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Real time monitoring of solid tumor progression by circulating stromal cells in early and late stage disease

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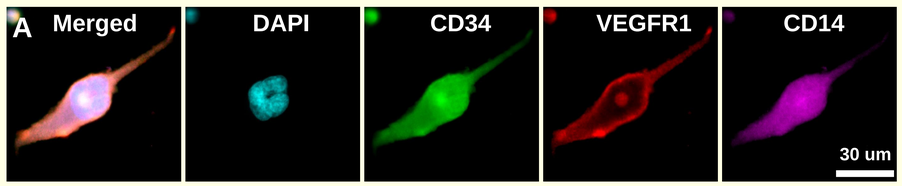
ABSTRACT

Blood based biomarkers (PSA, CEA, CA125) are used to track real time progression of disease in parallel with imaging. However while numerous blood biomarkers exist, they are specific to cancer type (i.e. PSA to prostate and CEA to colon) and may not appear in all diseased individuals. Recently cancer associated macrophage-like cells (CAMLs), a circulating stromal cell subtype, were identified in various solid cancer types which were observed increasing in size and in hyperlploidy during progressive disease. To assess whether CAML enlargement is a biomarker of progression/response, we tracked CAML growth/shrinkage in a pilot study of patients (n=34). Blood was drawn from patients with lung, prostate, or breast cancers over a 3 month period, baseline through 2 treatment cycles, followed by continued monitoring for 2 years. These data suggest that morphological assessment of CAMLs (growth/hyperploidy) appear to parallel cancer progression, or response to treatment, in multiple solid tumors.



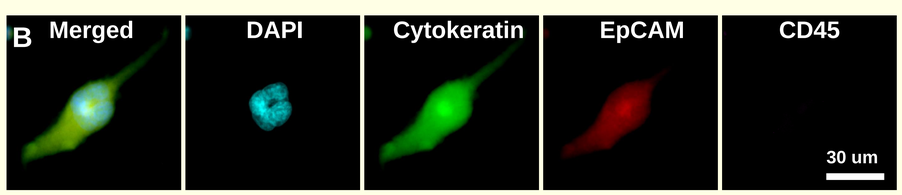


Figure 1. Example of subtyping markers on CAMLs, including epithelial (Cytokeratin/EpCAM), white blood cell (CD45), myeloid (CD14), & stem (CD34).

INTRODUCTION

CAMLs are specialized myeloid polyploid cells transiting the circulation of patients in various types of solid malignancies and appearing in all stages of cancer[1-4]. 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 endothelial markers.

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 circulating tumor cells (CTCs) from whole blood, making it possible to study both cell types in relation to malignant disease[1-4].

MATERIALS & METHODS

A prospective multi-institutional study used anonymized peripheral blood samples from 34 cancer patients undergoing therapy [stage I (n=2), II (n=3), III (n=8) & IV (n=21)] with breast (n=10), lung (n=16), & prostate (n=8). Samples were taken prior to therapy (BL), at ~1 month (FU1) follow up and a ~3 month (FU2) follow up, after induction of therapy. Blood was processed by the CellSieve™ microfiltration technique at 4 institutions and stained for cytokeratin 8, 18 & 19, CD14 and CD45. After identification and quantification CAMLs were measured based on hyperploidy and cell size.

Figure 2. Analysis of PFS at BL vs FU2 based on size of CAMLs

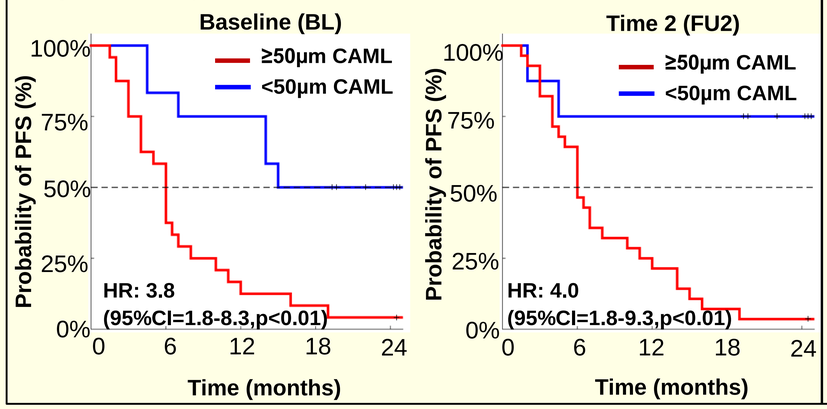
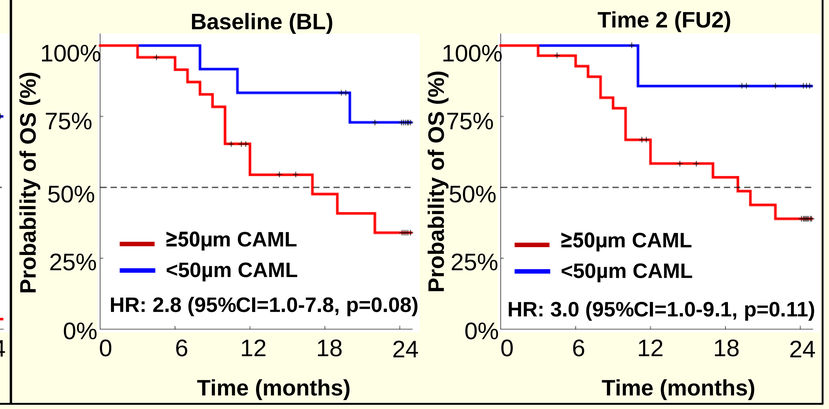


Figure 3. Analysis of OS at BL vs FU2 based on size of CAMLs



RESULTS

- CAMLs were found in 97% of cancer patients at BL, 97% at FU1 and 94% at FU2
- Over 2 years 7 patients showed no clinical disease progression (blue), while 29 patients had observable clinical disease progression (red).
- Of the patients with no progression (blue, n=7), 1 had CAMLs of ≥50µm at all time points while 6 had only small CAMLs at all time points
- Of the 29 patients that progressed,
  - 22 patients had ≥50µm CAMLs at all time points;
  - 5 patients had <50µm CAMLs at BL which increased in size by FU2;
  - 1 patient had ≥50µm CAMLs at BL that decreased by FU2
  - 1 patient had small CAMLs at all time points

CONCLUSIONS

- We show that increased CAML enlargement compared to baseline indicate shorter PFS in a variety of cancer types.
- By monitoring CAML changes overtime for individual patients we demonstrated ongoing progression, or response, in tumors correlates to the enlargement, or shrinkage, in CAMLs at follow up time points after treatment induction.
- This pilot study suggests that CAMLs have the potential to monitor the progression/regression of malignancy in real time and suggests the need for larger validation studies.

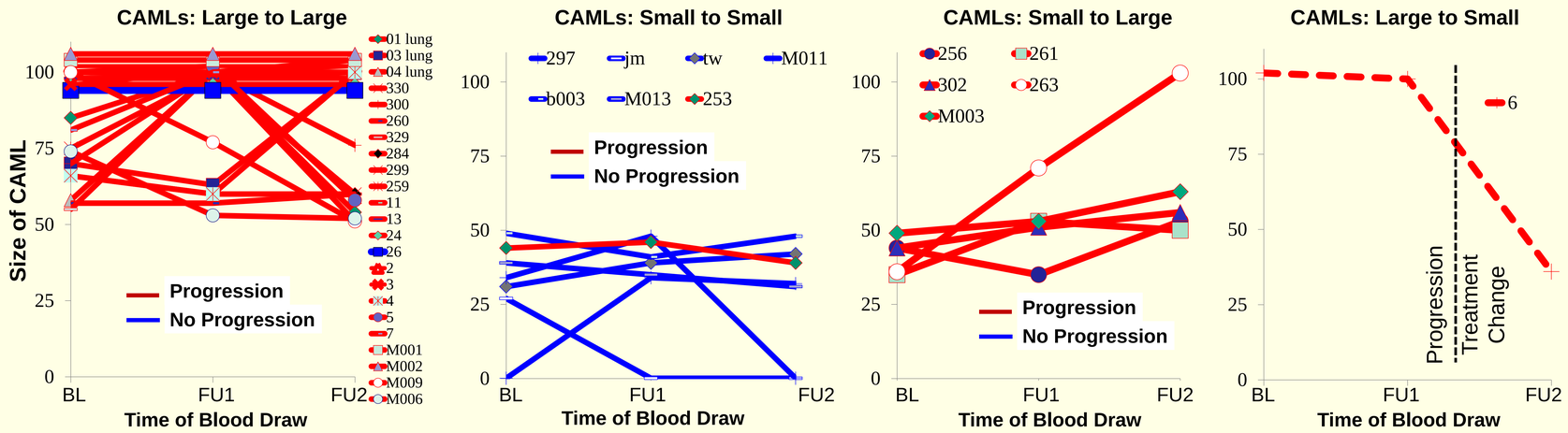


Figure 4. Increase in CAML size from baseline indicates poor response to treatments.

References

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