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Circulating Tumor Cells (CTCs) in clinically localized prostate cancer (PCa): searching a prognostic tool

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BACKGROUND

Despite the routine use of prostate-specific antigen (PSA) screening is matter of debate, it is undoubtable by it radical prostatectomy as a primary treatment for clinically localized prostate cancer (PCa) has increased dramatically over the past decade and has led to a reduction in advanced disease and disease-specific mortality. The other side of the coin is that there is still a vast number of men, which harbor occult extra-prostatic extension and develop recurrence after surgery; meanwhile we are dealing with an over-diagnosis of cases that would not have caused clinical consequences during a man's lifetime if left untreated. On this basis, accurate prognostic cancer patients are strongly sought. The dissemination of prostate cancer cells to secondary sites appears to be an intermediate step in the formation of tumor metastases. However, unlike breast cancer, in which prognostic and predictive impact of tumor cells in peripheral blood or bone marrow was largely provided, their role in localized PCa is far from clear.

METHODOLOGY

From July 2011 to August 2013, we enrolled 153 PCa patients stage T2a-T3b at three clinical sites (Roma, Orbassano and Padova). All the patients were candidate to undergo radical prostatectomy because of positive biopsy for cancer; we quantified their tumor burden at diagnosis in peripheral blood. We used the M30-integrated assay for enumerating viable and apoptotic CTCs (Rossi, Basso et al. 2010).
The standard CellSearch assay was perfomed at two clinical sites (Orbassano and Padova). In patients enrolled in Roma (Janus trial, a phase II study for the use of zoledronic acid as neoadjuvant treatment of invasive prostate cancer), we evaluated in parallel the tumor burden at bone marrow. Data obtained in Orbassano (n=50) and Roma (n=15) constituted the training set, meanwhile patients enrolled in Padova (n=88) constituted the validation set. Consistently with previous reports (Kraan, Sleijfer et al. 2011) reporting low inter-test and inter-lab variability, the baseline CTC count in the two sets did not significantly differ (Mann-Whitney Rank Sum Test, p= 0.170), so that they were further analyzed altogether.

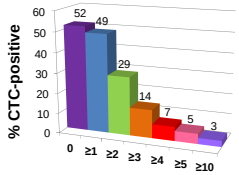
Patients and primary tumor characteristics by CTC count

PROSTATE CANCER PATIENTS		n	CTC negative		CTC positive	p value[a]
All subjects (males)		153	79	51.6%	74	48.4%
Age at diagnosis (n=143)	≤35 36-50 ≥51	3 140 44	1 44		2 96	p=1
PSA (n=148)	<4,0 ng/L ≥4,0 ng/L	15 133	7 73		8 60	p=0.593
GLEASON (n=137)	2<G<6 G=7 8<G<10	13 84 40	5 62 22		8 42 18	p=0.769*
T (n=135)	Tis T0 T1 T2 T3 T4	- - - 46 89 -	- - - 24 47 -		- - - 22 42 -	p=1
N (n=85)	N0 N1 Nx	49 4 32	23 2 13		26 2 19	p=0.907*
Risk (n=148)	Low Intermediate High Very High	8 41 77 22	3 18 44 12		5 23 33 10	p=0.655*

a: Fisher' exact test or Chi square (*) test were employed when appropriate

We found no association between CTC status and primary tumor characteristics.

CTC prevalence at the first blood draw in PCa patients T2a-T3b



We found a high frequency of CTC-positive patients among candidate to radical prostatectomy because of positive biopsy for cancer.

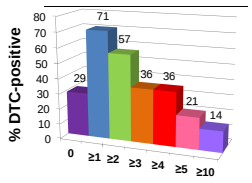
DTC and CTC synchronous detection in PCa patients T2a-T3b

1 out of 18 Pca patients enrollered in the Janus Trial

pt #5: 56 years old, pT3b N0, Gleason score 7, Intermediate Risk

- 28 DTCs/2 ml bone marrow aspirate
- 2 CTCs/7.5 ml peripheral blood

DTC Frequency at the first blood draw in PCa patients T2a-T3b

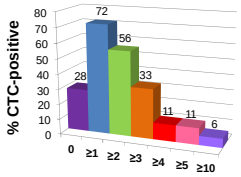


DTCs were quantifyed in 14 patients

age: 55-75 years (median 66)

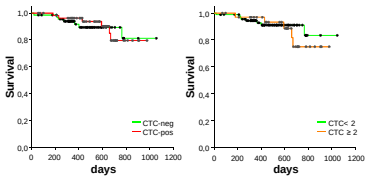
- 10 of 14 were DTC-positive at baseline
- median DTC number: 3 cells

CTC Frequency at the first blood draw in PCa patients from Janus Trial



- 13 out of 18 pts were CTC-positive
- lower CTC level were found in PB (median CTC number: 2 cells)

Is a CTC level > 1 cell (or more) predictor of biochemical relapse in early PCa patients?



The log rank statistic for the survival curves is not great enough to exclude the possibility that the difference is due to random sampling variability; there is not a statistically significant difference (p= 0.567).

CONCLUSIONS:

We found CTCs by CellSearch assay in close to 50% of biopsy-confirmed PCa patients, obtaining evidence of a systemic disease. Prospective studies will be required to investigate if CTC-status is associated with worst outcome in early PCa, as already provided in early breast cancer patients (Lucci, Hall et al. 2012).

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CTCTrap