OVERCOMING THE CHALLENGES IN THE TREATMENT OF STAGE IV BREAST CANCER BY USING NOVEL NANO DEVICES

Sri Balaji Prabhu Jothiramalingam*1

*1B.Tech, Department of Biotechnology, Kumaraguru College of Technology, Coimbatore, Tamil Nadu, India.

ABSTRACT

Nanotechnology is the field of innovative research which involves the development and utilization of nanoparticles in atomic, molecular and cellular levels. Recent development in the Nano devices connects the bridge between science and medicinal field. Cancer involves group of diseases associated with abnormal growth and proliferation of cells with motile nature and spreads over the body causing complex challenges in the view of diagnosing and treatment. Cancer Nano technology is an interdisciplinary area of research combining engineering, science and medicine which provides an easier way of diagnosis and treatment of Cancer. 90% of cancer death is because of metastasis tumour growth. The emerging new technologies increases the survival rate but the complete cure of the disease is not assured. Chemotherapy, Radiotherapy and Endocrine therapy are the current treatments for cancer metastasis to be undergone for a long period of time for prolonged survival. They also leave side effects such as affecting healthier cells and making it more complex to deal with further treatments. Nanotechnology offers a solution by developing multifunctional nanoparticles that are capable to target only cancerous cells and neoplasms, the Nano devices provide controlled drug dosage at the targeted site, guided surgical resection of tumours from the targeted site and killing the disseminated cells and micro metastasis that intravasate into the blood cells and remains in the circulation. This review provides an overview on the metastasis development, challenges faced in the treatment of cancer by conventional treatment. It also illustrates about the alternative treatment with the Nano shells and Nano robots of Nano technology for efficient cancer therapeutic application of metastasis breast cancer in the future perspective.

Keywords: Nanotechnology, Cancer Nanotechnology, Metastasis, Nano shells and Nano robots.

I. INTRODUCTION

The dissemination of tumour cells from the primary site to the secondary sites of the body is referred as metastasis that accounts for 90% of mortality in the cancerous patients. It is reported that 17.3 Lakh new cases of cancer are admitted and over 8.8 Lakh Deaths are recorded all over India by Nation Research Cancer Prevention & Research. Breast cancer is found to be present in 25.8 women per 1,00,000 women in India. On the whole, it is reported that 35,000 women in India are living with breast Cancer including all age group which is based on the study done in 2017. The survival rate of 5 years after the diagnosis is predicted to be 90% in US Women and 60% in India. National Cancer Registry Programme in India observed that women in metropolitan cities are more susceptible to breast cancer. Socio-cultural factors and lack in the awareness about the diagnosis and treatment about the breast cancer result in metastatic stage that dominates the mortality rate. This is because the disseminated cells from the primary tumour get into the circulation and to other distant sites. There is a challenge to remove these cells since chemotherapeutic treatment focus on the primary cancerous site and during certain period of time the cancerous cells shows resistance towards the drug. The available radiation therapy often leaves more common side effects such as fatigue, hair loss, nausea, blurry vision, lymphedema and reduction in the white blood cells count. The combined therapeutic approaches are given to the breast cancer patients for prolonged survival but the effectiveness and curability is not proven. In the past few decades, Nanotechnology has paved its own path in the world of innovation by making a revolution in the field of medicine and introducing a new field called Nano medicine. Nano cancer technology comprised within this field, brought a novel development in the treatment of metastasis tumour which covered up the challenges faced with other conventional treatments. The conventional method not only destructs the diseased cells but also kills the healthy cells and it is solved by this system. The main goal of Nano medicine is targeted drug delivery system with minimal or no toxicity. Early diagnosis of cancerous cells in the patients is one such unsolved question which is made easier by Nano devices.
This review mentions the sequential stages of metastasis cancer and the overall challenges faced in the treatment. It includes the possible solution to overcome the difficulties of conventional cancer treatment with the help of developing Nanotechnology. It focuses on the current metastatic breast cancer treatment trials made in-vivo by the Nano devices.

II. OVERVIEW ON METASTASIS DEVELOPMENT

Overview on the Theory of Metastasis:
The metastatic stage is the Risk IV stage where cancer has spread from its origin to various distant sites of the body. Joseph Recamier coined the term Metastasis – Spread of Cancer derived from a Greek word. Rudolf Virchow was the first to link the origin of cancer cells from the normal cells by proposing the “Theory of Embolism”. He believed that the cancer cells broke off from the primary tumour invading via body fluids and giving rise to new deposits of tumour cells in other sites. The growth of tumour cells from primary site to this secondary site is explained by the “Seed and Soil Theory” proposed by Stephen Paget based on the analyses of 735 fatal cases of Breast Cancer in 1889. He referred the cancer cell as seeds and the distribution of the secondary growth can be analysed by studying the properties of the congenial soil that is the secondary organs. James Ewing in 1928 came up with the theory that cancer cells were directed to the secondary site by the direction of lymphatic and circulatory systems. Josh Fidler collectively merged the works of Virchow. Paget and Ewing and demonstrated that metastasis occurred in sequential steps which involves cancer cells of different metastatic capabilities interacting with their micro environment and the cells leaving the primary site and landing on the congenial soil.

Stages involved in Metastasis:
Metastasis is a multi-step process enclosing the (1) Angiogenesis- the development of new blood vessels to the primary tumours leads to the supplement of nutrients and oxygen by the blood cells for their survival,(2) Epithelial to mesenchymal transition in order to obtain the motile phenotype character,(3) Invasion - local infiltration of tumour cells into the adjacent tissues,(4) Intravasation- breaking of blood vessel and move into the circulation,(5) Survival in the circulatory system,(6) Extravasation – the tumour reach the target organs and (7) State of Dormancy- tumour cell placed in the soil for a period of time and then proliferates, which is detectable as clinical metastasis. The disseminated tumour cells from the primary site of size 1cm approx. 1 x 10⁹ cells can infiltrate the circulatory system with one million cancer cells per day. However, the colonization is limited due to micro-environment which leads to lethal death of few cells or further proliferation is inhibited. But less than 0.1% of disseminated cancer cells successfully promote the distal metastasis.

Table-1: Different Stages of Breast Cancer based on distant metastasis in women with an early sign of breast cancer from a population based Cohort study.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour size</th>
<th>Secondary Site Involved</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (Non-invasive)</td>
<td></td>
<td></td>
<td>No evidence of cancer cells</td>
</tr>
<tr>
<td>Invasive Stages</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IA</td>
<td>Tumour ≤ 2 cm in breast</td>
<td>-</td>
<td>No spread outside the breast</td>
</tr>
<tr>
<td>IB</td>
<td>Microscopic metastases (&gt; 0.2 mm but ≤ 2mm)</td>
<td>Axillary Lymph nodes</td>
<td>No tumour presence in the breast</td>
</tr>
<tr>
<td></td>
<td>Tumour ≤ 2 cm in breast</td>
<td>Lymph nodes</td>
<td>Involved both primary and secondary sites</td>
</tr>
<tr>
<td>IIA</td>
<td>Macroscopic Cancer (&gt; 2mm)</td>
<td>1-3 Axillary Lymph nodes</td>
<td>No tumour presence in the breast</td>
</tr>
<tr>
<td></td>
<td>Tumour ≤ 2 cm in breast</td>
<td>Axillary Lymph nodes</td>
<td>Involved both primary and secondary sites</td>
</tr>
<tr>
<td></td>
<td>Tumour &gt; 2 cm but ≤ 5cm</td>
<td>-</td>
<td>No spread to axillary lymph</td>
</tr>
</tbody>
</table>
### Challenges in the Treatment of Metastatic Breast Cancer:

There are numerous challenges put forth in the treatment of metastatic breast cancer, because tumour cells get disseminated from the primary site to other secondary sites in the body. Beyond that, the diagnosis of breast cancer is detected only when it reaches the metastatic stage. A further developmental study on biomarkers for early tumour detection is carried out by the research scientists. In the view of treatment, there are challenges faced in complete palliation of this disease with minimal toxicity and prolonged survival. Other issues that are yet to be unsettled are (1) Combination of drugs dosages to be taken, (2) Development of Novel targeted Biological Agents, (3) Treating patients with HER2 Overexpressing tumours after adjuvant therapy with trastuzumab, (4) Drug elimination in a short period of time, (5) Production of Critical driving molecules for the drug, (6) Novel therapeutic agents for Elimination of micro metastasis, (7) Serial monitoring of changes occurring in tumour in order to know the best time to obtain biopsies for therapeutic effect detection and (8) Toxicity Accumulation. These challenges are yet to be studied in detail and there is a need for different collaborative approaches to be considered in order to make effective recognized therapeutic treatments.

### Nanotechnology to Overcome the Challenges:

Nanotechnology shows its potential in different areas of science, medicine, engineering and Technology. Because of their robust size, approximately one hundred to ten thousand times smaller than human cells, they readily interact with biomolecules on both the surfaces and with internal organelles. In the field of medicine, the emerging interdisciplinary field, cancer nanotechnology brought various efficient methodologies that are potentially safer compared to conventional breast cancer treatment. The versatility of Nanoparticles makes the targeted delivery of multiple active agents which has the ability to target different sites of various types of cancer. The different challenges in the treatment of metastatic cancer are solved by the emerging nanotechnology field. The methodology in the drug delivery combined with nanotechnology provides (1) Enhance absorption of the drugs into selective cancer tissues, (2) Early

---

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIB</td>
<td>Tumour &gt; 2cm but ≤ 5cm in breast</td>
<td>1-3 Axillary Lymph nodes</td>
</tr>
<tr>
<td></td>
<td>Tumour &gt; 5cm in breast</td>
<td>-</td>
</tr>
<tr>
<td>IIIA</td>
<td>Size Associated with Metastasis</td>
<td>4-9 Axillary Lymph nodes and Internal Mammary nodes</td>
</tr>
<tr>
<td></td>
<td>Tumour &gt; 5cm</td>
<td>Axillary or Internal Mammary Nodes</td>
</tr>
<tr>
<td>IIIB</td>
<td>Tumour of Any Size</td>
<td>Chest wall, Skin of the Breast and Axillary or Internal Mammary Nodes</td>
</tr>
<tr>
<td>IIBC</td>
<td>Tumour of any Size</td>
<td>≥ 10 Axillary Lymph Node</td>
</tr>
<tr>
<td></td>
<td>Tumour of any size</td>
<td>Lymph nodes above or below the collarbone</td>
</tr>
<tr>
<td></td>
<td>Tumour of any size</td>
<td>Axillary Lymph nodes and Internal Mammary nodes</td>
</tr>
<tr>
<td>IV(Metastatic)</td>
<td>Tumour of any size or even clumps of cells</td>
<td>Liver, Lung, Bone and Brain</td>
</tr>
</tbody>
</table>

---

**III. ANALYSIS**
degradation of drugs is prevented, (3) Control the toxicity of drug towards other normal cells and (4) Intracellular penetration of drug is achieved. The elimination of micro metastasis is achieved using a target Nano biomarker agent. Numerous targets have been studied and identified, utilized in the surface functionalization of different types of nanoparticles and are under preclinical trials. Passive and Active targeting is achieved via Nano particulates and in conjugation with ligands for the latter. Imaging using nanotechnology has the promising of (1) Advanced early detection of tumours in the micro metastasis stage, (2) Determining the primary site and localized spreading state of cancer, (3) Conformation of successful removal of disseminated tumour cells over the body, (4) Monitoring the real time effect of therapeutics towards the cancer cells and (5) Guiding or targeting the drug towards the located cancer site. Thus, nanotechnology overcomes all the multiple biological barriers addressed and successfully meets the diagnostic and therapeutic goals.

IV. NANODEVICES IN THE TREATMENT OF METASTATIC BREAST CANCER

Metal Nano shells in the treatment of metastatic breast cancer:

One of the novel developments in the field of nanotechnology that attracted the engineers was to research upon the creation of metal Nano shells in the field of medicine. Due to the highly regulated optical properties, there emerged a new therapeutic treatment for metastatic cancer. Metal Nano shells carry a dielectric compound mainly silica enclosed by an ultrathin in terms of Nano sized shell, often Gold particles which are chemically inert owing to restricted reactivity with other biomolecules. The size and the adjustable optical properties are designed in a way that they either absorb or scatter the light of wavelength in visible region and in the infrared region of the nearest electromagnetic spectra. This makes the advantage in targeting the metastatic tumour cells that is eliminated and makes sure that there is no damage to the normal or healthy cells near the tumour spread area. The principle beyond this mechanism is the Nano shells are engineered so that the gold Nano particles are conjugated with tumour specific antibodies which actively binds to the desired tumour target. The tumour cells further phagocytize the Nano shells and they have the capacity to absorb the nearest infrared waves to maximal since the penetration power of these rays is so high into the tissues. The gold Nano shells absorb the Infrared wave produces heat leading to the destruction of cancer cells. Ramasamy et al constructed Nano shells with a dielectric mesoporous silica-capped gold Nano Rod proved to inhibit the breast tumour cell lines MCF-7 and MDA-MB-231 by arresting the cell cycle and effectively killing the cancer cells by induced apoptosis by suppressing the signalling pathways of proto oncogene protein kinase Src/FAK/ AKT. Caprin et al developed the Nano shells made up of silica-gold for the patients to whom the tumour cells are resistance to the drug Trastuzumab approved by the U.S. Food and Drug Administration (FDA) shows a clinical efficacy against HER2 genes. The Nano shells are conjugated with anti- HER2 antibody that binds to both trastuzumab resistant tumour cell line BT474 and normal tumour cell line MDA-MB-231 confirmed by the two photon laser scanning microscopy which is then ablated by nearest infrared laser. The result shows that the introduction of Gold Nano shells mediated Photo thermal therapy improves the tumour cell killing in combination with other conventional treatments for cancer therapy.

Nano Robots in the field of cancer treatment:

Nano Robots are also referred to as Nanobots. The field of Nanobots is emerging in nanotechnology which involves the construction of devices at atomic, molecular and cellular levels. Due to their compact size, they easily traverse into the human blood vessels and are designed to perform a specific task in a Nanoscale Dimension. The two approaches to build the Nanobots are (1) Positional Assembly and (2) Self Assembly. Positional Assembly involves the investigators to design the molecules one-by-one by microscopic devices and assemble them together. Self-Assembly is based on the natural tendency of the particles wherein they themselves assemble together to form a Robotic structure. Saxena et al reported that the scientists use the carbon atoms constructed in a diamondoid shape to act as an external part of Nanobots because of their strength and inert nature. Different Biomolecules such as carbohydrates, peptides, proteins, DNA and few others are used for design, depending upon the specific function to be performed. Mainly, Oxygen, Glucose molecules and other natural sugars in the body is used for the propulsion of this miniature device in the body. Venkatesan et al reported that, Nano robots offer a non-depressed therapy where the conventional chemotherapy methods destroy healthy and normal cells more than that of tumour cells in the patients. Douglas et al designed Nanobots with the biomolecule DNA. 2D chains of DNA molecules are folded to form 3D structures that selectively open and close. It carries Gold Nanoshells and an antibody that targets the cancer cell. Aptamer, sensing agent recognizes
the surface of the target tumour cell with the help of DNA hinge. The DNA container gets dissolved once it recognizes, and when the Gold Nanoshells penetrate into the tumour cells it induces a self-Destruction. Li, Suping et al developed Nano scale robots with DNA molecules that are programmed in a way to bind to the nucleolin proteins expressed by the tumour endothelial cells, loaded with thrombin molecules. This targeted delivery of therapeutic thrombin protein blocks the tumour blood supply by inducing intravascular thrombosis and leading to tumour necrosis with the suppression of genes that inhibits the growth of tumour. Da Silva Luz et al quoted that Nanorobots analyse the chemotherapeutic effect of the body and diagnose for small tumours with the help of protein-based sensors within one week where the conventional treatments take a period of 2 weeks. E-Cadherin and Beta-Catenin levels can be detected by chemical Nano biosensors carried by the Nanobots to find the primary and metastatic phases of cancer.

V. CONCLUSION

The two main emerging devices in the field of Nano Technology have been summarized in the view of curing metastatic breast cancer compared to the other conventional treatments. Nano Technology brought a golden revolution in the aspect of cancer treatment. This is because of their compact size, mechanism of action in a controlled manner, Easy diagnosis, Low toxicity and other challenges of conventional cancer treatments are solved by Nano cancer Technology. The side effects and other problematic drug deliverying situation are completely solved by this new emerging field and it provides the promise that people in the metastatic cancer stage will be recovered and would lead a normal life. It is expected that even cancer treatment looks like taking antibiotics for normal fever. The Nano shells methodologies are performed under in-vitro conditions but, steps must be taken at an earlier stage in clinical trials in order to extend the mortality of Cancer patients. Construction of Nano Robots is still in the developmental stage and only few get into the practical applications such as destruction of tumour cells. Researches on Nano Robots are not enough to get a clear knowledge on them. Even then, scientists and researchers must come forward to get an in-depth view about it and funds must be provided by the regulatory authorities of the country for the research community for the same.

ACKNOWLEDGEMENTS

I express my sincere thanks to Dr. Simranjit Singh, the team of Edufabrica and IIT Kharagpur for providing this wonderful opportunity to write this review and helped me gain more knowledge in this field. I would also like to thank my colleagues Darsini Thiyagarajan, Dinakari Sarangan, Jerlin Vinodh, Krithika Balakrishnan and Raghuvandhanan K S who helped me in editing and reviewing my work.

VI. REFERENCES


