

**Title**

Circulating Tumor Associated Cells in Breast Cancers are Resistance Educated towards Prior Anthracycline Treatments.

**Authors**

Ajay Srinivasan, Dadasaheb Akolkar, Darshana Patil, Sewanti Limaye, Raymond Page, Anantbhusan Ranade, Revati Patil, Sanket Patil, Vishakha Mhase, Vineet Datta, Sachin Apurwa, Sushant Pawar, Rajan Datar

**Abstract:**

Background:

Doxorubicin and Epirubicin are two anthracycline agents commonly used in treatment of breast cancers. However, chemoresistance towards these agents and subsequent treatment failures are commonly reported. There are presently no means for real-time monitoring of innate and acquired chemoresistance. Repetitive invasive biopsies to obtain tumor tissue for in-vitro chemoresistance profiling (CRP) or viable tumor are not feasible. We describe a non-invasive approach for CRP using peripheral blood Circulating Tumor Associated Cells (C-TACs).

Materials and Methods:

We obtained 15 mL peripheral blood from 1034 known cases of breast cancers, among whom 353 were therapy naïve and 681 were pre-treated. Viable C-TACs were enriched and harvested from PBMCs using an epigenetically active media that selectively kills normal cells and simultaneously confers survival benefit on apoptosis-resistant cells of tumorigenic origin. Surviving cells (C-TACs) confirmed by immunostaining (EPCAM+, CK+, CD45±, GCDFP+). Viable C-TACs were seeded into multi-well plates and treated with Doxorubicin or Epirubicin and surviving C-TAC fraction was measured to determine % cell-death and chemoresistance.

Results:

Among therapy naïve patients (n = 353), innate resistance towards Doxorubicin and Epirubicin was observed in 44% and 46% of samples respectively (overall innate resistance = 45%). Among pre-treated patients (n = 681), acquired resistance towards Doxorubicin and Epirubicin was observed in 81% of samples.

*In press*

Conclusion:

Our study demonstrates the feasibility of CRR profiling of C-TACs in therapy naïve and pretreated patients. Adoption of C-TAC - CRR profiling can non-invasively provide real time oversight towards treatment selection, monitoring of drug resistance and timely therapeutic course correction.