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REVIEW ARTICLE

Circulating endothelial progenitor cell: a promising biomarker in clinical oncology

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Abstract Human cancers are endowed with sustained vascularization capability, and their growth, invasion, and metastasis are vascularization dependent. Recently, accumulated body of evidence suggests that endothelial progenitor cells (EPCs) can support vasculogenesis and induce angiogenesis through paracrine mechanisms. In addition, numerous clinical studies have revealed the increase in the number of EPCs in the peripheral blood of cancer patients and demonstrated the correlation of circulating EPCs (CEPCs) with the clinical outcomes. This review highlights current enrichment procedures and methods for the detection of CEPCs and different biomarkers to identify CEPCs as well as the functions of EPCs in tumor vascularization. Furthermore, we systematically review available studies on the clinical relevance of CEPCs in cancer patients to explore the potential diagnostic and prognostic values of CEPCs. Although several contrasting results exist, CEPCs can conceivably serve as a promising biomarker for the early diagnosis, prognosis prediction, and treatment response indication in the future. Additionally, further well-designed clinical studies with larger sample size and unique, specific enumeration procedures are warranted to achieve further insight into the clinical implications of CEPCs.

Keywords Endothelial progenitor cells · Cancer · Vascularization · Biomarker

Introduction

Cancer is a major public health problem which serves as the leading cause of death across the globe. An estimated 1,665,540 newly diagnosed cancer cases and 585,720 cancer-related deaths are projected to occur in the USA in 2014 [1]. Over the past few decades, numerous studies have been conducted to reveal the underlying mechanism of carcinogenesis. A rich and complex body of evidence

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has been generated, which suggests that sustained vascularization plays an important and fundamental role in the development and progression of human malignancies [2, 3].

Tumor neovasculature, a major hallmark of cancer, plays a crucial role in cell function and survival by supplying essential oxygen and nutrients. Tumor-related neovasculature has been conventionally recognized as the result of angiogenesis, which depends on the preexisting endothelial cells to form new capillaries [4]. Several lines of evidences have emerged indicating postnatal vasculogenesis supports as an alternative source of tumor-associated vascularization [5, 6]. Specifically, vasculogenesis is a multistep process, which includes the mobilization and homing of bone marrow (BM)-derived endothelial progenitor cells (EPCs) to neoplastic sites and subsequent proliferation and differentiation into mature endothelial cells (ECs) [7, 8]. In 1997, Asahara et al. [9] initially described EPCs as a specific subtype of stem cells that can migrate, proliferate, and differentiate into mature ECs. Since then, considerable attention has been paid on the potential roles of EPCs in the development and progression of human cancers [10–12] as well as further clinical implications [13–15]. However, inconclusive results were obtained from clinical studies. We conducted this review to present a state-of-the-art overview of the recent findings in this field, which may provide implications for the potential diagnostic and prognostic values of circulating EPCs (CEPCs) in clinical oncology.

Characteristics of EPCs

EPCs are a specific subgroup of mononuclear cells (MNCs) co-expressing vascular endothelial growth factor receptor 2 [VEGFR2, also known as kinase domain receptor (KDR) or fetal liver kinase-1 (Flk-1)] and CD34, which could proliferate and differentiate into mature ECs [9]. Intensive studies on EPCs have revealed specific membrane markers and molecular probes, such as fibroblast growth factor receptor (FGFR), Von Willebrand factor (vWF), CD38, CD31, c-kit/CD117, and vascular endothelial cadherin (VE-cadherin or CD144) [16–18]. However, given that EPCs and mature ECs share many identical surface markers, which include CD31, VEGFR2, vWF, and VE-cadherin, distinguishing EPCs and ECs is extremely difficult. Thus, an additional marker, CD133, has been suggested as a means of ensuring the identity of EPCs. CD133 is a precursor of an EC-like phenotype and has been applied in combination with CD34 and VEGFR2 to identify presumed CEPCs [19–22]. However, the CD34+CD133+VEGFR2+ cells only represent approximately 0.025 % of the peripheral blood MNCs [22], which complicates the reliable quantification of EPCs and limits the translation of prosperous findings about EPCs from bench to bedside. Furthermore, CD133 has also been suggested to be expressed in hematopoietic stem cells (HSCs) [23, 24], and cells identified by CD133 comprise one subtype of HSCs incapable of forming true endothelial phenotypes [25, 26]. Consequently, various definitions of CEPCs, such as CD34+VEGFR2+, CD34+VEGFR2+CD45−, and CD34+CD133, have been employed, which made the comparison and further integration of results across all individual studies quite challenging.

EPCs are mainly divided into two subtypes in terms of functional phenotypes: early and late outgrowth EPCs [27, 28]. Early outgrowth EPCs, also known as colony-forming unit-ECs (CFU-ECs) or CFU-Hill, appear after short-term (4–10 days) culture of MNCs from peripheral blood, display peak growth at 2–3 week, and live up to 4 week [9, 29]. By contrast, late outgrowth EPCs, now generally termed as endothelial colony-forming cells (ECFCs), are cobblestone-shaped cells that can be found after long-term culture (>2 week), achieve peak growth at 4–8 week, and survive up to 12 week [30–32]. Furthermore, the two types of EPCs have been proven to carry different gene expression signatures by genome-wide transcriptional profiling and protein electrophoresis methods [33]. Notably, over a decade have passed since the first description of CEPCs, but the understanding of the fundamental basic science governing the biology of EPCs is still incomplete, and no golden criteria for defining CEPCs exist.

Role of EPCs in tumor vascularization

Human cancers can sustain vascularization, and their growth, invasion, and metastasis are vascularization dependent [2, 3]. Tumor vascularization has long been considered solely through the mechanism of angiogenesis, which means sprouting from preexisting blood vessels [34, 35]. EPCs identification resulted in a paradigm shift, inducing vasculogenesis as a novel mechanism for vessel formation into the tumor setting. The first proof-of-principle of EPCs contribution to cancer-induced vasculogenesis was demonstrated by Lyden et al. in [36]. With the use of angiogenesis-defective Id-mutant mice, they reported that BM transplantation from wild-type mice rather than from Id-mutant mice could restore tumor vascularization and growth of several types of tumor cell lines [36]. In subsequent animal xenograft models, the levels of incorporated EPCs in newly formed blood vessels have been reported to be as high as 50 % [37], whereas lower but significant levels between 10 and 20 % were reported in another study [38]. However, other studies have challenged the contribution of EPCs to tumor vasculature because they hardly or even failed to observe the presence of EPCs in

tumor capillaries [39–41]. In a clinical study, Peters et al. [42] analyzed tumors from six patients who developed cancers after sex-mismatched BM transplantation. Fluorescence in situ hybridization studies with sex-chromosome-specific probes have demonstrated that BM-derived EPCs contributed to tumor endothelium, but with various levels as the incorporation levels which ranged from 1 to 12.1 %.

The inconclusive or even controversial findings from the different studies suggest that EPCs may induce tumor vascularization through an alternative autocrine/paracrine mechanism [43]. This paracrine aspect of EPCs activity was supported by Gao et al., who demonstrated that blocking EPCs mobilization could cause severe angiogenesis inhibition and remarkably impair cancer progression. Furthermore, gene expression analysis of EPCs revealed the upregulation of various key proangiogenic genes, such as *FGFR1*, *VEGF-C*, and *platelet-derived growth factor alpha* [44]. Along this line, our own study confirmed that EPCs could induce angiogenesis by synthesizing angiogenesis factors, such as SDF-1 and VEGF [45, 46]. In summary, a growing body of evidence indicates that EPCs can directly and indirectly contribute to tumor vascularization.

Circulating levels of EPCs in cancer patients

Given the important functions of vascularization in human malignancies, both as a pathogenic mechanism and treatment target, numerous efforts have been undertaken to identify surrogate biomarkers that could accurately reflect the angiogenic/vasculogenic activity of the tumor and therapy effects on tumor vasculature. Considered as potent surrogate biomarkers, microvessel density (MVD) and VEGF expression level have been extensively investigated and proven to be of both diagnostic and prognostic values in clinical oncology [47–50]. In addition to these two biomarkers, the EPCs concentration in the peripheral blood has emerged as a promising and potent biomarker because it could reflect the tumor vascularization activity more accurately, directly, and non-invasively. Various EPCs concentration in the peripheral blood of cancer patients was first reported in 2003, during which Kim et al. examined the CEPCs levels using a culture assay of peripheral blood MNCs after recruiting 16 healthy controls and 71 newly diagnosed cases (19 breast cancer and 52 gastric cancer patients). They found that the number of CEPCs in the cancer patients was comparable to that in the healthy controls (37.6 ± 4.2 vs. $40.2 \pm 10.2/\text{mm}^2$; $P > 0.05$). They also conducted subgroup analysis based on cancer types and failed to detect higher EPC concentration in the peripheral blood of both breast and gastric carcinoma patients [51]. Subsequently, Ho et al. [19] compared the circulating levels of EPCs in 80 hepatocellular carcinoma (HCC) and 14 healthy subjects by employing another culture assay described by Hill et al. [29]. They found a significantly elevated EPC level in HCC patients ($P = 0001$). Interestingly in the same study, fluorescence-activated cell sorting (FACS) quantification of EPCs, in which CD34, CD133, and VEGFR2 were used as markers, was also employed to validate the CFU scores.

Numerous studies that only used FACS technique have been conducted to reveal the dynamics of CEPCs in various cancer types such as lung cancer [22, 52–54], malignant glioma [20, 55, 56], HCC [21, 57], breast cancer [58, 59], head and neck cancer [60], ovarian cancer [61–63], cervical cancer [63], colorectal cancer [64], prostate cancer [65], renal cell carcinoma (RCC) [66, 67], osteosarcoma [68], and multiple myeloma [69] (Table 1). However, inconclusive and controversial results were obtained; although in most studies, a significantly higher EPCs concentration was observed in the peripheral blood of cancer patients. In five case–control studies, the number of CEPCs was demonstrated to be comparable to that in control subjects [51, 54, 56, 65, 68]. However, Goon et al. [59] reported a significantly lower EPCs concentration in breast cancer patients (median: 121 vs. 169 cells/ml; $P < 0.05$). The contrasting results may be attributed to the fact that the majority of the included patients were at early stage, and the "healthy" controls were actually patients with benign breast lesions. To validate the diagnostic value of CEPCs, the selection criteria of both cancer patients and healthy controls should be stricter because of numerous confounding factors such as background cardiovascular diseases, diabetes mellitus, and lifestyles, which include smoking status, physical exercise, among others [70, 71].

Prognostic value of CEPCs

The paradigm of CEPCs as a surrogate biomarker of vascularization has stimulated numerous researchers to explore the prognostic power of CEPCs in cancer patients. TNM classification and histological grade are the main prognostic indicators in clinical oncology. Supplementary Table S1 underscores the data from available studies [19, 22, 51–53, 55, 56, 58–62, 64, 65, 67–69, 72–74] that assessed the correlation of CEPCs with clinicopathological features such as TNM stage, pathological grade, and other specific variables, which could indirectly support the prognostic value of CEPCs in studies without long-term follow-up data. CEPCs levels have been confirmed to be significantly correlated with tumor stage [22, 61, 62, 64, 67, 69, 72, 74], tumor size [19, 58, 61], MVD [55, 73], and serum VEGF concentration [55, 67]. Further detailed information is presented in Supplementary Table S1.

Table 1 Selected outcomes and characteristics of studies assessing CEPCs levels in cancer patients and healthy controls

Author	Year	Cancer types	Case/controls	Detection	EPC definition	Circulating EPCs levels		*P* value
						Cases	Controls	
Kim 1	2003	Breast cancer	19/16	Culture assay	CD34+VEGFR2+	64.6 ± 10.8/mm^{2}[a]	40.2 ± 10.2/mm^{2}[a]	>0.05
Kim 2	2003	Gastric cancer	52/16	Culture assay	CD34+VEGFR2+	28.1 ± 3.5/mm^{2}[a]	40.2 ± 10.2/mm^{2}[a]	>0.05
Blann	2011	Prostate cancer	31/27	FACS	CD34+VEGFR2+CD45−	38 (15–74)/ml[d]	32 (18–82)/ml[d]	>0.05
DuBois	2012	Osteosarcoma	18/7	FACS	CD31+CD133+VEGFR2+CD45−	260 (0–10,670)/ml[c]	126 (0–5,320)/ml[c]	>0.05
Corsini	2012	Glioma (S IV)	25/34	FACS	CD34+CD133+CD45dim	3.8 ± 5.3/μl[b]	3.6 ± 2.8/μl[b]	>0.05
Corsini	2012	Glioma (S III)	9/34	FACS	CD34+CD133+CD45dim	2.6 ± 2.6/μl[b]	3.6 ± 2.8/μl[b]	>0.05
Pirro	2013	NSCLC	34/68	FACS	CD34+VEGFR2+	2.3 ± 0.32 n/ml[b]	2.3 ± 0.26 n/ml[b]	>0.05
Ho	2006	HCC	80/14	Culture assay	CD34+CD133+VEGFR2+	21.9 ± 20.1/mm^{2}[b]	8.3 ± 4.0/mm^{2}[b]	<0.01
Dome	2006	NSCLC	53/14	FACS	CD34+VEGFR2+	1,162.4 ± 242.4/ml[a]	345 ± 54.8/ml[a]	<0.002
Zheng	2007	Glioma	32/19	FACS	CD34+CD133+VEGFR2+	0.05 % (0.00–3.67 %)[c]	0.00 % (0.00–0.04 %)[c]	<0.001
Yu	2007	HCC	11/6	FACS	CD34+CD133+	0.82 ± 0.12 %[b]	0.26 ± 0.10 %[b]	<0.01
Richter-Ehrenstein	2007	Breast cancer	47/28	FACS	CD34+VEGFR2+	0.44 ± 028 %[b]	0.18 ± 0.13 %[b]	<0.001
Brunner	2008	HNC	16/18	FACS	CD133+VEGFR2+	4.5 (1–41)[c]	2 (0–7)[c]	<0.001
Bogos	2009	SCLC	88/32	FACS	CD34+VEGFR3+	1,625 (600–2,750)/ml[d]	455 (370–530)/ml[d]	<0.01
Sieghart	2009	HCC	24/15	FACS	CD34+CD133+VEGFR2+	0.14 ± 0.09 %[b]	0.06 ± 0.04 %[b]	<0.01
Goon	2009	Breast cancer	160/63	FACS	CD34+CD133+CD45−	121 (81–186)/ml[d]	169 (106–241)/ml[d]	<0.05
Rafat	2010	Glioma	12/10	FACS	CD34+VEGFR2+	1.23 ± 1.09 %[a]	0.08 ± 0.04 %[a]	<0.05
Nowak	2010	Lung cancer	36/15	FACS	CD34+CD133+VEGFR2+	0.11 ± 0.007 %[b]	0.025 ± 0.018 %[b]	<0.001
Su	2010	Ovarian cancer	42/25	FACS	CD34+VEGFR2+	1,260.5 ± 234.2/ml[a]	368 ± 34.5/ml[a]	<0.01
Bhatt	2011	RCC	10/17	FACS	CD34+CD133+CD146+CD45−	0.97 (0.39–5.88)/μl[d]	0.19 (0.08–0.47)/μl[d]	<0.01
Bhaskar	2012	MM	75/10	FACS	CD31+CD34+CD133+CD45−	14.0 ± 2.0/μl[b]	1.92 ± 0.6/μl[b]	<0.001
Yang	2012	RCC	53/40	FACS	CD34+VEGFR2+CD45−	0.281 % (0.262–0.300 %)[e]	0.076 % (0.059–0.094 %)[e]	<0.001
Qiu	2013	Ovarian cancer	54/31	FACS	CD34+VEGFR3+	0.98 (0.55–1.94) %[c]	0.15 (0.10–0.23) %[c]	<0.01
Ha	2013	Gastric cancer	55/46	FACS	CD34+CD133+	20 ± 13.9/ml[b]	4 ± 2.6/ml[b]	<0.05
Ramcharan	2013	Colorectal cancer	154/29	FACS	CD34+VEGFR2+CD45−	21 (10–44)/ml[d]	7 (0–14)/ml[d]	<0.001
Kim	2014	Ovarian cancer	8/14	FACS	CD31+CD133+VEGFR2+CD45−	0.012 ± 0.002 %[b]	0.002 ± 0.002 %[b]	<0.05
Kim	2014	Cervical cancer	6/14	FACS	CD31+CD133+VEGFR2+CD45−	0.032 ± 0.014 %[b]	0.002 ± 0.002 %[b]	<0.01

EPC endothelial progenitor cell, *HCC* hepatocellular carcinoma, *NSCLC* non-small cell lung cancer, *HNC* head and neck cancer, *SCLC* small cell lung cancer, *RCC* renal cell carcinoma, *MM* multiple myeloma, *S* stage, *FACS* fluorescence-activated cell sorting, *VEGFR* vascular endothelial growth factor receptor

[a] Mean ± standard error; [b] mean ± standard deviation; [c] median (range); [d] median (interquartile range); [e] mean (95 % confidential interval)

To illustrate the usefulness of the circulating levels of EPCs in predicting long-term outcomes such as progression, recurrence, or survival, the impacts of pre-treatment, post-treatment level, and/or intratreatment changes in the EPCs on disease outcome have been assessed in several studies with long-term follow-up [52–54, 61, 69, 75–77] (as summarized in Table 2). Patients with lower pre-treatment CEPCs levels have achieved longer overall survival (OS) length [52, 53, 61, 77], recurrence-free survival (RFS) [54], and response duration (RD) [69]. However, Sakamori et al. [76] failed to detect any association of EPC concentration with progression-free survival (PFS). Interestingly, Bhaskar et al. [69] analyzed the association between the number of CEPCs at baseline and RD and found that the median RD was higher (23 months) for the group with $\leq$19.6/µl ($n = 44$) than that (14 months) for the group with >19.6/µl ($n = 15$). Furthermore, they analyzed the prognostic power of circulating level of EPCs after therapy and confirmed that the arm with $\leq$6.5/µl benefitted in longer median RD (23 vs. 9 months; $P = 0.001$). Similarly, in another cohort of patients with multiple cancers, CEPCs level at day 7 after chemotherapy was significantly median PFS (<11.5 vs. >6.2 months; $P = 0.046$) [75]. The prognostic value of the changes in the number of CEPCs has also been investigated [54, 76] and will be discussed in the next section. Thus, although divergence exists, the prognostic value of CEPCs is so overwhelming, and further clinical studies are warranted to validate the conclusion.

CEPCs as an indicator of treatment response

The efficacy of antitumor treatments is typically assessed by measuring the direct effects on tumor burden and/or survival and is mostly confined to imaging techniques such as X-ray, computed tomography, magnetic resonance imaging, and ultrasound [78]. However, the assessment of these parameters cannot reflect the efficacy immediately and directly, thus necessitating a reliable surrogate biomarker. The potential of CEPCs in the prediction and response monitoring to a therapeutic intervention is determined by distinguishing the impact of various interventions (e.g., surgery, chemotherapy, and radiation) on CEPCs in different cancers, including breast cancer [59, 72], head and neck cancer [60], lung cancer [22, 54, 76], ovarian cancer [61, 63], RCC [66, 67], colorectal cancer [79], multiple myeloma [69], glioma [56], gastric cancer [74], and mixed types [75] (Table 3). In all studies, the CEPCs levels were quantified by FACS technique, which are not presented in Table 3.

With respect to chemotherapy (including anti-angiogenic target therapy), a significantly decreased CEPCs concentration was demonstrated in three studies [69, 72, 76], whereas others reported no significant changes [22, 79], and another presented a remarkably higher EPCs level post-treatment [75]. Roodhart et al. analyzed the changes in CEPCs in a cohort of patients receiving chemotherapy and found that the increase in EPCs level started a few hours after the initiation of chemotherapy, exceeded to 114 % (95 % CI 78–151 %; NS) after 7 days and continued to increase to 304 % (95 % CI 176–1,431 %; $P < 0.01$) on day 21, and was not limited to the regimens applied in the chemotherapy [75]. However, they included heterogeneous population of chemotherapy and cancer types as well as applied the definition of EPCs as CD31+CD133+CD45− cells, which could partially explain the contradictory results. Notably, timing is a relevant issue because the circulating level of EPCs changes time-dependently [76].

The postoperative EPCs concentration in cancer patients has been compared with the preoperative level in several studies, but inconclusive results were obtained [54, 56, 59, 63, 66, 67, 74]. Yang and his colleagues quantified the CEPCs levels in 38 RCC patients who underwent surgery and found that the CEPCs level 3 months after surgery was significantly lower than the preoperative level ($P < 0.001$; Table 3) [67]. However, similar results have not been replicated in other studies. Such contradictory findings could be explained by confounding factors such as surgery types, BM-EPCs mobilization, and consumption caused by recruitment to surgical injury sites and to stress reaction to surgical insult [80]. Additionally, the time to assess the post-surgery CEPCs varies greatly, ranging from 2 days to 6 months. Furthermore, EPCs concentration has been examined in a cohort of patients with head and neck cancer who had been receiving radiation therapy, but no significant change was found [60].

The prognostic value of varying CEPCs post-treatment has been investigated in two clinical studies [54, 76] (Table 2). After classifying 38 patients according to the changes in the number of CEPCs relative to day 1 level before the second cycle of chemotherapy, Sakamori et al. [76] demonstrated that patients with high percentage changes in the number of CEPCs did not achieve a significantly longer median PFS (139 vs. 120 days; $P = 0.295$). Subsequently, Pirro et al. reported that a total of 15 non-small cell lung cancer patients experienced a 48-h postoperative increase in the number of CEPCs, whereas the remaining 19 patients had stable or decreased EPCs level compared with preoperative levels. Thus, patients with stable or decreased EPC level achieved a significantly longer RFS ($P = 0.012$) [54]. Therefore, CEPCs can act as potent indicator of clinical response to various interventions after validation by further large-scale clinical studies.

Table 2 Selected outcome and characteristics of eligible studies examining the prognostic power of circulating EPCs

Author	Year	Cancer types	No.	Follow-up time (months)	Definition of EPCs	Cutoff value	Results (median time, months)		*P* value
							High	Low	
Pre-treatment level of circulating EPCs									
Dome	2006	NSCLC	53	Median 15	CD34+VEGFR2+	1,000/ml	OS 6.5	OS 13.9	<0.01
Bogos	2009	SCLC	88	15 (4–27)[a]	CD34+VEGFR3+	1,625/ml	OS 11.5	OS 20.0	<0.01
Su	2010	Ovarian Cancer	42	20.2 (18–24)[a]	CD34+VEGFR2+	945/ml	OS 19.0	OS 27.4	<0.05
Bhaskar 1	2012	MM	75	8 (1–32)[a]	CD34+CD133+CD31+CD45−	19.6/µl	RD 14	RD 23	<0.01
Massard	2012	Mixed cancer	58	21.5 (0–39)[a]	CD45dimCD34+VEGFR2+7AAD−	1 %	OS 9.0	OS 17	<0.01
Pirro 1	2013	NSCLC	34	(6–19)[b]	CD34+VEGFR2+	320/ml	RFS (shorter)	RFS (longer)	<0.05
Sakamori 1	2012	NSCLC	38	(2–16)[b]	CD31+CD34+CD133+CD45−	NA	PFS NA		>0.05
Post-treatment level of circulating EPCs									
Roodhart	2010	Mixed types	71	19 (12–28)[a]	CD31+CD133+CD45−	30 %	PFS 6.2	PFS 11.5	<0.05
Bhaskar 2	2012	MM	55	8 (1–32)[a]	CD34+CD133+CD31+CD45−	6.5/µl	RD 9	RD 32	<0.01
Sakamori 2	2012	NSCLC	38	(2–16)[b]	CD31+CD34+CD133+CD45−	NA	PFS NA		>0.05
Intratreatment change of the circulating level of EPCs									
Pirro 2	2013	NSCLC	34	(6–19)[b]	CD34+VEGFR2+	1 SE[c]	RFS (shorter)	RFS (longer)	<0.05
Sakamori 3	2012	NSCLC	38	(2–16)[b]	CD31+CD34+CD133+CD45−	168.7 %	PFS 4.6	PFS 4	>0.05

No. number of cancer cases, *EPCs* endothelial progenitor cells, *NSCLC* non-small cell lung cancer, *SCLC* small cell lung cancer, *MM* multiple myeloma, *VEGFR2* vascular endothelial growth factor receptor 2, *NA* not available, *OS* overall survival, *PFS* progression-free survival, *RD* response duration, *RFS* recurrence-free survival

[a] Median (range); [b] (range); [c] one standard error of the mean EPC level in the control subjects

Table 3 Selected outcome and characteristics of eligible studies examining the changes in the number of circulating EPCs

Author	Year	Cancer types	N	Definition of EPCs	Treatment	POT time	Circulating EPCs level		*P* value
							Pre-treatment	Post-treatment	
Brunner	2008	HNC	16	CD133+VEGFR2+	Radiation	NA	NA		>0.05
Goon	2009	Breast cancer	15	CD34+CD133+CD45−	Surgery	6–8 w	128 (62–226)/ml[b]	148 (70–236)/ml[b]	>0.05
Nowak	2010	Lung cancer	20	CD34+CD133+VEGFR2+	Chemotherapy	6 m	NA		>0.05
Pohl	2011	CRC	23	CD34+VEGFR2+	Chemotherapy	One cycle	NA		>0.05
Corsini	2012	Glioma	11	CD34+CD133+CD45dim	Surgery	4 days	1.55 ± 2.2/μl[f]	1.8 ± 2.0/μl[f]	>0.05
Pirro	2013	NSCLC	34	CD34+VEGFR2+	Surgery	2 days	2.3 ± 0.32 n/ml[f]	2.3 ± 0.30 n/ml[f]	>0.05
Naik	2008	Breast cancer	12	CD133+VEGFR2+	Chemotherapy	NA	162,500[a]	117,500[a]	= 0.01
Roodhart	2010	Mixed types	71	CD31+CD133+CD45−	Chemotherapy	21 days	Change 304 (176–1,431) %[c]		<0.05
Su	2010	Ovarian cancer	42	CD34+VEGFR2+	Surgery/chemotherapy	1 m	1,260.5 ± 234.2/ml[d]	659 ± 132.6/ml[d]	<0.05
Bhatt	2011	RCC	20	CD34+CD133+CD146+CD45−	Surgery	6 w–6 m	Change 0.02/μl (-0.06–1.2)[e]		= 0.05
Bhaskar	2012	MM	55	CD34+CD133+CD31+CD45−	Chemotherapy	4 m	14.9 ± 2.6/μl[f]	7.0 ± 1.8/μl[f]	<0.001
Sakamori	2012	NSCLC	38	CD31+CD34+CD133+CD45−	Chemotherapy	8 days	mean 40/μl	mean 4/μl	<0.001
Yang	2012	RCC	38	CD34+VEGFR2+CD45−	Surgery	3 m	0.297 % (0.274 %–0.320 %)[c]	0.081 % (0.062 %–0.100 %)[c]	<0.001
Ha	2013	Gastric cancer	9	CD34+CD133+	Surgery	1 w	29 ± 19.5/ml[d]	12 ± 8.3/ml[d]	<0.05
Kim	2014	Ovarian cancer	8	CD31+CD133+VEGFR2+CD45−	Surgery	NA	0.012 ± 0.002 %[d]	0.0005 ± 0.0001 %[d]	<0.01

N number of cancer cases, *POT* post of treatment, *EPCs* endothelial progenitor cells, *HNC* head and neck cancer, *RCC* renal cell carcinoma, *CRC* colorectal cancer, *MM* multiple myeloma, *NSCLC* non-small cell lung cancer, *VEGFR2* vascular endothelial growth factor receptor 2, *NA* not available, *w* week, *m* month

[a] The median number is 162,500 EPCs/5 $\times$ 10^6 mononuclear cells (MNCs) and 117,500 EPCs/5 $\times$ 10^6 MNCs; [b] median (interquartile range); [c] mean(95 % confidential interval); [d] mean ± standard error; [e] median(range); [f] mean ± standard deviation

Future directions and conclusions

Further, basic studies are required with the following objectives: To clarify the origin, function, and molecular pathways of EPCs; to refine the identification, isolation, and molecular characterization of CEPCs; and to understand the process of tumor vascularization. After the unique specific markers have been determined, higher-quality clinical studies with larger sample size to allow adjusted analysis focusing on clinically important outcomes will aid in clarifying the potent diagnostic and prognostic values of CEPCs. Despite several diverging results, our review of the available literature apparently supports the diagnostic and prognostic power of CEPCs in clinical oncology.

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Conflict of interest None.

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