

Towards a precision oncology for cholangiocarcinoma patients guided by circulating tumor cells analyses

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Cholangiocarcinoma (CCA) represents the second most common primary hepatobiliary cancer (1). This cancer comprises a heterogeneous group of pathologic subtypes which are anatomically classified as intrahepatic CCA (ICCA), perihilar CCA (pCCA), or distal CCA (dCCA) (2). CCA development is normally associated with an early lymph node and distant dissemination causing that only a low rate of patient can be candidates for surgical curative resection. The standard of care in patients with unresectable tumors or metastatic disease is combined chemotherapy with gemcitabine and cisplatin, although targeted therapies are considered as a promising alternative to standard treatment (3). Nowadays one of the challenges to improve the management of patients with CCA is the identification of new prognostic markers to decide the appropriate therapeutic strategy; surgery only in patients with a localized disease, systemic chemotherapy in patients with locally advanced or metastatic disease and palliative or supportive treatment for patients with biliary obstruction, pain or declining performance status (3). At this scenario, the monitoring of circulating tumor cells (CTCs) in CCA patients emerges as valuable tool to improve the clinical intervention.

CTCs, rare cells that circulate in the blood of cancer patients originating either from primary tumors or metastases, have clearly demonstrated prognostic value in a number of metastatic diseases. Baseline epithelial CTC counts were prognostic for patient survival in metastatic breast (4), colorectal (5), prostate (6), and lung (7) cancers, among others. In non-metastatic cancers, CTCs are even rarer than in the metastatic setting. However, the subgroup of patients with detectable CTCs, usually comprising

10-20% of the patients, does have a considerable worse prognosis than those without CTCs (8,9). It is also important to note that, at least a subpopulation of CTCs, possibly hold all the necessary properties for the initiation of a metastatic tumor at a distant site, as recently reported in breast cancer (10).

Although many studies have demonstrated the association between the presence of CTCs and the increased risk of recurrence after surgery in patients with localized HCC or a poor evolution in metastatic HCC patients (11), little is known about the clinical impact of CTCs in patients with CCA. A recent work by the group of Lewis R. Roberts has now associated the presence of CTC with more aggressive tumor characteristics and independently associated with survival in 88 patients with CCA, prospectively enrolled at Mayo Clinic Rochester (12). In particular, the presence of ≥ 2 CTC in 17% of patients (HR, 2.5; 95%CI, 1.1-5.4; $P=0.02$) and ≥ 5 CTC in 9% of patients (HR, 4.1; 95%CI, 1.4-10.8; $P=0.01$) were both independent predictors of survival. Detection of CTC has been performed with the FDA approved Cell Search System technology, showing a sensitivity of 53% (≥ 1 CTC) in patients with distant extrahepatic metastasis, although more than 90% of positivity in EpCAM expression used for CTC immunoisolation has been previously described in CCA (13). This sensitivity drops to 37% when ≥ 2 CTC was used as cut-off value, in concordance with a previous report (14), and probably reflecting the limitations of a simple epithelial marker for the isolation of the subpopulation of tumor cells with metastatic potential that may exhibit a high level of plasticity (15).

The apparent limitation of an ongoing technical development for reliable isolation and detection of an expected heterogeneous population of CTCs does not preclude the high potential of real-time CTCs monitoring in CCA clinical practice. An improved stratification of patients based on the detection of CTC as a complementary assessment of tumor burden and extension, should help defining patients suitable for liver transplantation or biliary stenting. In this sense, the study of Lewis and collaborators demonstrated that CTC levels ≥ 2 or 5 were associated with an extensive tumor burden in terms of bigger tumor size, presence of multinodular and bilobar disease, lymph node infiltration and distal metastasis. These results support the value of CTCs to avoid inefficient surgery approaches. Likewise, patient recruitment to trials combining chemotherapy with photodynamic therapy should also benefit from CTCs detection. But more interestingly, CTC detection represents a promising alternative to physical examination, CT scan and laboratory biomarkers like CA 19-9, for follow-up of patients after surgery or assessment of therapy response. Regarding chemotherapy, with modest survival benefits recorded by the latest recommendation of treating advanced or metastatic disease with gemcitabine and cisplatin, CTCs detection signifies an excellent companion for the translation of targeted therapies based on emerging evidence from laboratory and/or molecular studies to clinical trials and outcomes. As a devastating malignancy with a worldwide increasing incidence, a late diagnosis and an associated high mortality, with surgical resection as the only chance for cure, and a limited benefit for chemotherapy and radiotherapy in combination with liver transplantation or palliative treatments, CCA is clearly needed for new clinical tools like CTCs detection leading to a better management of patients. Importantly, although new studies including a bigger and more homogenous population are required to state the clinical significance of CTCs in CCA, the work by Yang and co-workers represents a robust evidence to go ahead with the clinical implementation of CTCs analyses to reach a personalized medicine for these CCA patients.

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Footnote

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References

1. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. *Cancer* 1995;75:171-90.
2. Bridgewater J, Galle PR, Khan SA, et al. Guidelines for the diagnosis and management of intrahepatic cholangiocarcinoma. *J Hepatol* 2014;60:1268-89.
3. Schweitzer N, Vogel A. Systemic therapy of cholangiocarcinoma: From chemotherapy to targeted therapies. *Best Pract Res Clin Gastroenterol* 2015;29:345-53.
4. Cristofanilli M, Budd GT, Ellis MJ, et al. Circulating tumor cells, disease progression, and survival in metastatic breast cancer. *N Engl J Med* 2004;351:781-91.
5. Cohen SJ, Punt CJ, Iannotti N, et al. Relationship of circulating tumor cells to tumor response, progression-free survival, and overall survival in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:3213-21. Erratum in *J Clin Oncol* 2009;27:1923.
6. de Bono JS, Scher HI, Montgomery RB, et al. Circulating tumor cells predict survival benefit from treatment in metastatic castration-resistant prostate cancer. *Clin Cancer Res* 2008;14:6302-9. Erratum in *Clin Cancer Res* 2009;15:1506.
7. Krebs MG, Sloane R, Priest L, et al. Evaluation and prognostic significance of circulating tumor cells in patients with non-small-cell lung cancer. *J Clin Oncol* 2011;29:1556-63.
8. Pierga JY, Bidard FC, Mathiot C, et al. Circulating tumor cell detection predicts early metastatic relapse after neoadjuvant chemotherapy in large operable and locally advanced breast cancer in a phase II randomized trial. *Clin Cancer Res* 2008;14:7004-10.
9. Thorsteinsson M, Söletormos G, Jess P. Low number of detectable circulating tumor cells in non-metastatic colon cancer. *Anticancer Res* 2011;31:613-7.
10. Baccelli I, Schneeweiss A, Riethdorf S, et al. Identification of a population of blood circulating tumor cells from breast cancer patients that initiates metastasis in a xenograft assay. *Nat Biotechnol* 2013;31:539-44.
11. Schulze K, Gasch C, Staufer K, et al. Presence of EpCAM-positive circulating tumor cells as biomarker for systemic

- disease strongly correlates to survival in patients with hepatocellular carcinoma. *Int J Cancer* 2013;133:2165-71.
12. Yang JD, Campion MB, Liu MC, et al. Circulating tumor cells are associated with poor overall survival in patients with cholangiocarcinoma. *Hepatology* 2015. [Epub ahead of print].
 13. de Boer CJ, van Krieken JH, Janssen-van Rhijn CM, et al. Expression of Ep-CAM in normal, regenerating, metaplastic, and neoplastic liver. *J Pathol* 1999;188:201-6.
 14. Al Ustwani O, Iancu D, Yacoub R, et al. Detection of circulating tumor cells in cancers of biliary origin. *J Gastrointest Oncol* 2012;3:97-104.
 15. Joosse SA, Gorges TM, Pantel K. Biology, detection, and clinical implications of circulating tumor cells. *EMBO Mol Med* 2014;7:1-11.

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