



# CD133 expression in patients with peripheral neuroblastic tumor: a systematic review

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### ARTICLE INFO

#### Article type

Systematic review article

#### Article history

Received: 27 Dec 2014

Revised: 13 Jan 2015

Accepted: 28 Jan 2015

#### Keywords

Cancer stem cells

CD133

Neuroblastoma

### ABSTRACT

**Introduction:** Neuroblastoma is known as one of the most common solid tumors in children, which is recently under the investigation for the expression of CD133, a marker of cancer stem cells. Revealing the prognostic value of CD133 marker expression is important in predicting the outcome and survival of neuroblastoma patients. In this systematic review, we aimed to review the studies on association between CD133 expression and other peripheral neuroblastic tumor prognostic factors.

**Methods:** PubMed was searched for the relevant articles. No time and language limitation were included in our search strategy. Data regarding the patients' number and age, tumor stage, histology and CD133 expression were extracted.

**Results:** Overall, only 4 relevant articles were retrieved. One articles revealed the positive association between CD133 expression in neuroblastoma samples and its resistance to chemotherapy treatment. Three of the included articles showed the positive relation between CD133 expression rate and tumor stage progression. Two of the included studies revealed much worse survival of the neuroblastoma patients with more expression of CD133.

**Discussion:** Based on included studies, CD133 expression is positively related with poor outcome prognosis in patients, more advanced tumor stage, shorter disease-free survival and overall survival.

**Conclusion:** Although the expression of CD133 has shown increasing trend by advancing the neuroblastoma tumor stage, more studies with larger sample size are needed to accurately reveal the relation.

Please cite this paper as:

Nazarzadeh H, Shams Hojati Y, Nazarzadeh R. CD133 expression in patients with peripheral neuroblastic tumor. Rev Clin Med. 2015;2(4):164-167.

## Introduction

Cancer stem cells are a small population of cancerous cells in tumor tissue, which have shown stemness characteristics including the ability of self-renewal ability, proliferation, developing into multiple lineages. These types of cells are characterized by presence of various markers such as CD133, CD24, CD90, CD34, CD117 and CD20 (1,2). These cells that are known as responsible cells for tumorigenesis, metastasis, recurrence, resistance

to chemotherapy, suggested to be targeted during cancer treatment procedures. Pediatric solid tumors are different from adults in many aspects and CD133, as a most common marker for detecting cancer stem cells in pediatric solid tumors, has attracted the attention of researchers.

Neuroblastoma (NB) is a cancerous embryonic tumor and most common extracranial solid cancer in childhood originating from neural crest.

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The presence of cancer stem cells in NB is under investigation through detecting the expression of CD133 as a putative marker of stem cells.

CD133 (known as prominin-1), a trans-membrane protein with 120 kD molecular weight, is proposed as a hematopoietic stem cell marker. Various studies have revealed the expression of CD133 in different types of human cell lines (3), colorectal cancer (4) and breast malignancies (5). PROM1 gene on chromosome 4p15 is responsible for coding CD133 (6). Due to immunohistochemistry results, CD133 antigen is applied as a marker of human neural crest stem cells. Neural cells with CD133 expression have shown stem cell characteristics (7,8). Some investigations have proposed CD133 as an independent prognostic agent of low survival rate in colorectal cancer, hepatocellular carcinoma and glioblastoma (9). Self-renewal property and differentiation ability are proposed as the characteristics of CD133 positive stem cells (8). It is suggested that the presence of CD133 positive stem cells could be regarded as an indicator of neural crest tumor origin.

The presence of cancer stem cells in peripheral neuroblastic tumors might be associated with tumor metastasis, relapse and resistance to chemotherapy. Some studies have investigated the expression of NB-stem cell proliferation and differentiation markers and its relation with prognostic factors of malignancy. According to studies, there are some adverse prognostic factors for NB tumors including patients' age, tumor stage, unfavourable Shimada histological category (2).

Comprehensive information regarding the relation between cancer stem cell marker and tumor prognosis factors could affect and change the future therapeutic procedures. Finding the CD133 expression in NB could have a potential to reveal the patients prognosis and treatment strategy (10).

In this systematic review, we aimed to study all the articles, which investigated the prognostic effect of CD133 expression in patients with peripheral neuroblastic tumors.

## Methods

### Literature search strategy

This systematic review was performed based on PRISMA guideline. We searched PubMed with the following search terms to obtain the relevant articles: ("Peripheral neuroblastic tumor" OR neuroblastoma OR ganglioneuroblastoma OR ganglioneuroma) AND CD133. Last search was completed in December 2014. After the first search, title and abstract of the obtained articles were studied to exclude the irrelevant articles. Therefore, we studied the full text of the remaining articles and deleted other irrelevant articles with the purpose of our study. Eventually, to decrease the possibility of missing any related article,

not only reference list of each article was read, but also cited option of the Google Scholar was studied for each included article.

### Study selection

We did not have any time language limit in our search strategy. Inclusion criteria were all the clinical studies, which investigated the expression of CD133 in pediatric patients with peripheral neuroblastic tumors. Exclusion criteria were case reports, editorials and all the experimental and in-vitro studies.

### Data extraction

Data about authors, publication date, country, patient characteristics, tumor characteristics, CD133 expression and the relation between CD133 expression and tumor histology, stage, resistance to chemotherapy and patients' survival were extracted.

### Outcome variable

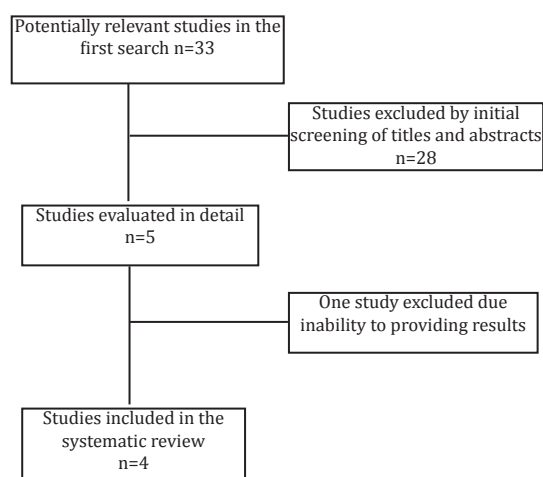
All the data about the relation between CD133 expression in different stage of tumor, different tumor histology and patients' survival were compared to reveal the prognosis value of CD133 expression in NB samples.

## Results

### Search results

A total of 33 articles were identified in PubMed. There was 5 remaining relevant articles. One recent Spanish language article performed in 2013 study was also omitted due to inability in providing results related to CD133 expression in neuroblastoma samples (11). Figure 1 shows the PRISMA flowchart of the study. Table 1 summarized data of included studies (9,10,12,13).

Figure 1. PRISMA flowchart of the study



**Table 1.** Results obtained from the included studies

Author Year Reference	Patients number, Age Tumor histology	Tumor stage or histology: <sup>1</sup> CD133 patients/total	Results
Xing 2014 (12)	<sup>2</sup> NB:20 (10 with Pre Chem + 10 without Pre Chem)	-	CD133 expression in 9/10 patients with <sup>4</sup> Pre Chem and 10/10 without Pre Chem
Mehrazma 2013 (10)	NB:20 Mean age:34 months 6Female/14Male <sup>5</sup> FH: 5 <sup>6</sup> UFH:15	Stage I: 0/2 Stage II: 9/10 Stage III: - Stage IV: 7/8	Expression of CD133 was significantly related with tumor stage
Sartelet 2012 (13)	NB:280 Median age 18 months FH:145 UFH:135	Stage1: 2/68 Stage2: 2/40 Stage3: 8/44 Stage4: 84/106 Stage4S: 4/27 FH:37/145 UFH:63/135	3-year event-free survival rate 43 ± 5% and overall survival rate 51 ± 5%, in patients with positive CD133 expression 3-year event-free survival rate 89 ± 2% and overall survival rate 96 ± 2% in patients with positive CD133 expression RR in survival of patients and CD133:6.907
Tong 2008 (9)	NB: 32 <sup>7</sup> GNB:8 Mean age: 2.7years 16Female/24Male FH:19 UFH:21	Stage 1-2: 4/13 Stage 3-4: 11/19 Stage 4S: 3/8 FH: 7/19 UFH:11/21	Survival time (months) in patients with positive and negative CD133: 14.53±1.26 and 23.22±2.25

<sup>1</sup>CD133: tumors expressing CD133 as compared with tumors not expressing CD133; <sup>2</sup>NB: neuroblastoma; <sup>3</sup>Chem: chemotherapy; <sup>4</sup>Pre Chem: preoperative chemotherapy; <sup>5</sup>FH: favorable histology; <sup>6</sup>UFH: unfavorable histology; <sup>7</sup>GNB: ganglioneuroblastoma.

## Discussion

### Chemotherapy resistance

Despite various experimental studies on human cell lines, only one study evaluated the chemotherapy resistance characteristic of NB cancer stem cell specimen. Immunohistochemistry was performed in these articles to reveal the expression rate of CD133 as a putative surface marker of cancer stem cell. According to these articles the expression of CD133 did not change significantly after performing chemotherapy procedure, which showed the existence of cancer stem cells in NB specimens even after the chemotherapy. Therefore, NB stem cells are related with chemotherapy resistance and should be targeted during the treatment procedures. These finding might be beneficial in future therapeutic strategies for treating and preventing peripheral meroblastic tumors.

### Tumor stage

There are limited number of studies that investigated the association between CD133 expres-

sion and the prognosis factors such as stage.

The relation between CD133 expression rate and NB tumors stage was investigated in all the included studies(10,13,14). Immunohistochemistry with rabbit polyclonal anti-CD133 and tissue microarray were mostly used to reveal the expression level of NB samples obtained from children at different stages of tumors.

Mehrazma et al. did not observe CD133 expression in majority of patients with NB at stage 1 only in 1/8 patients with NB tumor stage IV. All the other 7 patients with Stage IV NB showed intense-weak levels of CD 133 expression (10). In this regard, they proposed a possible significant relation between patients' tumor stage and CD133 expression level; positive expression rate increased at more advanced tumor stage. Similar results were obtained in previous study, which showed the expression of CD133 in 84/106 NB patients with stage IV disease and in 37/97 patients with NB tumor metastasis (13). Positive relation between CD133 expression rate and tumor stage was also confirmed in another study

by Tong et al. in 2008 (14). In the study of Tong et al. and Sartelet et al. patients with disease at stage 3-4 showed a significantly higher expression of CD133 and positive rate of the marker elevated with the progress of the tumor stage. According to the obtained results, CD133 expression showed more advanced tumor progression, which has been associated with much worse disease-free overall survival of the patients (13,14).

### Patients' survival

Overall, 2/4 included studies investigated the survival rate of patients with NB tumors based on various prognostic factors such as CD133, patients age and tumor stage and histology (13, 14). Survival time was defined as time interval between the first day of surgery and last day of follow-up, day of disease recurrence, metastasis and death. According to the study of Tong et al. in 2008, patients with peripheral neuroblastic tumor and positive CD133 had significantly longer survival time compared with NB CD133 negative patients. In a recent study by Sartelet et al. CD133 was detected in almost one third of the investigated population. Evaluating 3-year event free and total survival rated by Kaplan-Meier plot revealed significantly higher survival rate in CD133 negative NB patients compared with CD133 positive ones (13). Sartelet et al. not only revealed the adverse association between CD133 expression rate and patients survival, but also detected this relation between NB patients age and tumor stage with survival time (13). According to these studies, expression of CD133 is associated with shortened patients' survival. This relation shows the prognostic value of CD133 expression in NB patients.

### Conclusion

Investigating the CD133 expression in NB tumors is important for evaluating the prognosis of patients with peripheral neuroblastic tumors and demonstrating the responsible mechanism in NB development. Despite various in-vitro studies investigated the expression of CD 133, there are limited number of studies about the relation between expression of this cancer stem cell marker and tumor prognostic factors. According to the positive relation between CD133 expression and tumor development and negative relation be-

tween CD133 expression and patients' survival identified in this review, CD133 expression could be proposed as a strong and independent prognosis indicator, which is associated with poor outcomes in patients with NB.

### Acknowledgement

We would like to thank Clinical Research Development Unit of Ghaem Hospital for their assistant in this manuscript.

### Conflict of Interest

The authors declare no conflict of interest.

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