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Combining circulating tumor cells (CTCs) and circulating cancer associated macrophage-like cells (CAMLs) for accurately predicting responsiveness of new line therapies in late stage cancers

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ABSTRACT

The discovery of cancer associated macrophage like cells (CAMLs) as independent prognostic indicators of survival has highlighted the need for more in depth analysis of blood based diagnostics. We have previously demonstrated CAMLs are cancer specific giant polyploid cells circulating in the blood of patients which appear prognostic for overall survival (OS). Further, it is well established that Circulating Tumor cells (CTCs) transit the circulatory system and are also prognostic for OS. As CTCs & CAMLs are isolated in parallel from a single blood sample and both are prognostic for therapy response, we hypothesized that monitoring CTCs & CAMLs before and after initiation of therapy might increase their prognostic value in a large array of cancer subtypes.

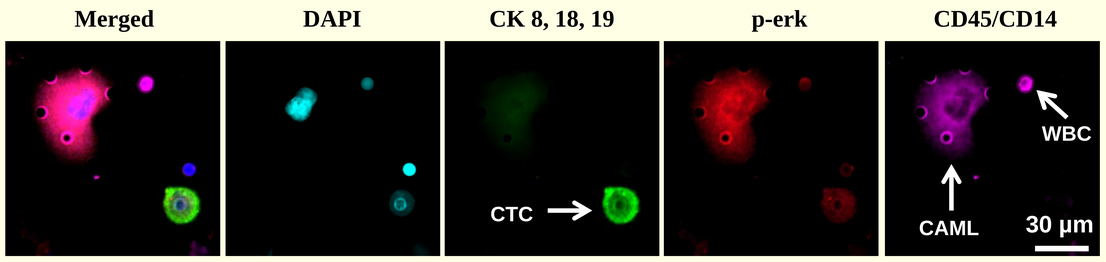


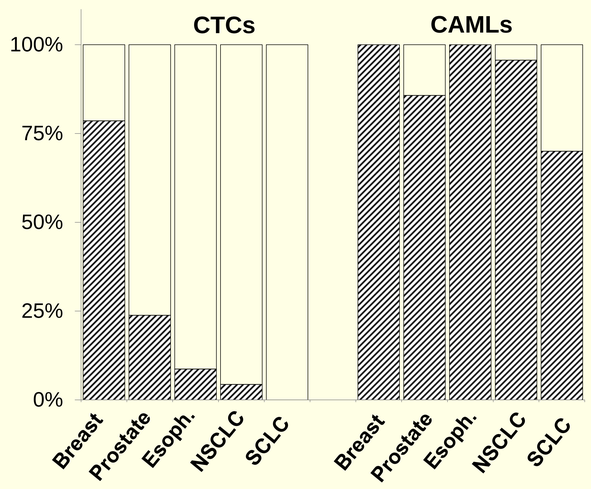
Figure 1. Example of CTC isolated with a CAML in a breast cancer patient. CTCs are Cytokeratin positive (green) and CD45/CD14 negative. In contrast, CAMLs are CD45/CD14 positive (purple) and may be weakly positive for Cytokeratin (green). White blood cells (WBCs) are normal sized CD45/CD14 positive cells.

INTRODUCTION

CAMLs are specialized myeloid polyploid cells transiting the circulation of patients in various types of solid malignancies whose size increase is prognostic for survival[1-3]. While CAMLs are easy to identify by their large size and polyploid nucleus, they appear to present as stem cell like phenotype with multiple heterogeneous epithelial, myeloid, and angiogenic markers. CTCs are cancer cells that originate from a primary solid tumor and are found transiting the circulatory system. While CTCs have been shown to be an indicator of metastatic malignant disease and predict survival outcomes in late stage patients, CTCs are not detected in all disease stages and rare a number of cancers (e.g. NSCLC and Esophageal).

Size exclusion is the only known technique for isolating large cells from peripheral patient blood irrespective of their surface markers. CellSieve™ microfilters are size exclusion membranes which efficiently isolate CAMLs and CTCs from whole blood, making it possible to study both cell types in parallel as they relate to malignant disease[1-4].

Figure 2. Positivity of CTCs and CAMLs by Cancer

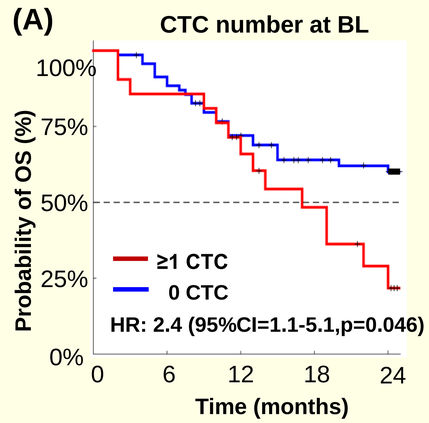


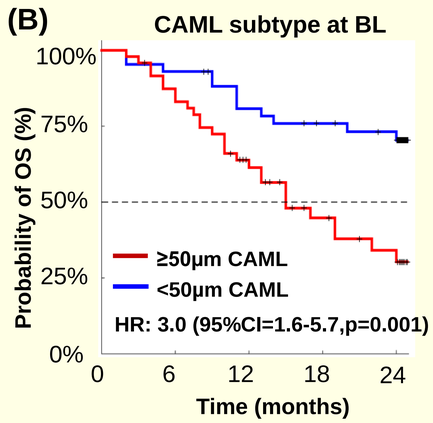
MATERIALS & METHODS

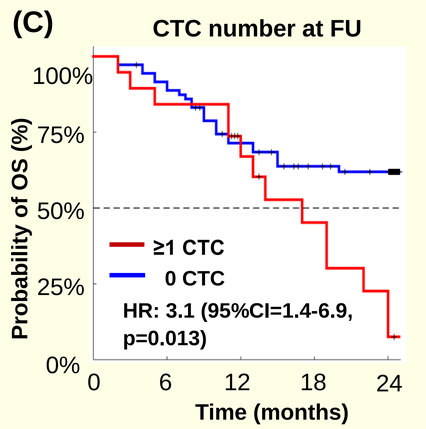
A prospective 2 year blind multi-institutional study was undertaken to evaluate CTCs & CAMLs before, and after, induction of a new line therapy. Patients with breast (n=14), esophageal (n=23), NSCLC (n=23), prostate (n=21), and SCLC (n=10) in Stage III (n=53) or Stage IV (n=38) disease were recruited. A baseline (BL) blood sample was taken prior to induction of a new therapy and a 2nd sample (T1) taken after initiation of new systemic therapy (~30 days). Blood was filtered by CellSieve™ filtration at 5 institutions and stained for cytokeratin 8, 18, & 19, CD14 and CD45. The CTCs were enumerated and CAMLs were sized by ≥50µm, both previously defined prognostic parameters. OS hazard ratios (HRs) were run by censored univariate & multivariate analysis.

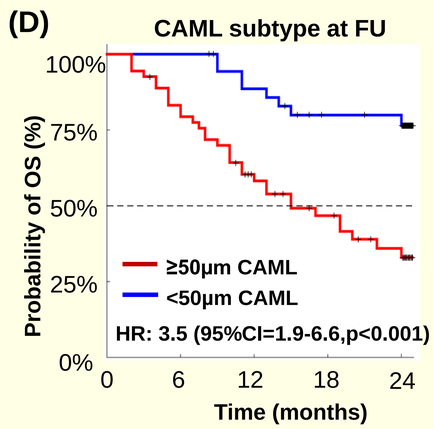
RESULTS

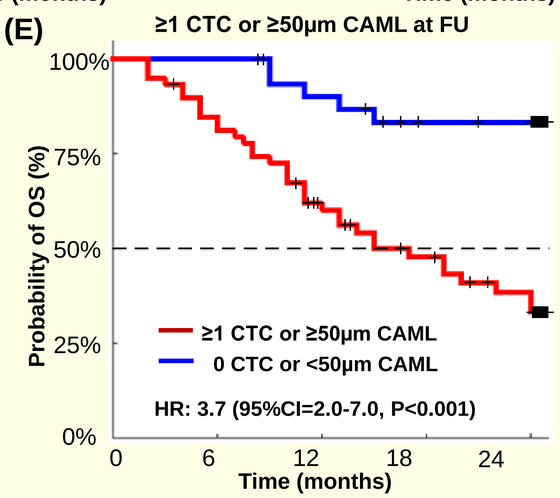
- CTCs were identified in 21% of patients at BL and 23% at follow-up (FU) with both being prognostic for OS (Fig. 1)
- CTCs were rare in lung (6%), esophageal (4%) and prostate (24%), but common in breast (79%)
- CAMLs were common, found in 92% of BL samples and 98% of FU samples with both times being prognostic for OS (Fig. 1)
- After induction of systemic therapy, ≥1 CTCs or a ≥50µm CAML was highly prognostic for OS and 75% accurate at predicting OS over 24 months











CONCLUSIONS

- In the first large scale prospective study on the clinical utility of CAMLs and CTCs, both cell types were prognostic for OS in invasive solid cancers.
- A single CTC at BL (Fig A) or FU (Fig C) was associated with poorer OS.
- A single ≥50µm CAML at BL (Fig B) or FU (Fig D) was also associated with poorer OS.
- In a multivariate analysis, CAML size was the most predictive variable for OS and independent of other clinical variables, while CTC presence was associated with metastasis
- Simultaneous measurement of both CTCs and CAMLs may increase the prognostic value of blood based diagnostics and may be predictive of benefit of subsequent therapies. (Fig. E)

References

1. Adams DL, et al "Circulating giant macrophages as a potential biomarker of solid tumors." Proc Natl Acad Sci, 2014, 111(9):3514-3519
2. Mu et al, Detection and Characterization of Circulating Tumor Associated Cells in Metastatic Breast Cancer" *Int. J. Mol. Sci.* 2016, *17*(10), 1665
3. Cristofanilli M, "Liquid Biopsies in Solid Tumors" *Springer Intl Publish.* 2017
4. Adams DL, et al, "Sequential tracking of PD-L1 expression and RAD50 induction in circulating tumor and stromal cells of lung cancer patients undergoing radiotherapy" *Clin Can Res. 2017. 23(19):5948-5958*

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