The Clinical Application of CTCs in Solid Tumors

Subjects: Oncology

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Circulating tumor cells (CTCs) are tumor cells shed from the primary tumor into circulation, with clusters of CTCs responsible for cancer metastases. CTC detection and isolation from the bloodstream are based on properties distinguishing CTCs from normal blood cells. CTCs may play significant roles in cancer screening, diagnosis, treatment navigation, including prognostication and precision medicine, and surveillance.

Keywords: circulating tumor cells ; liquid biopsy ; ctDNA ; solid tumors

1. Introduction

Cancer has emerged as the leading cause of death in the United States and the world. It is projected that 1,958,310 new cancer cases will be diagnosed—and more than 600,000 Americans will die from cancer—in 2023 [1][2][3]. However, in contrast with other leading causes of death, cancer-related mortality continues to decline. From 1991 to 2020, there was an overall reduction in cancer death by 33% [3]. Many factors, including effective cancer screening, better diagnostic tools, the advancement of surgical and radiation techniques, as well as emerging systemic treatments, including chemotherapy, immunotherapy, and targeted therapies, are believed to be the reason behind the decrease in cancer-related mortality. The ability to detect cancer as early as possible, personalize cancer treatments, and effective strategies to prevent or reduce the risk of metastasis will be key in further reducing cancer-related mortality.

Most solid tumor diagnoses are established based on radiographic findings, physical examination, or direct visualization and confirmed by pathologic findings with tissue biopsy. An alternative method to detect cancer is a liquid biopsy. Circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA) are the two main biomarkers detected in liquid biopsies. Although CTCs and ctDNA were identified in 1869 and 1948, respectively, they were not utilized until recently [4].

CTCs are tumor cells that are shed from the primary tumor into circulation, and clusters are responsible for cancer metastases [5]. CTCs evaluation may play an integral role in cancer management in the future. The CTC detection assays and current evidence regarding the implementation of the detection of CTCs into clinical practice were discussed.

2. Breast Cancer

The clinical utility of CTC detection and its use in prognostication, tailoring therapies based on CTC characteristics, and guiding treatment based on CTC response to therapy has been most extensively evaluated in breast cancer at this time.

2.1.1. Prognostication

Many studies have been conducted evaluating the prognostic value of detectable CTCs at breast cancer diagnosis, both in localized disease and metastatic disease, demonstrating worse progression-free survival (PFS) and overall survival (OS) when compared to patients with undetectable levels or below a threshold of 5 CTCs/7.5 mL whole blood [6][7][8][9][10][11]. This negative prognostic value holds true after initiation of treatment, with worse PFS and OS when levels remain elevated despite therapy [7].

Beyond simply quantifying CTCs, molecular analysis of these cells can provide additional prognostic information. As previously mentioned, as malignant epithelial cells become metastatic, they will undergo epithelial to mesenchymal transition in which they undergo a phenotypic transformation allowing for tissue invasion. In a study of 427 patients with breast cancer, polymerase chain reaction (PCR) was able to detect epithelial to mesenchymal transcription factors within CTCs of 18% of patients, with these patients manifesting a shorter disease-free survival [12]. A subsequent study evaluating the presence of TWIST1, a marker of epithelial to mesenchymal transition, in patients with EpCAM-positive CTCs, found a correlation with shorter overall survival [13]. Beyond transcription factors, others have evaluated surface

marker expression on CTCs, with one study finding an association of high expression of CD47 and/or PD-L1 with shorter PFS [14].

2.1.2. Precision Medicine

CTCs can additionally play a role in guiding targeted therapies. With breast cancer, CTCs are able to be evaluated for HER2 expression, which can be dynamic over time [15]. In a study evaluating HER2 expression in CTCs of patients with advanced-stage breast cancer, those with ≥2 HER2 + CTCs/8 mL who received anti-HER2 therapy had longer PFS compared to those not receiving HER2-directed therapy [16].

However, the discrepancy between the HER2 status of the primary tumor and CTCs has been observed [11][17]. As such, multiple studies have sought to determine the therapeutic implications of this discrepancy. In a multicenter phase 2 trial that included seven patients with HER2 non-amplified tumors who had ≥2CTCs/7.5 mL having at least 50% HER2 positivity, treatment with lapatinib, a HER2-directed therapy, resulted in objective response in 0 patients [18]. A similar study conducted using trastuzumab-emtansine in a similar population of 11 patients with metastatic HER2-negative breast cancer with HER2 amplified CTCs (at least 1 HER2 amplified CTCs/7.5 mL) showed partial response in only one patient [19]. The lack of efficacy of HER2-directed therapies in patients with HER2-expressing CTCs with negative expression in the primary tumor was shown in an additional phase II trial including 20 patients, with only partial response observed in 1 patient [20]. Why there is a discrepancy in HER2 status between the primary tumor and CTCs remains unclear. Prior study has shown discordance between the HER2 status of a primary tumor and metastatic disease infrequently [21]. Different hypotheses have been proposed regarding this discrepancy, including the acquisition of HER2 amplification during the mesenchymal to epithelial transformation or heterogeneity of HER2 status within the primary tumor reflected in heterogeneous CTCs [18]. At this time, evidence is lacking in support of tailoring therapy based on CTCs when discrepant from the primary malignancy, although this does remain an area of interest and will require additional study.

An additional application of CTCs in guiding targeted therapy includes single-cell CTC genomic DNA sequencing to detect mutations in the *ESR1* gene, as mutations have been associated with resistance to estrogen deprivation therapy [22][23]. In a study of 46 patients with luminal breast cancer, *ESR1* mutations were detected via sequencing of genomic DNA in the CTCs of 12 patients, all of whom had been treated with estrogen deprivation therapy [22]. However, these mutations were absent in the primary tumor tissue sample but were detected in metastases obtained after CTCs analysis. A study evaluating the detection of *ESR1* mutations in CTCs found concordance with ctDNA in 95% of cases [24]. However, an additional study suggested that the detection of *ESR1* mutations and splice variants may be less sensitive in CTCs compared to ctDNA, although this was a smaller study [25]. In another study evaluating *ESR1* methylation, high concordance was found between detection in CTCs and ctDNA, with methylation associated with poor response to everolimus/exemestane [26].

Within breast cancer, other markers can be evaluated to help guide therapy. For example, multiple studies have demonstrated the ability to detect *PIK3CA* mutations within CTCs, and as mutations in PIK3CA can predict resistance to HER2-directed therapies, this is a potential mechanism to guide treatment [27]. Much like HER2 expression, there may be a discrepancy in mutational status between the primary tumor and CTCs [28]. At this time, to the knowledge, tailoring treatment based on the assessment of *PIK3CA* mutational status in CTCs has not been clinically evaluated.

2.1.3. Treatment Guidance

Multiple studies have demonstrated the negative prognostic value of persistently elevated CTCs in spite of systemic chemotherapy [29][30][31]. Based on this observation, multiple clinical trials have been conducted with the intention of changing therapeutic strategy based on CTCs elevation, essentially allowing CTCs response to guide therapeutic decisions.

SWOG S0500 was an early trial that evaluated 288 women with metastatic breast cancer with CTCs elevation at baseline. Of these, 123 had persistently elevated CTCs after 21 days of chemotherapy and were randomly assigned to continue the current chemotherapy or change to a different chemotherapy [32]. Ultimately, there was no difference in OS observed between these groups. EORTC 90091-10093 BIG 1-12 Treat CTCs was a similarly designed phase II trial, enrolling 63 patients with non-HER2 amplified breast cancer who had at least 1 CTCs/15 mL following neoadjuvant chemotherapy and surgery, and randomized them to receive trastuzumab-based on the prior observation that patients with non-HER2 amplified breast cancer received a benefit from trastuzumab [33]—with 1 hypothesis that this benefit may stem from the targeting of HER2 positive CTCs, versus observation, with a primary endpoint of the rate of detection of CTCs at 18 weeks [34]. However, this study was discontinued early due to futility.

Later, CirCe01 was a prospective, multicenter randomized trial in which 204 patients with metastatic breast cancer who had progression on two prior lines of therapy were enrolled [35]. Patients with elevated CTCs were randomized to standard care or a CTCs-driven arm in which the change in CTCs suggestive of treatment failure would prompt a transition to the next line of therapy. OS was ultimately not different between the two arms, although this study was limited by patient accrual and compliance.

STIC CTCs was a randomized, open-label phase 3 noninferiority trial enrolling women with hormone receptor-positive, ERBB2-negative metastatic breast cancer who were randomized to either clinician-driven first-line treatment versus treatment based on CTC count, with those with CTCs ≥ 5/7.5 mL receiving chemotherapy and CTCs < 5 receiving endocrine therapy [36]. A primary endpoint of noninferiority was achieved. However, a higher rate of chemotherapy-related adverse events was seen in the CTC-driven arm.

Overall, CTC monitoring for treatment guidance remains an area of interest in breast cancer. However, at this time, clinical data are lacking in support of its routine use. Additional clinical trials will be necessary going forward to determine its value in breast cancer management.

2.2. Prostate Cancer

Within the field of prostate cancer, CTCs have shown value in the prognostication of patient outcomes. Beyond this, there has been great interest in monitoring androgen receptor splice variants (AR-V) within CTCs to assist in the guidance of therapy.

2.2.1. Prognostication

Much like breast cancer, the elevation of CTCs has been demonstrated to have a negative prognostic value in prostate cancer. Studies have demonstrated poorer PFS and OS among patients with metastatic castration-resistant prostate cancer (MCRPC) [37][38], as well as patients with castration-sensitive prostate cancer [39][40]. Additionally, beyond the initial elevation of CTCs before therapy, multiple studies had shown the persistence of negative prognostic value when the CTCs were continually elevated despite chemotherapy [41][42][43].

Beyond simple detection and quantification, CTCs have been evaluated for various markers, allowing for better prediction of patient outcomes. AR-Vs are one such marker. For example, AR-V7 detected in CTCs has been associated with more aggressive and advanced disease and poorer patient outcomes [44][45]. Another study aimed at determining other prognostic markers in prostate cancer evaluated transcriptional profiles of patients with MCRPC and was able to identify two distinct transcriptional clusters, one of which was associated with worse OS [46]. Additionally, CTC detection has been evaluated in combination with other makers. For example, a study of 711 patients with MCRPC found the combination of CTCs ≥ 5CTCs/7.5 mL with LDH > 250 U/L after 12 weeks of therapy was predictive of 2-year survival of 2% versus 46% observed in patients lacking these markers [47].

2.2.2. Precision Medicine

Much interest has been generated in the evaluation of AR-Vs present in CTCs and the impact of these splice variants on patient response to therapy. A study evaluating the expression of AR-Vs in CTCs from 118 patients with metastatic prostate cancer undergoing treatment with cabazitaxel found that CTCs reduction to <5CTCs was less frequently observed in patients with AR-V9 positive CTCs at baseline and that those with AR-V1 expression after two weeks of therapy exhibited worse OS [48]. An additional study evaluating outcomes of patients with MCRPC who were on their second line or greater of therapy found that those with CTCs with detectable AR-V7 trended towards superior survival when treated with taxanes over an androgen receptor signaling inhibitor (ARSI), whereas those not expressing AR-V7 had superior survival with an ARSI over taxanes [49]. However, another phase II study (PROPHECY) conducted in 118 men with metastatic prostate cancer found that AR-V7 positivity in CTCs prior to treatment with abiraterone or enzalutamide was associated with worse PFS and OS [50]. These studies demonstrate the potential utilization of CTCs for AR-V analysis, which may assist with the selection of therapy.

Other studies have evaluated different markers and their predictive value for response to therapy. A recent phase IB/II study evaluating ribociclib plus docetaxel in MCRPC found non-amplified MYC in baseline CTCs to be associated with longer radiographic PFS [51]. Another phase 2 trial evaluated BIND-014, a prostate-specific membrane antigen (PSMA)-directed docetaxel-containing nanoparticle, and found that after treatment, there was a selective reduction in PSMA-positive CTCs [52], which suggests a role for treatment monitoring of various marker expression in CTCs in guiding further therapeutic choices.

2.3. Non-Small Cell and Small Cell Lung Cancer

2.3.1. Prognostication

Within non-small cell lung cancer (NSCLC), multiple studies have demonstrated the negative prognostic implications of elevated CTCs in patients with early-stage disease [53][54][55], with elevation following surgical resection also predictive of poorer prognosis and earlier disease recurrence [56][57][58]. The negative prognostic value also holds true in patients with advanced disease [59][60], including those with persistently positive in spite of treatment [61]. In addition to simple quantification, a recent study utilizing PCR was able to evaluate gene expression and identify a genetic panel predictive of poorer prognosis in NSCLC [62].

Beyond CTCs sampling from peripheral blood, 1 study evaluated CTC detection within the pulmonary venous system and found that in 100 patients with early-stage NSCLC, pulmonary venous CTCs were detected in 48% and associated with poorer PFS [63]. Interestingly, a recent trial randomized patients with early-stage lung cancer undergoing lobectomy to a vein-first (ligation of effluent vessels completed first) or artery first-procedure and found that those who had artery-first ligation had a higher risk of CTC increase during surgery, with a propensity-matched analysis demonstrating better 5-year overall survival in the vein-first group [64]. This demonstrates a role for the understanding of CTC physiology contributing to the improvement in disease management.

Detection of circulating tumor cells in patients with small cell lung cancer (SCLC) is a poor prognostic marker as well [65][66][67][68][69]. Different from other malignancies, higher rates of CTCs have been reported in SCLC. For example, a study of 60 patients with extensive stage SCLC identified CTCs in 90% of patients, with a range from 0 to 24,281 per 7.5 mL [70]. This same study reported that prognostic accuracy using CTCs detection was greatest in patients who had a reduction of CTCs count by 89% following chemotherapy. Other studies have supported the prognostic value of CTCs reduction following chemotherapy in SCLC [71][72]. Beyond the reduction in CTCs, monitoring tumor markers may also hold value in treatment navigation. One study evaluated vascular endothelial growth factor receptor (VEGFR) expression on CTCs of patients with SCLC undergoing treatment with pazopanib (VEGFR inhibitor), finding an initial reduction in CTCs expression with treatment initiation, but with disease progression, a significant increase in CTCs were observed with a significant increase in VEGFR expression [73]. This suggests a role for tailoring therapies to receptor expression of CTCs in SCLC.

2.3.2. Precision Medicine

A recent prospective study evaluated CTC PD-L1 expression in patients with recurrent or metastatic NSCLC prior to and after initiation of ICI therapy and found that increased expression of CTC PD-L1 from prior treatment to after treatment was associated with better PFS and OS, which may potentially allow for determination of which patients may benefit from further ICI therapy [74]. In a study evaluating 30 patients with NSCLC without targetable mutations who had progression on first-line platinum-based chemotherapy and were now receiving sintilimab (PD-1 inhibitor) plus docetaxel, patients with high PD-L1 expression on CTCs had longer median PFS and longer median OS when compared to patients with low CTC PD-L1 levels [75]. These studies suggest a role for monitoring PD-L1 expression on CTCs in NSCLC to guide therapeutic decisions.

2.4. Colorectal Cancer

Within colorectal cancer, an active area of research surrounds the determination of which patients with stage II and stage III disease may benefit from adjuvant chemotherapy. As such, much of the research regarding the utility of CTCs has sought to evaluate a possible role in this population of patients.

2.4.1. Prognostication

Among patients who are CTC-positive, quantification has been shown to help predict the extent of disease involvement. In a study of 121 patients with advanced colorectal cancer, of whom 71 were CTC-positive, CTC positivity was predictive of the depth of invasion, lymphatic involvement, distant metastatic disease, TNM staging, and serum CEA level, and was overall predictive of less favorable PFS and OS, with persistent presence during chemotherapy also associated with poorer PFS and OS [76]. Additional studies have correlated baseline CTC count ≥3/7.5 mL with stage IV disease at diagnosis, at least three sites of metastasis, elevated CEA levels, and increased TNM staging [77][78]. Beyond disease characteristics, additional studies have supported the negative prognostication associated with CTC detection in both localized and advanced CRC prior to intervention [79][80][81][82].

As previously mentioned, an important question in colorectal cancer remains in regard to which patients benefit from adjuvant chemotherapy versus which patients may be able to be spared this intervention. A study published in 2019 suggested that post-operative CTC levels were more predictive of recurrence-free survival in patients with stage II–III CRC undergoing surgical resection [83]. However, conflicting results have also been published suggesting that CTC elevation following surgical resection was not predictive of patient outcomes [81][84]. This discrepancy may, in part, be due to the timing of sample analysis and represents an area where further study may be required.

However, CTCs do have prognostic value following chemotherapy in patients with stage III colon cancer, with a study demonstrating post-chemotherapy persistence correlated with worse DFS and OS [85]. An additional phase II trial enrolling patients with metastatic CRC found that persistently negative CTC status during chemotherapy predicted better OS [86].

2.4.2. Treatment Guidance

An interesting phase II trial including 48 patients with advanced CRC who received a regimen of irinotecan, oxaliplatin, and tegafur-uracil—and made cross-trial comparisons to patients who received capecitabine, oxaliplatin, and bevacizumab +/− cetuximab—stratified patients by CTC count < 3 or ≥3 and found that median OS was similar for both treatment groups if the baseline CTCs count was <3. However, patients receiving the regimen consisting of irinotecan, oxaliplatin, and tegafur-uracil had better survival when the CTC count was ≥3 [87]. While no significant conclusions can be drawn based on the design of the study, the authors note that this is a hypothesis-generating study, suggesting that patients who have elevated CTC counts may benefit from more aggressive treatment regimens and allow for avoidance of higher toxicity chemotherapy in lower risk groups.

This was followed by the phase III VISNU-1 trial, which was an open-label, phase III study that enrolled 349 patients with untreated, unresectable metastatic CRC with CTCs count ≥3 and randomized them to receive FOLFOXIRI (irinotecan 165 mg/m^2, oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, and 5-fluorouracil 3200 mg/m^2) plus bevacizumab or FOLFOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, 5-fluorouracil 400 mg/m^2, then 2400 mg/m^2) plus bevacizumab, and found that those who received FOLFOXIRI plus bevacizumab had longer PFS [88]. It is important to note that grade 3 toxicity was more frequently reported in the FOLFOXIRI arm. However, it is challenging to draw any conclusions from this study using a primary endpoint of PFS when comparing a triplet chemotherapy backbone to a doublet backbone, recognizing that a meaningful endpoint would be OS or time to second progression following receipt of a second doublet in those who received a doublet in the first line.

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