Teaching Lecture

E8. Clinical applications of circulating tumour cells

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Introduction

The clinical potential of detecting minimal residual disease (MRD) in primary and metastatic breast cancer stretches far beyond its mere prognostic relevance, and may contribute to individualising systemic treatment. The role of MRD in the development of tailored treatment may comprise the following aspects:

- detection of MRD could serve as an early tool for evaluating treatment efficacy, leading to a more individualised therapeutic approach;
- detection of MRD could be implemented in everyday patient care to select patients with an increased risk for recurrence of their disease, and who might benefit from a change in treatment, or where there might be a need for additional therapeutic interventions;
- MRD could serve as a source to understand tumour biology in MRD well after the completion of primary treatment;
- phenotyping MRD might lead to a more individualised and thus targeted treatment based on the phenotype of persistent MRD.

Thus, the significance of MRD may reach far beyond the potential of established prognostic parameters at the time of primary diagnosis of breast cancer.

Prognostic relevance of circulating tumour cells in peripheral blood

In metastatic disease, the detection of circulating tumour cells (CTCs) is facilitated by the high tumour burden which results in increased numbers of tumour cells released into the bloodstream. Cristofanilli et al. observed a shorter median progression-free survival (PFS) (2.7 months versus 7.0 months, $P < 0.001$) and overall survival (OAS) (10.1 months versus >18 months, $P < 0.001$) in 177 metastatic breast cancer patients with elevated levels of CTCs compared to patients with less than 5 CTCs before the start of a new line of treatment [1,2]. This difference persisted for up to 14 weeks after the initiation of therapy. In multivariate analysis, CTCs were confirmed as the most significant predictor of PFS and OAS both before start of treatment and at first follow-up.

The same group published a comparison of monthly CTC evaluation with radiological imaging – computed tomography (CT), magnetic resonance imaging (MRI) and bone scan – conducted every 3 months [3]. While both methods could equally predict PFS and OAS for patients treated with first-line endocrine or cytostatic treatment, CTCs allowed an early and more accurate assessment of OAS in higher lines of treatment ($P = 0.0009$ for CTCs, $P = 0.2209$ for radiological response). Furthermore, the reproducibility of CTC counts was increased compared to radiological assessment, with an inter-reader variability of 0.7% versus 15.2% [4]. The integrated use of CTCs and modern metabolism-based imaging techniques might improve treatment monitoring in these patients.

The most relevant clinical impact of MRD, however, can be anticipated during adjuvant treatment and recurrence-free follow-up. Most trials published recently have reported a significant correlation of CTCs with outcome in early breast cancer patients [5–10].

Therapeutic interventions

Recent studies seeking to optimise chemotherapy in various tumour entities have yielded mostly moderate, rather limited improvements in efficacy. A possible explanation for this observation might be the fact that chemotherapy optimally targets highly proliferative cells. However, evidence indicates that disseminated tumour cells (DTCs) are mostly slowly proliferating, 'dormant' cells, explaining the frequent failure of conventional adjuvant therapy e.g. in breast cancer. Targeting DTCs by different approaches (e.g. inhibition of angiogenesis), as described below, could therefore open up new therapeutic options.

Moreover, not only the tumour cell but also the specific microenvironment determines the extent of DTC proliferation and survival. Therefore, therapeutic approaches could not only aim at DTCs but also modify the surrounding microenvironment.

An additional potential of DTC could be to re-evaluate therapeutic targets on DTCs during cancer treatment, which might enable a more individualised therapy in cancer patients.

(a) Therapeutic interventions inhibiting angiogenesis

Angiogenesis is a critical feature of tumour growth above the single-cell stage. In the context of eliminating dormant DTCs, an anti-angiogenic therapy might be sufficient to maintain the non-proliferative state of the

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DTCs by preventing angiogenic activation of growth progression. This is the rationale for the use of antiangiogenetic agents, i.e. bevacizumab in ongoing (neo)adjuvant clinical trials.

(b) Therapeutic interventions to modify the microenvironment

The specific microenvironment determines the extent of cell proliferation, angiogenesis, invasion and survival of DTCs. Bisphosphonates influence the microenvironment by altering secretion of growth factors and cytokines. Moreover, bisphosphonates reduce tumour-cell adhesion, induce apotosis in tumour cells, have an anti-angiogenic effect, and enhance the antitumour activity of cytotoxic agents [11]. Therefore, bisphosphonates could be one treatment option to modify the metastatic potential of DTCs. Small trials have already demonstrated that persistent DTCs of primary breast cancer patients can be eliminated by bisphosphonates, probably due to a combined effect on the microenvironment and the tumour cells [12,13].

(c) Therapeutic interventions to eliminate HER2-positive CTCs

HER2-positive patients are eligible for treatment with anti-HER2 agents. The phenotype of the primary tumour is the current clinical standard to select breast cancer patients for HER2-targeted therapy. However, studies have indicated that the HER2 status may differ between the primary tumour and DTCs [14]. In metastatic patients it has also been demonstrated that patients with HER2-negative primary tumours have HER2-positive circulating tumour cells in the blood. Moreover, a subset of these patients were treated with trastuzumab and showed a clinical response [15]. The German multicentre Detect III trial will evaluate the efficacy of lapatinib against HER2-positive CTCs in patients with HER2-negative metastatic breast cancer.

(d) Therapeutic interventions to eliminate CTCs by activation of the immune system

Single tumour cells might be a better target for immune cells than large tumours. This could be the rationale for the hypothesis that therapeutic vaccines are particularly effective in patients with (dormant) MRD since the effector-target ratio is more favourable. Therefore, an additional treatment strategy as therapeutic intervention to eliminate CTCs may be the use of cancer vaccines.

Conflict of interest statement

Brigitte Rack has received unrestricted research grants from Veridex. Ulrich Andergassen, Julia Neugebauer, Bernadette Jäger and Wolfgang Janni have no conflicts of interest to declare.

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