What makes us human?

Prologue
Cancer: The Emperor of All Maladies

The term "cancer" was derived from an observation by Hippocrates more than 2,300 years ago that the long, distended veins that radiate out from some breast tumors look like the limbs of a crab. From that observation came the term karkinoma in Greek, and later, cancer in Latin. With the work of Hooke in the 1600s, and then Virchow in the 1800s, came the understanding that living tissues are composed of cells, and that all cells arise as direct descendants of other cells [Mukherjee S. et al; 2010]. Cancer, we now know, is a disease caused by the uncontrolled growth of a single cell. This growth is controlled by mutations that specifically affect genes that stimulate unlimited cell growth. In a normal cell, powerful genetic circuits regulate cell division and cell death. In a cancer cell, these circuits have been broken, unleashing a cell that cannot stop growing. Normal cell division allows the organisms to grow, to adapt, to recover, to repair-to live, distorted and unleashed. Whereas, the mutated genetic circuits allows cancer cells to grow, to flourish, to adapt, to recover, and to repair—to live at the cost of our living. Cancer cells grow faster and adapt better.

Cancer, by definition, is a disease of the genes. A gene is a small part of DNA, which is the master molecule of the cell. The cells in our body are growing, dividing, and replacing themselves. Many genes produce proteins that are involved in controlling the processes of cell growth and division. An alteration or mutation in the DNA molecule can disrupt the genes and produce faulty proteins. This causes the cell to become abnormal and lose its restraints on growth. The abnormal cell begins to divide uncontrollably and eventually forms a new growth known as a "tumor" or neoplasm. The secret to battling cancer, then, is to find means to prevent these mutations from occurring in susceptible cells, or to find means to eliminate the mutated cells without compromising normal growth. Therefore, the genetics studies have an enormous significance in cancer research. Malignant growth and normal growth are so genetically intertwined that unbraiding the two might be one of the most significant scientific challenges faced by human. Cancer is built into our genomes: the genes that release
from normal cell division are not foreign to our bodies, but rather mutated, distorted versions of the very genes that perform vital cellular functions [Pierotti MA. et al; 2010].

The burden of cancer worldwide varies across countries according to differences in risk factors, detection practices, treatment availability, age structure, and completeness of reporting. According to estimates from the International Agency for Research on Cancer (IARC 2008), there were 12.7 million new cancer cases in 2008 worldwide, of which 5.6 million occurred in economically developed countries and 7.1 million in economically developing countries. The corresponding estimates for total cancer deaths in 2008 were 7.6 million (about 21,000 cancer deaths a day), 2.8 million in economically developed countries and 4.8 million in economically developing countries [Ferlay J. et al; 2010]. Overall, the number of people dying from cancer worldwide was projected to grow more than 16 million in 2050 because cancers in developing countries more often result in death largely because they are generally diagnosed at late stage and the resources for early detection and treatment are limited [DeVita VT. et al; 2011]. The early diagnosis of leukemia and other hematological malignancies is more difficult because of various factors.

The total incidence of Leukemia was 5 per 100,000 and newly diagnosed cases in year 2008 were more than 350,434. The number of newly diagnosed Acute Leukemia (AL) cases in the year 2008 was projected more than 300,000 worldwide, that is 2.8% of all cancers. The corresponding numbers of deaths of patients with AL were 257,000 globally, that is 3.4% of all cancers. The total mortality ratio of AL was 3.6 per 100,000. The numbers of newly diagnosed AL cases in the year 2008 were projected more than 33,307 that is 3.5% of all cancer in India. The total incidence of AL was 3 per 100,000. The corresponding numbers of AL deaths were 26282 that is 4.1% of all cancer in India. The total mortality ratio of AL was 2.5 per 100,000 [Ferlay J. et al; 2010]. In India frequency of acute lymphoblastic leukemia (ALL) is 15 -25% of overall AL incidence and the annual incidence rates of ALL is 30.9 per million populations [Venkateswaran SP. et
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al; 2012]. ALL is characterized by physical examination, morphology, Immunophenotype and most importantly by cytogenetic and molecular genetic studies.

The cross-fertilization between cytogenetics and molecular genetics has led to conceptually new advances and insights into the fundamental cell biology mechanisms that are disrupted when neoplastic transformation occurs. In addition, the clinical usefulness of cytogenetic abnormalities as diagnostic and prognostic aids in acute leukemia has been increasingly appreciated. The ultimate goal of cytogenetic is to establish diagnosis and to identify specific therapies individualized to counter those molecular mechanisms that have gone twisted during leukemogenesis. Accordingly, cytogenetic and molecular analyses are considered obligatory for analyzing outcomes of many clinical trials, and detection of specific chromosome aberrations or their molecular equivalents, such as t(9;22)(q34;q11.2) and BCR-ABL1, is used to assign ALL patients to specific targeted therapy (Imatinib Mesylate). Following this breakthrough for targeted therapies many similar success stories are unfolding as; cancer genetic research helps to obtain more effective and less toxic treatments for malignant diseases. Thus, in the little over 100 years since Von Hansemann’s initial report [Hansemann VD. et al; 1890], cancer cytogenetics has come of age. It is no longer a purely descriptive discipline but the one that attempts to synthesize information from several investigative approaches. Cancer cytogenetics has become both a central methodology in basic cancer research and an important clinical tool in oncology [Harrison CJ. et al; 2009]. Recurrent chromosome changes are distinctive features of tumors. Specific aberrations are markers for prediction of disease outcome, response to therapy and identifiers of genes for targeted therapy or prevention. The less common cytogenetic sub-clones provide clues to disease progression, and serve as diving boards for gene identification by molecular methods. Documentation is warranted in all the recurrent findings for possible prognostic significance and for improving biological understanding of leukemias.
Cytogenetics has remained the "gold standard" tool for the genetic classification of ALL. Applications of the cytogenetic data have played a pivotal role in the diagnosis, treatment, and prognosis of ALL patients. The usual clinical applications of cytogenetic studies of acquired abnormalities are to; (1) establish the presence of a malignant clone (2) establish the diagnosis (3) indicate a prognosis (4) assist with the choice of a treatment strategy (5) monitor response to treatment and (6) support further research for better management of the disease.

In the recent years, the applications of conventional and molecular cytogenetic approaches have documented different structural and numerical abnormalities. The total number of leukemia cases in which clonal cytogenetic abnormalities have now exceeds to huge numbers: 61,846. To date, almost 8834 patients are reported with cytogenetic abnormalities in ALL [Mitelman F. et al; 2013]. Several of the ALL specific chromosome aberrations and their molecular counterparts have been included in the 2008 World Health Organization (WHO) classification of ALL. Morphology, cytochemistry, immunophenotyping, and clinical characteristics are together being used to define individual disease entities [Campo E. et al; 2011]. New abnormalities are added every year, because state-of-the-art technologies are increasingly being introduced into ALL diagnostics which include Fluorescent In Situ hybridization (FISH), Multiplex-FISH (M-FISH) and array based analysis.

One of the major challenges in developing a more sophisticated cytogenetic profile of ALL and assessing the utility of cytogenetics is that there are no reports clearly describing the incidence of ALL in developing countries [Pullarkat V. et al; 2008, Mac Nally RJQ. et al; 1999]. The most important studies about outcome of ALL are reported from developed countries, whereas most of the patients with this disease are in developing countries [Charafeddine KM. et al; 2009]. Moreover, there is scarcity of data in the literature reflecting systematic clinical status of these patients including clinical features, description of prognostic factors and predictors of the outcome. There is a great paucity of documentation of characterization of cytogenetic abnormalities in ALL.
patients from India. ALL is one of the most challenging malignant diseases with respect to the intricacies of clinical presentation, diagnosis, and treatment. This investigation was therefore planned to study details of clinical features of ALL patients and presenting the significance of cytogenetic study and its role in translational cancer research for ALL patients. Therefore, the major aim of the present study was to evaluate the significance of cytogenetic studies at the time of clinical presentation and diverse cytogenetic changes with favorable, intermediate and unfavorable prognosis of a large number of ALL patients (n=273) from Gujarat Cancer and Research Institute (GCRI), Ahmedabad. The study was carried out on ALL patients at diagnosis and during/after anticancer treatment with following objectives:

Objectives:

1) Identification of chromosomal rearrangements at diagnosis and during/after anticancer treatment and their correlation with clinical parameters in terms of response to therapy and overall survival.

2) Characterization and documentation of known, rare and novel as well as random and non-random chromosomal rearrangements along with the clinical features.

3) Study of the prognostic significance of karyotypic subgroups with respect to various clinical and laboratory factors.

4) Study of clinical outcome of simultaneously present favorable and unfavorable cytogenetic subgroups.

5) Documentation and risk stratification of cytogenetic abnormalities for prognostic evaluation.

6) Study of the molecular mechanisms involved in variant translocations with the help of conventional and molecular cytogenetic tools.

7) Study of the significance of complex chromosomal rearrangement by applying M-FISH.
8) Evaluation of the prognosis in terms of treatment outcome, conventional chemotherapy i.e. MCP841 in all patients and targeted therapy i.e. Imatinib mesylate for ALL patients having t(9;22).

9) Documentation of a large cohort of patients to evaluate the relative roles of Conventional Cytogenetic (CC) and FISH in the classification of ALL.