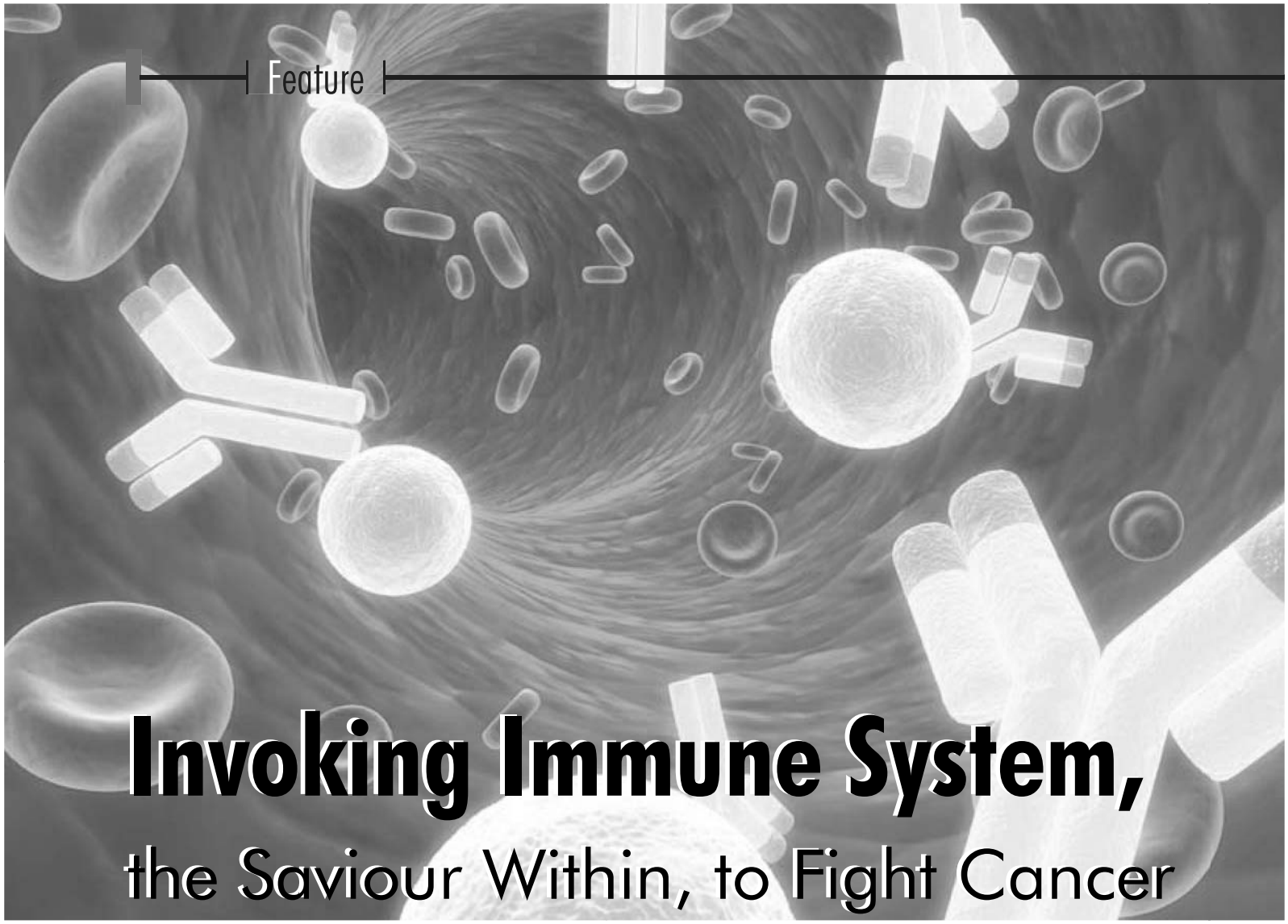

Invoking Immune System,
the Saviour Within, to Fight Cancer

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NCRM is the first and only institute in India to provide this Autologous Immune Enhancement Therapy (AIET) involving NK Cells and CTLs for patients with cancer. The Biotherapy institute in Japan, the technology providers to NCRM treats almost 10-20 patients every day with an overall efficacy of this treatment more than 20-30 per cent (1). NCRM's technology uses only the patient's own plasma for the procedure of cell culture of NK cells and CTLs and it doesn't employ any feeder layers used in techniques elsewhere, which makes the procedure much safer (2). Dr Samuel J K Abraham, Director, NCRM, Chennai, India and a Faculty at Yamanashi University Hospital, Chuo, Japan, gives us his insight into immunotherapy as a major alternative approach to cancer.

Cancer – A Unique Illness

In the earlier ages of human era, the threat to the existence was mainly from pathogen-borne diseases such as anthrax and cholera, which have been tackled by medical advancements including antibiotics and vaccines at different eons of time. However, the major threat to existence in the present days is due to diseases and disorders owing to lifestyle changes and increased longevity among which Cancer remains a myth, it being multifactorial by origin, development and progression.

The irony behind cancer when compared to other lifestyle diseases is that in other lifestyle diseases, a dysfunction or inadequacy of an organ or a system becomes the major factor causing the illnesses such as diabetes or hypertension, whereas in cancer, the basic cell division, which is an indispensable component for the maintenance of the body's composition and function itself becomes corrupt and starts producing "malfunctioning" and "uncontrollable-rogue" cells.

These uncontrollable rogue cells, which apart from invading the other normal cells and organs, steal the nutrition of the normal cells and jeopardise their welfare, besides proliferating uncontrollably throughout the body. Nature has provided us an inherent controlling mechanism for preventing this from happening, which is our immune system. However, when the immune system becomes either weak or when the cancer causing mechanisms overpower the immune system, then cancer becomes a full-blown disease.

Cancer requires a multipronged treatment strategy that should be targeted to kill only the cancer cells leaving the normal cells unaffected, which is quite tricky, but is possible, if the potentials of the native immune system are fully explored and exploited to our advantage.

Immune System – The Saviour Within

Awareness among the common people on the capabilities of immune system to fight cancer is still very little. Many believe that immune system is mainly meant to tackle foreign organisms such as viruses or bacteria and not cancer, but the fact is that human immune system is composed of cells comprising the Lymphocytes, Macrophages, Dendritic cells, Natural Killer cells (NK Cell), Cytotoxic T Lymphocytes (CTL), and lymph nodes, that work together to defend the body against attacks by the "foreign or non-self" invaders including cancer cells.

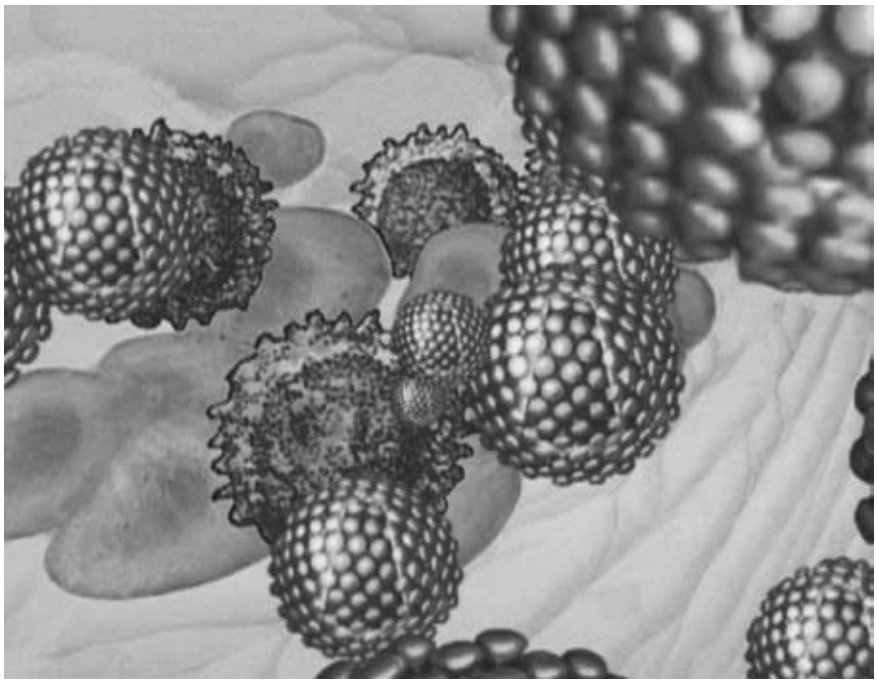
The body's immune system is well equipped to consider the cancer cell as foreign (though it is actually an altered cell of the same individual), which is because they possess an altered cell surface antigen. This cell surface antigen is a specific marker or code of identity expressed on all the cells and it is altered in the cancer cells compared to other cells in that individual.

The immune system like an army has several vertical and horizontal tiers of mechanisms to tackle cancer. The Dendritic Cells (DC) facilitate the antigen presentation, which evokes the next line of cells called Cytotoxic T-Lymphocytes (CTL), which destroys the cancer cells. Independent of this mechanism, the Natural Killer Cells (NK) destroy the cancer cells by injecting a cytolytic material called Perforin to kill the cancer cells.

Now a question may arise why did the immune system allow the cancer to develop? There are several reasons. Cancer causing mechanisms such as an intake of heavy load of carcinogens or an exposure to lethal dose of radiation can surpass the power of the immune system leading to development of cancer. The cancer cells when formed,

CASE STUDY 1-To mention a few, A male patient aged 40 years with Stage III (advanced) adenocarcinoma of the pancreas was given three transfusions of expanded NK and Cytotoxic T Lymphocytes along with surgery and adjuvant chemotherapy by NCRM. There was considerable improvement in the quality of life of the patient after the first transfusion. The patient subsequently underwent two more transfusions of AIET and improved with a significant tumor response proven by a steady decrease in tumour marker CA 19-9 values from 3800 to 750 and a tumour progression-free survival beyond 24 months (11).

CASE STUDY 2-A 54 years old female diagnosed with papillary serous cystedenocarcinoma of Ovary with lymph node metastasis, lesions in the liver and spleen (stage III-C) was given four cycles of AIET along with Chemotherapy. The CA-125 cancer marker before the therapy was 243 U/Ml. After three cycles of AIET, the PET-CT images showed marked regression of lesions in the spleen, stable hepatic lesions and decrease in size of the inguinal lymph nodes with no recurrence in the pelvic region. After another three cycles of AIET, the CA-125 came down to 4.7 U/ml. The patient reported improvement in appetite and quality of life with no adverse reactions (12).



create a unique environment within their site of origin and are capable of spreading the same at distant sites and this unique environment called "tumour microenvironment" behaves not only in an uncontrollable manner, but also equips the cancer cells to evade the immune systems surveillance. Therefore, to tackle the cancer, a super-multipronged strategy is mandatory.

Immunotherapy of Various Types

Immunotherapy is a broad term encompassing approaches that modulate the immune system to fight against non-self antigens, either directly or indirectly. Starting with food supplements, which boost the immunity, the term "Immunotherapy against Cancer" is used for a diverse range of approaches involving treatment using cytokines, granulocyte colony-stimulating factor (G-CSF), interferons, IL-12 and various other chemokines to fight against cancer at a molecular and cellular level and these agents act mainly indirectly. The most advantageous, safe and the direct cancer tackling mechanism using immune system is the autologous cell-based immunotherapy in which we take the immune cells from patient's own blood, multiply the CTLs and NK cells and then re-inject to the patient enabling them to directly attack and destroy the cancer cells. This approach is known as Autologous Immune Enhancement Therapy (AIET).

The Multipronged Cell-based Immunotherapy: AIET

A question on why among the various immune cells only the NK cells and CTLs are preferentially expanded in AIET may arise. Among the cancer cells, a portion of them posses the cancer antigens and others don't. In order to tackle both types of cells, we need a combined or double-barrel approach. The Autologous Immune Enhancement Therapy (AIET), using patients own immune cells, is one such approach. The natural killer cells (NK) can tackle all non-self antigens irrespective of whether they possess the cancer antigen or not, whereas the Cytotoxic T-lymphocytes target the cancer-antigen possessing cells. Now by combining these two types of cells, we are able to destroy majority of the cancer cells.

AIET is safe as these cells are taken from the patient's own blood and then in the laboratory (in vitro) they are multiplied, activated and transfused intravenously to the patient and being one own cells doesn't cause any adverse reaction as these immune cells target only the non-self cancer cells doing no-harm to the normal cells.

How does AIET Work in the Background of Cancer and Conventional Therapies?

To explain in simple terms, a body can be compared to a house in which cells and organs are nested like the inmates, pets etc. Like a terrorist who enters the house, cancer enters the human body by stealth and destroys the human body cells and tissues. A terrorist will plant bombs at various places in the house as his sole aim is destruction of the house as cancer spreads the metastases at various organs of the body. The immune cells of our body can be compared to the guard dogs of the house that will attack not the inmates of the house, but the outsiders. This situation perfectly describes the cancer tackling mechanisms using the guard dog-immune cells as explained below.

Conventional Therapies for Cancer

i. Surgery: Surgery aims at totally removing the cancer (terrorist). Like the terrorist is located using equipments such as Radar, cancer is diagnosed with the help of Diagnostic equipments like CT, MRI, and PET scan. Once its location (cancer location/terrorist location) is clear

and the removal is not going to jeopardise the function of any major organ, then the cancer is removed by surgical procedure. For this removal of the terrorist, some entry into the house is necessary. Similarly, the risk of surgical removal affecting the neighbouring organs and tissues is not ruled out. Surgical approach is possible when the tumour is in one region without spread. The scar will take time to heal and post-operative care is necessary.

ii. Chemotherapy: When surgical removal is not possible or when bombs (several sites of tumour metastasis) are there, then poisonous gas is sent through chimney, which will not only kill the terrorist, but also the guard dogs within the house and the inmates. Similarly Chemotherapy not only destroys the cancer cells, but also the normal cells depending upon the dosage and type of Cancer treated. Since it also brings down the peripheral blood count, the immune cells are also affected. Until the effect of poison is gone, no one can enter in. When the effect of chemotherapy is profound, immunotherapy in combination with the chemotherapy has to be planned appropriately so that the effect of AIET is not jeopardised by chemotherapy.

iii. Radiotherapy: Laser guns also could be used to target the terrorist when locations are clearly known. But again, some damage to surrounding structures are unavoidable, especially the entry point. Radiotherapy can be compared to a laser gun and is given for specific tumours, which are amenable to it depending on the type of organ. There could be some minor to major scarring of skin and surrounding tissues depending upon the dosage tissue and tumour location.

The Cell-based Immunotherapy AIET

In contrast to the above treatments, the AIET brings out the guard dogs (Immune cells), which have been restrained by the terrorist. The guard dog-immune cells are released from restraints as they are taken out from the body, rejuvenated, bred and multiplied in the lab and then sent into the house. Being the guard dogs of the same house, they know the terrorist to be destroyed and accomplish the same while leaving the inmates and belongings of the house undamaged which is why this is considered the least toxic therapy. The recent shot-in-the–arm for AIET is the finding that the cancer stem cells are preferentially killed by NK cells (3) and the T cells (4). With these evidences, it is appropriate to say that AIET apart from destroying the tumour would benefit the patient by destroying the circulating cancer stem cells also thereby preventing metastases and recurrence.

Track Record of Autologous Cell-based Immunotherapy

AIET is a cell-based immunotherapy, which is routinely practised in Japan and some developed nations since late 1990s. There are several randomised clinical trials (5,6,7,8), which have proven the efficacy with significant increase in survival rates as well disease free duration in patients treated with immunotherapy compared with those who have not been treated.

Fujita et al in 1995 (5) treated 13 patients of ovarian cancer with cell based immunotherapy along with surgical resection and chemotherapy and these patients had increased survival rate and increased disease free survival rate ($P<0.01$; $P<0.05$) compared to the controls. In a phase III randomised clinical trial by Kimura et al(6) in 1997, 82 patients with Stage III and IV advanced lung cancer had an increased survival rate ($P<0.001$). Clinical trials by Takayama et al (7), Kono et al (8) have proven the efficacy in cancers of liver and stomach also.

AIET can be administered alone or in combination with conventional treatments to all cancers in general including renal cell cancer (kidney), malignant melanoma (skin), advanced pancreatic tumours(9), lymphomas, breast cancer, ovarian cancer, liver cancer, lung cancer, colon cancer, cancer of oesophagus and some types of blood cancers. Terminally ill patients with metastases in the lungs, liver and bone have also been treated with AIET, with the number of transfusions ranging 12-24 (10).

Egawa et al(1) presented a comprehensive review of nearly 1401 patients who were administered immunotherapy for various solid cancers and the results have shown that the efficacy of the cell-based immunotherapy when combined with conventional treatment improves by 20-30 per cent. Less than one per cent of the patients experienced minor adverse problems such as fever or rash making this treatment free of significant side effects when compared with other cancer therapies.

Efficacy of AIET Alone Without Other Treatments:

The AIET alone without other treatments has been administered to 11 patients with advanced stage of cancers which resulted in static non-progressive disease (10). Breast cancer patients with bone and liver metastases could survive beyond 15 months. Stomach, uterus and oesophagus cancer patients, all with lymph node metastases could live beyond 14 months. Ovarian cancer, lung cancer and lLiver cancer patients could live beyond 26, 22 and 12 months respectively, to mention a few. In another study, 13 out of 46 patients with advanced pancreatic tumour were given cell-based immunotherapy alone and had a 50 per cent survival time of 14.5 months (9).

AIET for Wellness

The mode of tackling viral and cancer cells being the same and given the association of viral etiologies for cancer, the concept of using the tool of autologous immune cells have started emerging as a preventive strategy. With studies by Imai et al (13) and Montelli et al (14) having proven that the NK cell profile of cancer victims is significantly lower than their peers without cancer, this finding could form the basis for a study of long term effects of intermittent AIET in people with cancer history in their family and in those with a lower NK cell profile.

As the antigenic sensing of the tumor cells and viruses are almost the same (15), the AIET could be tried in victims of HIV and HCV in bringing down the viral load as well.

Future Potentials

The future will see further advances in immunotherapy as a major alternative approach to cancer. One of the latest modalities is Monoclonal Antibody-based approach in which antibodies designed against specific cancer antigens are employed to destroy the cancer cells.

This is now administered in combination with AIET as a more effective weapon in the fight against cancer in Biotherapy institute, Japan. Autologous cells being the safest bet, this least toxic therapy will continuously be explored to exploit the fullest of its potentials, so that one day it can be used in combination with other approaches in the prevention and treatment of cancer.

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