Clinical Utility of Circulating Tumor Cells Enumeration in Breast Cancer Prognosis

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GVK BIO
Accelerating Research

Background

The cells that escape from the primary tumor and settle down at a secondary site to cause metastasis are called Circulating Tumor Cells (CTC).

Molecular characterization of CTC play a crucial role in cancer research as they can be used to confirm the disease malignancy, help stratifying patients for individual therapies, and predict treatment response.

CTCs are considered as a potential blood marker as their presence at baseline is strongly associated with poor prognosis and whose changes under treatment are correlated with Progression-Free Survival (PFS) and Overall Survival (OS) in cancer patients.

Recent technical advancements in CTCs detection include RT-qPCR methods, image-based approaches like the FDA cleared CellSearch system.

In spite of having sensitive assays, the prognostic significance of CTCs in patients with metastatic breast cancer is controversial. There is a need to improve sensitivity, reproducibility and reliability of their use in disease monitoring.

Objective

Our objective was to collate the published information on all clinical studies where CTC count was taken as basis to understand metastatic breast cancer and analyze the following –

How changes in CTC count is associated with Progression-free survival, Overall survival using the predefined 5 CTC/7.5ml threshold in metastatic breast cancer patients?

How CTC count is correlated to other tumor markers?

How CTC count is associated with hormonal status of diseased patients?

How CTC count differ in patients at baseline and after therapy?

GOBIOM Database

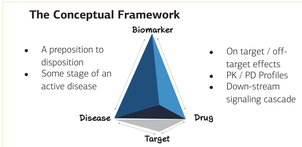
GVK BIO Online Biomarker Database (GOBIOM) is a comprehensive biomarker database that provides information on Biochemical, Genomic, Imaging, Metabolite, Clinical Scoring scales and Cellular markers for 16 different therapeutic areas, covering 750 therapeutic indications with its reported utilities like diagnosis, prognosis, monitoring disease progression, treatment response, surrogate, efficacy and toxicity.

Data is manually curated from

- Authenticated clinical trial registries
- Validated clinical trial results from pharmaceutical and biotech companies
- Annual meetings focused on different therapeutic areas
- A large number of peer-reviewed journals
- Other web resources and patents

Database is developed in collaboration with a big pharma and USFDA.

The Conceptual Framework



- A preposition to disposition
- Some stage of an active disease
- On target / off-target effects
- PK / PD Profiles
- Down-stream signaling cascade

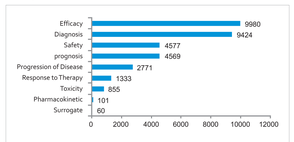
The Proprietary Tetrahedron database model evolved in conjunction with relevant industry participants, allows the user in understanding the complexity of the process involved in biomarkers discovery and validation.

A proprietary tetrahedron model is adopted in the framework of database by linking biomarkers, indication, drug, target and study population. This model simplifies the process of biomarker data.

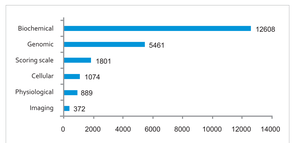
GOBIOM Statistics

Therapeutic Area	# Biomarkers	# Indications
Oncology	10480	175
Diseases of the circulatory system	1709	130
Endocrine, nutritional and metabolic diseases	1519	99
Diseases of the musculoskeletal system and connective tissue	1473	38
Diseases of the nervous system	1124	52
Others	1080	1
Mental and behavioral disorders	946	41
Diseases of the digestive system	891	46
Diseases of the respiratory system	822	32
Infectious and parasitic diseases	800	42
Diseases of the genitourinary system	583	37
Injury, poisoning and certain other consequences of external causes	266	11
Diseases of the skin and subcutaneous tissue	261	19
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	154	13
Diseases of the eye and adnexa	93	14
Diseases of the ear and mastoid process	4	1
Total :	**22205**	**751**

Utility of Biomarkers



Types of Biomarkers



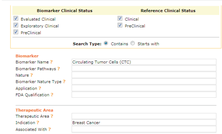
Methodology

GOBIOM
GVK BIO Online Biomarker Database

Following steps were carried out in the analysis

- Entire published information on CTC and its association with breast cancer prognosis was extracted from GOBIOM database.
- Information from 107 references (including journals, patents, scientific conferences) was present in GOBIOM as on 5th March 2013

Search Criteria



Using the intuitive features of GOBIOM, data was filtered in the following manner for further analysis

- Out of 107 references, only datapoints on metastatic breast cancer was considered. This is obtained by using 'disease subtype' filter in GOBIOM database.
- CTC count and its association with endpoints like PFS, OS, tumor markers was extracted along with the details of study population and sample size from 'experimental details' section.

Following are the snapshots from the 'experimental section' of the database

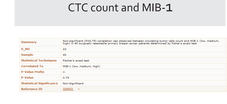
CTC Vs tumor stage

CTC count at baseline

CTC count and Estrogen receptor status

CTC count and its correlation with OS, other tumor markers and hormonal positivity was extracted from 'biomarker statistics' section

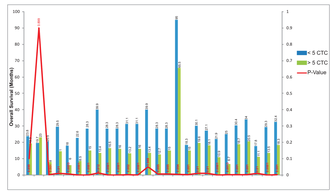
CTC count and MIB-1



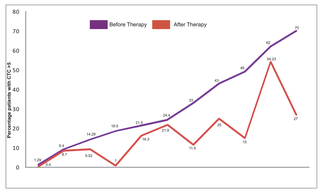
Correlation between CTC count and overall survival

Summary level study was carried out to understand the relation between CTC versus Overall Survival (OS), Progression-Free Survival (PFS), and its correlation with other tumor markers and hormonal positivity

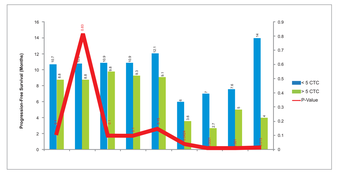
Analysis



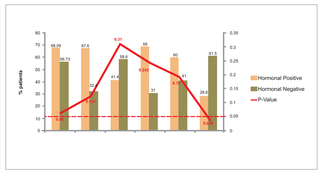
Overall survival (Months) in patients with CTC>5 Vs <5
Total No. of studies: 26
No. of patients analysed: 3271



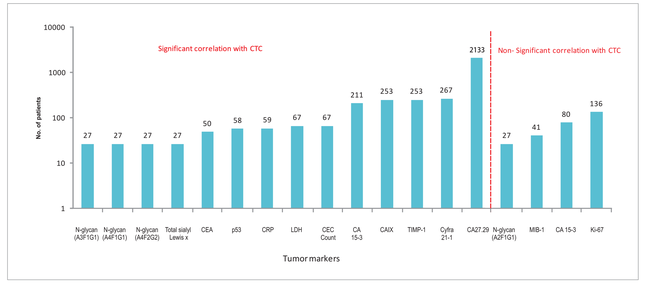
Percentage population with CTC >5
Total No. of studies: 11
No. of patients analysed: 6182



Progression-Free survival (Months) in patients with CTC>5 Vs <5
Total No. of studies: 9
No. of patients analysed: 1197



Percentage of patients with Hormonal status (ER, PR or Both) Vs CTC>5
Total No. of studies: 6
No. of patients analysed: 1070



No. of patients with CTC positivity (>1) Vs tumor markers
Total No. of studies: 18
No. of patients analysed: 3382

Conclusion

CTC is concluded as a good prognostic marker in 35 studies, with a total sample size of 4468 patients, with a good correlation to Overall survival and Progression-Free survival

There was no association found between CTC and Hormonal status (ER, PR) in 5 out of 6 studies with a total sample size of 1070 patients.

Out of 18 studies, 14 studies showed significant correlation between CTC count and tumor markers while 4 studies showed non-significant correlation.

There was no clear correlation observed in CTC count of patients at baseline and after therapy.

Though CTC enumeration is considered as a potential method to detect prognosis, further studies are required to explore the clinical utility of CTC in metastatic breast cancer.

Database Strengths

Data Content

- Biomarker nature
- Therapeutic indication
- Utilities of biomarker
- FDA/EMEA approval data for biomarkers and associated assay methodologies
- Analytical and Clinical qualification
- Drugs/Intervention details
- Endpoints observed
- Efficacy and Safety characteristics
- Clinical and Preclinical qualification
- Study population
- Drug-Induced organ toxicities

Data Features

- Web-enabled search application for quick and easy access
- Controlled vocabulary through out
- Instant generation of 'biomarker report'
- Data export options in custom format to Excel, XML and PDF
- Intuitive User Interface with comprehensive search features
- "Alert a Colleague" option to share the data with other users
- Biweekly update with auto alert function
- Custom alert by therapeutic area and biomarker name
- A dedicated server located in USA with backup server in India
- Provision of user-required data in their own formats
- Easy integration with client proprietary data
- Alert service on new marker addition or updates of existing markers
- On-demand service for any biomarker addition into the database
- Competitive intelligence analysis
- On-demand training sessions

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