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RESEARCH COMMENTARY

Circulating tumor cells in high-risk nonmetastatic colorectal cancer

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Abstract The identification of patients at higher risk of recurrence after primary colorectal cancer resection is currently one of the challenges facing medical oncologists. Circulating tumor cell (CTC) may represent a surrogate marker of an early spread of disease in patients without overt metastases. Thirty-seven high-risk stages II–III colorectal cancer patients were evaluated for the presence of CTC. Enumeration of CTCs in 7.5 ml of blood was carried out with the FDA-cleared CellSearch system. CTC count was performed after primary tumor resection and before the start of adjuvant therapy. CTC was detected in 22 % of patients with a significant correlation with regional lymph nodes involvement and stage of disease. No significant correlation was found among the presence of CTC and other clinicopathological parameters. These data suggest that CTCs detection might help in the selection of high-risk stage II colorectal cancer patient candidates for adjuvant chemotherapy.

Keywords Circulating tumor cells · Early colorectal cancer · Prognosis

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Introduction

Circulating tumor cells (CTC) enumeration has an independent prognostic significance in metastatic colorectal cancer [1]. Limited data exist regarding the prognostic value of CTC in nonmetastatic colorectal cancer patients and the correlation with clinicopathological parameters [2–4]. The identification of patients at higher risk of recurrence after primary colorectal cancer resection is currently one of the challenges facing medical oncologists. While the benefit of adjuvant therapy for stage III colon cancer is well established, adjuvant chemotherapy is not considered a standard approach for unselected patients with stage II colorectal cancer. Thus, identifying new markers to improve patients risk stratification is of relevant clinical interest. To this purpose, CTC may represent a surrogate marker of early spread of disease in colorectal cancer patients without overt metastases, consistently with preliminary data recently published in early breast cancer [5]. A significant variability in CTC detection rates in nonmetastatic colorectal cancer patients has been reported. In particular, by the use of the FDA-cleared CellSearch system, CTC have been detected in a variable proportion of patients, ranging from 7 to 26 % [6]. The prognostic significance for PFS and OS of ≥3/7.5 ml CTC in metastatic colorectal cancer patients has been clearly demonstrated. A threshold of ≥2 CTCs/7.5 ml was chosen in three different studies evaluating the clinical relevance of CTC detection through CellSearch system in stages I–III colorectal cancer patients. Nevertheless, the sensitivity of this cutoff seems not appropriate to detect positive CTC in early stages of colorectal cancer. Indeed, available data in nonmetastatic breast cancer demonstrate that the presence of at least one CTC in 7.5 ml [5] or one CTC in 23 ml [7] has independent prognostic significance. Studies conducted in patients with metastatic disease led to the definition of different cutoff levels of CTC in breast, colorectal, and prostate cancers, with the lowest threshold selected for colorectal cancer patients. It may

be thus postulated that the cutoff of ≥2 CTCs/7.5 ml might underestimate the CTC detection rate in patients with stages I–III colorectal cancer. The reported proportion of patients with stages I–III colorectal cancer with ≥2 CTC/7.5 ml ranges from 5 to 25 %, without a clear correlation with clinicopathological parameters. In the present study, we evaluated for the first time the presence of CTC in a population of nonmetastatic colorectal cancer patients at high risk of recurrence.

Patients and methods

A total number of 37 high-risk stage II or III colorectal cancer patients were prospectively evaluated for the presence of CTC (Table 1). According to international guidelines, high-risk stage II cancer was defined as T4 tumors, poor histologic grade, lymph vascular or perineural invasion, perforation, acute bowel obstruction, close, indeterminate or positive margins, and <12 lymph nodes sampled. Enumeration of CTCs in 7.5 ml of blood was carried out with the FDA-cleared CellSearch system. CTC count was performed after primary tumor resection and before the start of adjuvant therapy.

Results

The presence of CTC was detected in eight of 37 patients (22 %). Median number of CTC was 1.25 (range 1–2). A significant correlation was found between CTC presence, regional lymph nodes involvement, and stage of disease. Indeed, a high proportion of CTC-positive patients had N1–2 disease (87.5 %) and stage III of disease (87.5 %). Conversely, in the group of CTC-negative patients, a regional lymph node involvement was found in 34 % of cases, and a large proportion of patients had high-risk stage II disease (66 %). No significant correlation was found among the presence of CTC and other clinicopathological parameters. In a median follow-up period of 8 months, only one patient experienced a progression of disease; interestingly, this patient, who was found positive for CTC presence, had a high-risk stage II disease.

Table 1 Characteristics of 37 patients with high-risk colorectal cancer

Patient no.	TNM	Stage	G	CTC no. (CellSearch)
1	T3N1M0	IIIB	G3	1
2	T4N2M0	IIIC	G3	1
3	T4aN1M0	IIIB	G3	1
4	T3N0M0	IIA	G2	2
5	T3N1M0	IIIB	G2	1
6	T4aN2bM0	IIIC	G2	1
7	T3N1aM0	IIIB	G3	2
8	T3N1aM0	IIIB	G2	1
9	T3N0M0	IIA	G2	0
10	T3N1M0	IIIB	G3	0
11	T4N0M0	IIB	G2	0
12	T4N1M0	IIIB	G2	0
13	T4N1M0	IIIB	G3	0
14	T4N0M0	IIB	G3	0
15	T3N2M0	IIIB	G3	0
16	T4N0M0	IIB	G2	0
17	T3N0M0	IIA	G3	0
18	T3N0M0	IIA	G2	0
19	T3N0M0	IIA	G3	0
20	T3N0M0	IIA	G2	0
21	T3N0M0	IIA	G2	0
22	T3N1M0	IIIB	G2	0
23	T3N1M0	IIIB	G2	0
24	T4N0M0	IIB	G2	0
25	T4N2M0	IIIC	G3	0
26	T3N0M0	IIA	G2	0
27	T3N0M0	IIA	G3	0
28	T3N0M0	IIA	G3	0
29	T2aN0M0	IIA	G3	0
30	T3N0Mo	IIA	G2	0
31	T3N2M0	IIIB	G2	0
32	T3N0M0	IIA	G1	0
33	T3N1bM0	IIIB	G2	0
34	T3N1bM0	IIIB	G3	0
35	T4bN0M0	IIC	G2	0
36	T3N0M0	IIA	G2	0
37	T3N1aM0	IIIB	G2	0

Discussion

These data suggest that CTCs detection might help in the selection of high-risk stage II colorectal cancer patient candidates for adjuvant chemotherapy. Previously published works in nonmetastatic colorectal cancer patients reported the correlation with CTC presence and TNM stage of disease. Conversely, the higher CTC detection rate in high-risk stage II colorectal cancer, compared to low-risk stage II, has never been highlighted before. The detection of CTC through CellSearch in nonmetastatic setting of disease may allow to identify stage II patient candidates for adjuvant chemotherapy and to select stage III patients for more or less aggressive approaches. Similar results have been recently published in non-muscle invasive bladder cancer, where CTC count through CellSearch was able to distinguish patients with high risk of recurrence from those with high risk of progression, as well as to early identified patient candidates for adjuvant treatment [8]. The AJCC cancer staging manual, seventh edition, has now introduced for breast cancer the category

cM0 (*i*+) as "the absence of clinical or radiological evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood or bone marrow." The prognostic significance of CTCs detection in nonmetastatic setting, particularly in a very early stage of disease, should lead one to further thinking about significance of cM0 (*i*+). We strongly believe that cM0 (1+) is a clinical, not biological concept. Follow-up of these patients will be crucial to define the potential role of CTC as prognostic factor in colorectal cancer patients at high risk of recurrence.

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Conflicts of interest None.

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