COMMENTARY

Comments on the "Prognostic Impact and Clinicopathological Correlation of CD133 and ALDH1 Expression in Invasive Breast Cancer"

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To the Editor,

We read the paper by Kim et al. [1] concerning the potential predictive role of Prominin 1 (CD133) and aldehyde dehydrogenase 1 (ALDH1) expression in invasive breast cancer, which appeared in the latest issue of this Journal, with great interest. CD133 and ALDH1 have been considered as markers of cancer stem cells, with documented activities in liver, colorectal, prostate, brain, pancreatic, gastric, and breast cancers [2-6].

The precise biological function of CD133 in breast cancer is still controversial since it has been hypothesized that this marker might be involved in different neoplastic processes, such as initiation, cellular migration, and circulation [1,7]. In our opinion, the paper by Kim et al. [1] raises some interesting and relevant points that we have already addressed in our previous papers [8,9]. While some methodological aspects were identical, including the procedure used for antigen retrieval, overnight incubation at 4°C with the primary antibody, the use of polyclonal rabbit anti-CD133 antibody, and the substrate-chromogen system (3,3′-diaminobenzidine tetrahydrochloride), the immunohistochemical assessment used for obtaining the CD133 score of immunopositivity was different. Kim et al. [1] defined negative staining in all cells with a score of 0; weakly positive or focally positive staining in <10% of the cells with a score of 1+; intermediate positive staining covering 10%–50% of the cells with a score of 2+; and strongly positive staining, including >50% of the cells, with a score of 3+. On the contrary, we used a scoring method [8,9] that required the quantification of immunostained aggregates (2–5 cells) at three different areas; a score of 1 or 2 was assigned to cases with <3 or ≥3 aggregates respectively, while the intensity of immunostaining was scored as 1 for weak, 2 for moderate, and 3 for strong. Finally, an intensity distribution score was calculated for CD133 immunopositivity by multiplying the score of aggregates with that of the staining intensity. In the study by Kim et al. [1], the immunohistochemical expression of CD133 was documented in the cytoplasm of neoplastic breast cells in 24.7% of the patients; on the other hand, in our series we have found a rate of positivity >33.2% in patients with node-negative breast cancer [8,9]. Therefore, reported differences in the rate of immunopositivity should be attributed either to different scoring methodologies, or to surgical samples of different origin.

In the study of Kim et al. [1], CD133 expression appeared to be significantly associated with some adverse parameters, such as tumor dimension, nodal metastasis, stage, estrogen receptor/progesterone receptor negativity, human epidermal growth factor receptor 2 (HER2) positivity, and recurrence. In our series [8,9], no significant relationships were noted between CD133 immunopositivity and histotype, tumor grade, stage, and hormone receptor expression, while a significant correlation between CD133 and bone metastasis, Ki-67 score, and HER2 status was identified. However, previous studies showed that CD133 expression was associated with worse clinical behavior in colorectal cancer, although not associated with clinicopathological features [10-12].

In conclusion, Kim et al. [1] suggested that CD133 expression, alone or in combination with ALDH1, was widely associated with the presence of adverse biomarkers and subtypes of breast cancer, and could be used in identifying biologically aggressive cases, and in predicting survival outcomes. Similarly, we have revealed interesting relationships between CD133 and predictive parameters (Ki-67 and HER2 status) of poor prognosis in breast cancer, allowing the identification of

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CD133 immunopositive cases in pN0 breast cancer, characterized by worse clinical behavior. Therefore, we fully agree with the suggestion of Kim et al. [1] that the predictive role of CD133 should be emphasized and, consequently, it should be extensively utilized in the management of patients with breast cancer.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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Author's reply

We appreciate the comments by Ieni and Tuccari on our paper concerning the potential predictive role of CD133 and ALDH1 [1].

Cancer stem cells (CSCs) are an emerging concept in breast cancer research, and it is considered that they may play an important role in cancer initiation, migration, metastasis, recurrence, and resistance to chemotherapy [2-5]. The CSC hypothesis has fundamental implications for cancer biology, in addition to its clinical implications for cancer risk assessment, early detection, prognosis, and prevention.

Identification and characterization of CSCs could lead to the development of more direct and effective treatments for cancer [2]. The functions of CD133 and ALDH1 in breast cancer have been studied; however, the precise mechanism of CD133 function in breast cancer is still debated.

There is no standardized scoring system for CD133. In our study, only the extent of CD133 immunopositivity in the cell membrane and/or cytoplasm was used for scoring CD133 staining [1,6-9]; however, other studies used both the extent and intensity of immunohistochemical staining, supported by the studies of Ieni and Tuccari [10-13].

Different scoring methodologies resulted in CD133 immunopositivity rates in the range 18.1%–53.1%; while Kapucuoğlu et al. [7] and Collina et al. [9] reported the rate of CD133 positivity to be 18.1% and 20.5%, respectively, Mansour and Atwa [8] and Han et al. [13] reported the rate of CD133 positivity to be 53.1% and 48.6%, respectively.

We also reported that CD133 expression was correlated with a number of adverse parameters that are traditionally associated with poor prognosis, and an independent indicator of poor prognosis in invasive breast cancer. This was supported by the study of Zhao et al. [11], in which CD133 expression of 67 triple-negative breast cancer patients was correlated with tumor size, lymph node status, and clinical stage, and it was greatly associated with overall survival and disease-free survival .

We appreciate the good discussion and comments on our study.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

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