcome in grade 1–2 endometrioid ovarian carcinoma.
- L1CAM predicts poor prognosis in concurrent ovarian and endometrial carcinomas.

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ABSTRACT

Objective. Our aim was to study the expression of L1CAM in endometrioid and clear cell ovarian carcinomas and to evaluate its correlation with clinical parameters and patient prognosis.

Methods. Tissue microarray -based immunohistochemical analysis of L1CAM expression was performed in 249 endometrioid and 140 clear cell ovarian carcinomas. Concurrent endometrial carcinoma was found in 57 of these patients.

Results. L1CAM expression was found in 15% of endometrioid and 23% of clear cell ovarian carcinomas. L1CAM expression was strongly associated with poor disease-specific overall survival and poor disease-free survival in endometrioid ($p < 0.0001$, $p = 0.0005$), but not in clear cell ovarian carcinomas. Significant association of L1CAM expression with poor overall survival was observed in grade 1–2 carcinomas ($p < 0.0001$), but not in grade 3 tumors. In endometrioid ovarian carcinomas, L1CAM expression was associated with aggressive tumor characteristics, such as higher grade and stage, and incomplete response to primary therapy. However, L1CAM expression was not an independent prognostic factor for overall or disease-free survival. Of the 57 patients with concurrent endometrial carcinoma L1CAM positivity was found in 4 cases both in the ovarian and endometrial tumors, and in 3 cases only in the endometrial tumor. All these seven patients with L1CAM positive tumors had poor outcome.

Conclusions. L1CAM expression could serve as a biomarker for predicting clinical outcome and response to therapy in patients with endometrioid ovarian carcinoma, but not in clear cell carcinomas. L1CAM positivity also predicts poor outcome in patients with concurrent endometrioid ovarian and endometrial carcinomas.

1. Introduction

Ovarian cancer is the seventh most common cancer in women and a primary cause of death from gynecologic cancers [1]. Late diagnosis and acquired platinum resistance often result in poor overall prognosis [2]. Ovarian carcinomas are histologically divided into serous, endometrioid, clear cell, mucinous, undifferentiated, mixed and Brenner subtypes [3]. A dualistic model of ovarian carcinogenesis has been proposed: type I carcinomas being more indolent and often confined to the ovary resulting in good prognosis and type II tumors being more aggressive and accounting for 90% of the deaths from ovarian cancer. Type II tumors include high grade serous and undifferentiated carcinomas as well as carcinosarcomas. Other histological types belong to type I tumors. However, molecular studies have shown that there is heterogeneity within different types of ovarian carcinoma. Tumors with different biology, clinical behavior and prognosis can be found [4].

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Currently, the conventional treatment of ovarian carcinomas includes staging/debulking surgery and adjuvant platinum-taxane based chemotherapy for all cases regardless of the tumor type (except no chemotherapy in stage IA grade 1 disease) [2]. Of the novel targeted therapies, bevacizumab and olaparib have been approved for treatment of ovarian cancer. Olaparib is the first drug with a predictive marker (BRCA mutation), which selects patients who are likely to have the greatest benefit of the treatment [5]. To individualize treatment of the ovarian cancer patients, we need more biomarkers for detecting tumors with different biological behavior and to select patients for novel targeted therapies.

L1CAM (CD171) is a cell adhesion molecule, a transmembrane glycoprotein of 200–220 kDda, which belongs to the immunoglobulin superfamily. L1CAM is involved in myelination, fasciculation, cell migration and axon guidance, thus playing an important role in the development of the nervous system [6–8]. L1CAM overexpression has been found in several cancers as well: e.g. ovarian [9–11], endometrial [9,12–16], colorectal [17,18], gastric [19,20] and breast cancer [21,22].

In endometrial carcinomas L1CAM positivity has been associated with aggressive disease characteristics, such as advanced stage, poor differentiation, non-endometrioid histology, lymph node involvement, lymphovascular space invasion, cervical stromal invasion, positive peritoneal cytology and distant recurrences [9,12,13,15,16]. In endometrial carcinomas L1CAM expression predicts poor outcome particularly in the endometrioid but not in the serous or clear cell subtypes [15,16]. Thus L1CAM is a potential marker of high risk disease in stage I endometrioid endometrial carcinomas which are considered clinically as low risk carcinomas.

Endometrioid endometrial and ovarian carcinomas are histologically similar and they are known to share some pathogenetic changes like mutations of PTEN and β-catenin genes as well as microsatellite instability [4,23]. Clear cell carcinoma in turn resembles endometrioid ovarian carcinoma by sharing background of endometriosis and mutations of ARID1A and catenin β1 as well as PI3K pathway activation [4]. Approximately one third of endometrioid and clear cell ovarian carcinomas have already spread at the time of the diagnosis and in these cases the prognosis is poor. The prognosis in stage I endometrioid and clear cell ovarian carcinomas is generally favorable. However, in some patients the disease relapses and the outcome is poor. New biomarkers are needed to better understand the pathogenesis of these diseases and distinguish groups with different biological behavior and prognosis.

In ovarian carcinomas, L1CAM expression and its clinical relevance has mainly been investigated in the most common subtype, high grade serous carcinoma [9,10,24–26], and only a limited number of endometrioid carcinomas have been studied [9–11]. Survival analyses and clinical correlations on the endometrioid type do not exist and expression of L1CAM in clear cell ovarian carcinomas has not been previously investigated.

Our study involves a large number of consecutive patients treated for endometrioid (249 patients) and clear cell (140 patients) ovarian carcinomas at the same institution. In 57 cases concurrent endometrial carcinoma was diagnosed. Our aim was to investigate the expression of L1CAM in these carcinomas and to evaluate its correlation with various clinical parameters and patient prognosis.

2. Materials and methods

2.1. Patients

The study included 249 patients treated for endometrioid ovarian carcinoma and 140 patients treated for clear cell ovarian carcinoma at the Department of Obstetrics and Gynecology of the Helsinki University Central Hospital between January 1, 1989 and December 31, 2013.

Consecutive patients treated for endometrioid and clear cell ovarian carcinoma were searched according to pathological records. Approval from the Ethics Committee was obtained.

A gynecological pathologist had determined the histology of those carcinomas at the time of diagnosis. Histological diagnoses were reviewed by a gynecological pathologist before including cases in the study. Clinical data of the patients was collected from the hospital records, and additional survival information was received from the Population Register Center.

All the patients included in the study underwent surgery. Median age at surgery was 59.0 years in the endometrioid ovarian carcinoma group and 58.0 years in the clear cell carcinoma group. Our institution is a tertiary hospital, where treatment of ovarian carcinoma is centralized. Radical surgery was started at the end of the 1980's. In 278 of the 389 patients total abdominal or laparoscopic hysterectomy, bilateral salpingo-oophorectomy, omentectomy as well as pelvic and/or para-aortic lymphadenectomy were performed. In 73 patients, total abdominal or laparoscopic hysterectomy and bilateral salpingo-oophorectomy (and omentectomy) were performed in conjunction with surgical removal of tumor masses. In 38 patients, uni-or bilateral salpingo-oophorectomy or explorative laparoscopy was performed. In most of the cases where lymphadenectomy was not performed, there was presence of carcinosis/advanced disease. The rate of lymphadenectomy increased a little over the study period: it was 67.9% before year 2000 and 74.5% after year 2000. In the beginning of the study period, the optimal debulking was regarded as <2 cm of residual tumor. Gradually the optimal debulking goal decreased to no residual tumor. To minimize bias in this study, we used the limit of 0 cm for optimal surgery for the whole study period. The information was extracted from the operation records. The tumor specimens for the study were obtained from the primary surgery.

In 52 endometrioid ovarian carcinoma patients and 5 clear cell ovarian carcinoma patients concurrent endometrial carcinoma was diagnosed. In all endometrioid ovarian carcinoma cases, the concurrent endometrial carcinoma was of endometrioid type. In three of the clear cell ovarian carcinoma cases, the concurrent endometrial carcinoma was of clear cell type and in two cases of endometrioid type. The staging of tumors was performed according to the year 2009 FIGO staging system. Grading was applied only to the endometrioid carcinomas.

In 256 cases platinum-taxane-based combination therapy was given as first-line chemotherapy, and in 7 of those cases bevacizumab was added to the treatment. In 5 cases, the patient received platinum plus other than taxane-based chemotherapy. In 29 cases, the patient received carboplatin as single therapy. Other than platinum-based chemotherapy was administered to 40 patients (in the late 1980s and in the beginning of the 1990s). In 55 cases no adjuvant chemotherapy was given. Most of the patients who did not receive chemotherapy had stage I A grade 1 endometrioid ovarian carcinoma. A few patients had low performance status or high age or refused the treatment.

Response to therapy was assessed after the initial 6–8 cycles of chemotherapy on the basis of gynecological examination, vaginal ultrasonography, CA125 measurement, and/or computed tomography scan. In the late 1980s and in the beginning of the 1990s second look laparotomy was performed routinely. Patients who did not receive chemotherapy were evaluated 5–6 months after the surgery. Disease-specific overall survival was calculated from the date of diagnosis (primary surgery) to death from ovarian carcinoma. Patients who died of other causes or were alive at follow-up were censored. Disease-free survival was calculated for patients who presented with complete response after the primary treatment (surgery and first-line chemotherapy, if given) and it was the time from the date of diagnosis to relapse of the disease. The median follow-up time for patients who were cencored at the end of the follow-up was 7.8 years (range 0.75–23.6 years) for endometrioid ovarian carcinoma and 9.3 years (range 1.7–25.3 years) for clear cell ovarian carcinoma.

2.2. Tissue microarray construction

Histological slides were examined by a gynecological pathologist and representative areas of each tumor were selected for biopsies. Four