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Determinants of bone specific metastasis in prostate cancer

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ABSTRACT

Prostate cancer is one of the most common type of cancer in Western countries. Although the majority of patients with PCa have a minimally aggressive disease, some of them will experience relapse and formation of metastasis. Bone metastasis are a major cause of quality of life impairment and death among patients with metastatic prostate cancer. Different "bone targeted therapies" and several follow-up strategies were developed in order to optimize bone metastasis prevention and treatment. Nevertheless there is still a great clinical need of identifying patients more likely to benefit from those interventions as not all patients will develop metastatic disease and not all patients with metastatic disease will develop bone metastasis. Here we review markers predictive of bone metastasis occurrence that have been tested in clinical settings, particularly focusing on the ability of such markers to predict bone metastasis over visceral metastasis occurrence.

1. Introduction

As for any type of metastasis, bone-metastatic tumor cells retain specific properties that make them specifically fit only for the establishment of skeletal metastasis (Croucher et al., 2016). Although most patient with metastatic prostate cancer (PCa) will develop bone metastases, visceral metastasis occur in up to 15% of patients with PCa and, depending on the series, roughly 5% of PCa patients will develop only visceral metastasis (Gandaglia et al., 2015).

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The metastatic process occurs through different steps (Massague and Obenauf, 2016). Each of these steps is potentially detectable and useful in a clinical setting. Prediction of bone metastasis might help change the clinical approach as for prevention and treatment is concerned. Patients at high risk for bone metastasis would likely benefit more from adjuvant androgen deprivation therapy or from bone targeted therapy to prevent or delay bone metastasis, and could be monitored proportionally to their clinical risk, allowing an optimization of disease follow up (Briganti et al., 2014).

The pathophysiology of bone metastasis formation is still far to be fully understood but is increasingly being elucidated by different experimental models and clinical evidences. Here we aim to review all those factors that demonstrated to predict bone metastasis occurrence in PCa patients.

2. CTCs and DTCs

The metastatic process, in order to occur, needs some cancerous cells from the primary tumor to acquire the capability of enter and survive in the systemic circulation. A minority of these circulating tumor cells (CTCs) can extravasate to other site and enter a quiescent status: these dormant cells are referred to as disseminated tumor cells (DTCs). Eventually these dormant cells can start proliferate and – even years after their establishment – form new metastasis (Massague and Obenauf, 2016). It has been recently shown that CTCs do not move unidirectionally from primary tumors to metastasis but they can move backward from metastasis to primary tumor and also from a metastasis to another one, hence reflecting the coexistence of different subpopulations with different aggressiveness and metastatic ability (Gundem et al., 2015).

CTCs quality and quantity can be used both as prognostic and predictive markers in PCa. High levels of CTCs before treatment with Docetaxel in patients with PCa from the SWOG S0421 study were prognostic of a worse 2-year OS in a Cox regression model comparing patients with <5 CTCs/7.5 ml count with those with ≥5 CTCs/7.5 ml; in the same study a drop or an increase of CTCs after treatment retained respectively a positive and a negative prognostic value (Goldkorn et al., 2014). Another study demonstrated that the presence of the splicing variant of Androgen Receptor AR-V7 in CTCs could predict response to Abiraterone or Enzalutamide in patients with metastatic castration resistant PCa (mCRPCa) – AR-V7 presence confers PCa cells resistance to androgen deprivation therapy (Antonarakis et al., 2014).

In respect of bone relapse prediction, Jie-Fu Chen et al. found that high levels of a particular population of CTCs characterized by a very small nuclear size were more common in patients with visceral and bone metastases compared to patients with sole bone metastasis (Chen et al., 2015a), suggesting that only a subpopulation of PCa cell retain viscera metastatic properties. Morgan et al. found that the presence of detectable DTCs from bone marrow aspirates of patients undergone radical prostatectomy enhances the likelihood of disease relapse, showing that dissemination to bone marrow is a critical event that precede bone metastasis occurrence and that surgery is more likely to be effective if it takes place before CTCs dissemination (Morgan et al., 2009). Similarly Kollermann et al. (2008) found that the presence of DTCs in bone marrow aspirates in patients undergoing neoadjuvant hormone therapy followed by radical prostatectomy was predictive of subsequent biochemical recurrence. It should be noted, however, that Todenhofer et al. (2015) failed to correlate DTCs amount from intraoperative BM biopsies with subsequent biochemical relapse free survival and overall survival in a cohort of high risk localized PCa patients undergoing radical prostatectomy (Table 1).

Danila et al. (2007) showed that the amount of CTCs in peripheral blood differed when comparing patients with sole bone

Table 1
Studies exploiting CTCs and DTCs quality and quantity in clinical settings.

Authors (year)	Patients characteristics	CTCs/DTCs source	Findings	Reference
Chen et al. (2015)	57 patients with localized and metastatic PCa	Peripheral blood	CTCs with small nuclear size are more common in patients with visceral and bone metastasis compared patients with sole bone metastasis	Chen et al. (2015a)
Kollerman et al. (2008)	193 patients with localized and locally advanced PCa (T1-4N0M0) undergoing hormone therapy and subsequent radical prostatectomy	Bone marrow aspirates	Presence of DTCs is a negative prognostic factor and predicts biochemical recurrence	Kollermann et al. (2008)
Morgan et al. (2009)	569 patients undergoing radical prostatectomy without evidence of disease (98 undergoing follow-up after prostatectomy) and 34 healthy controls	Bone marrow aspirates	Presence of DTCs before and after prostatectomy predicts shorter time to relapse	Morgan et al. (2009)
Todenhofer et al. (2015)	248 patients (199 undergoing follow-up) with localized PCa with Gleason score of ≥7 or pT3-4 in final histology or a PSA serum concentration of ≥10 ng/ml	Bone marrow aspirates	Presence of DTCs intraoperatively was not predictive of change in biochemical free survival	Todenhofer et al. (2015)
Danila et al. (2007)	120 patients with progressive clinical castrate PCa of whom 57% had received local therapy (radical prostatectomy or radiation) and 43% were metastatic at presentation	Peripheral blood	Higher number of CTCs were found in patients with sole bone metastasis or bone and visceral metastasis compared to those with sole visceral metastasis	Danila et al. (2007)
Thalgott et al. (2013)	80 patients of whom 20 were locally advanced PCa, 45 were mCRPCa and 15 were metastatic taxane-refractory PCa; 15 healthy controls were enrolled	Peripheral blood	Higher number of CTCs were found in patients with sole bone metastasis or bone and visceral metastasis compared to those with sole visceral metastasis; the number of CTCs did not differ between sole visceral metastasis and healthy control	Thalgott et al. (2013)