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MONTH OF AUGUST, 2023

VOL 6: 50 | PP19292/03/2018 (034850)

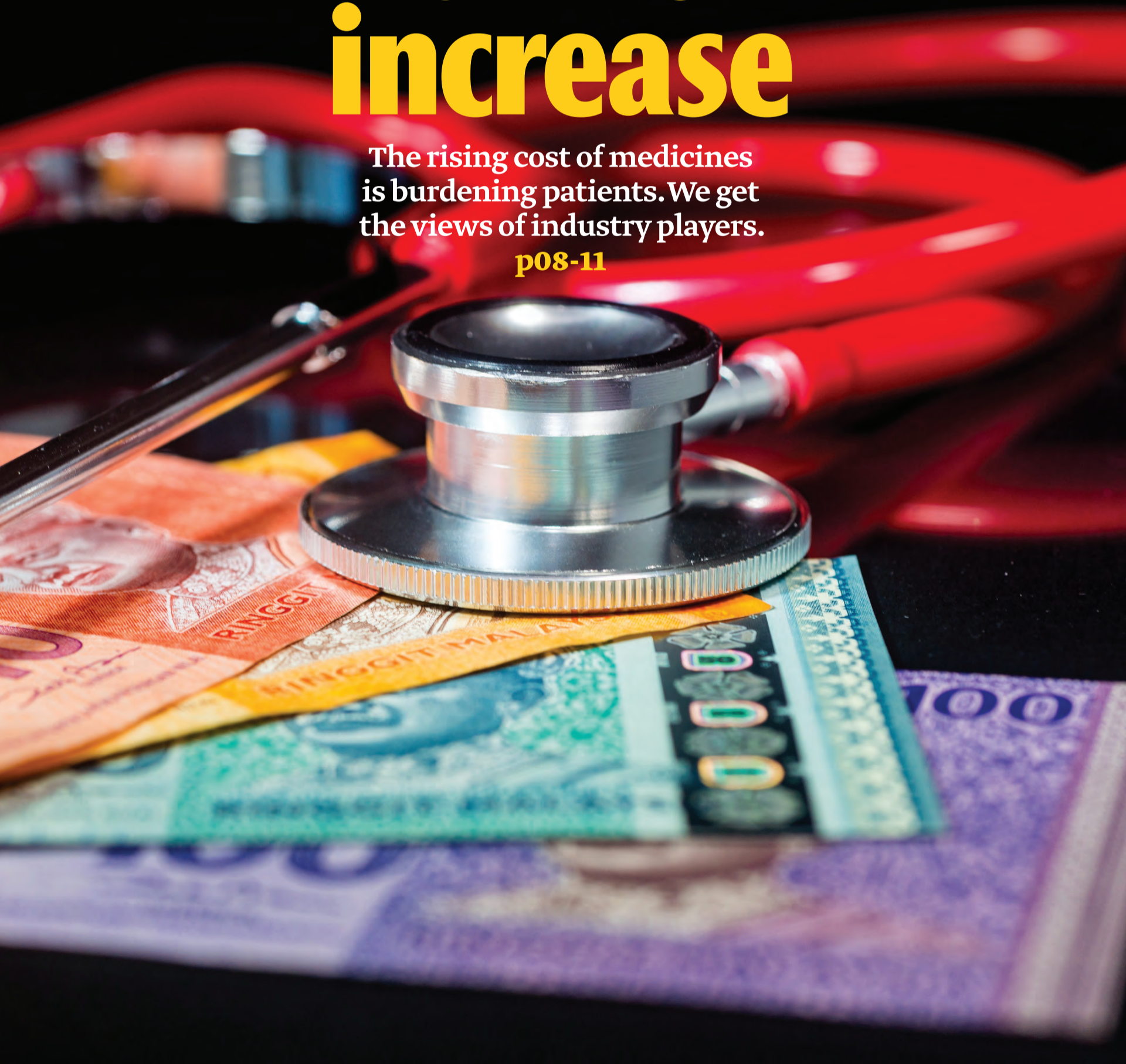
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## Painful increase

The rising cost of medicines  
is burdening patients. We get  
the views of industry players.

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# Using natural killer therapy to fight cancer

In precision medicine, cell therapy provides hope to combat senescence and boost immunity against cancer and viral infections

BY PROF MANICKAM RAVICHANDRAN AND DR THAM SENG KONG

**T**HE LIFETIME risk of getting diagnosed with cancer in Malaysia is roughly one in 10. The five most common cancers in the country are breast, colorectal, lung, nasopharyngeal and liver. Cancer is a condition where our body's cells grow abnormally due to a combination of genetics, environmental and dietary habits. According to Cancer.org, cancer is responsible for 10 million deaths worldwide. It is the second-highest cause of death in Malaysia.

Hence early cancer detection and optimal treatment are crucial for achieving a favourable outcome. In addition to traditional treatment options, immune cell therapy can offer an adjunct option in cancer therapy.

The human genome comprises 23 pairs of chromosomes and contains about three billion DNA base pairs, consistent across all human cells. The human body has around 30-40 trillion cells. Although DNA replication is typically a seamless process, mutations can occur among these three billion base pairs replication in every cell, leading to cancer development. Fortunately, cancer cells are usually eradicated by the immune system, which fights them off.

In human blood, we have two types of cells: Red and white blood cells. The white blood cells play a pivotal role in our immune system. White blood cells consist of T-cells, B-cell, Macrophages, Natural Killer (NK) cells and many other subsets.

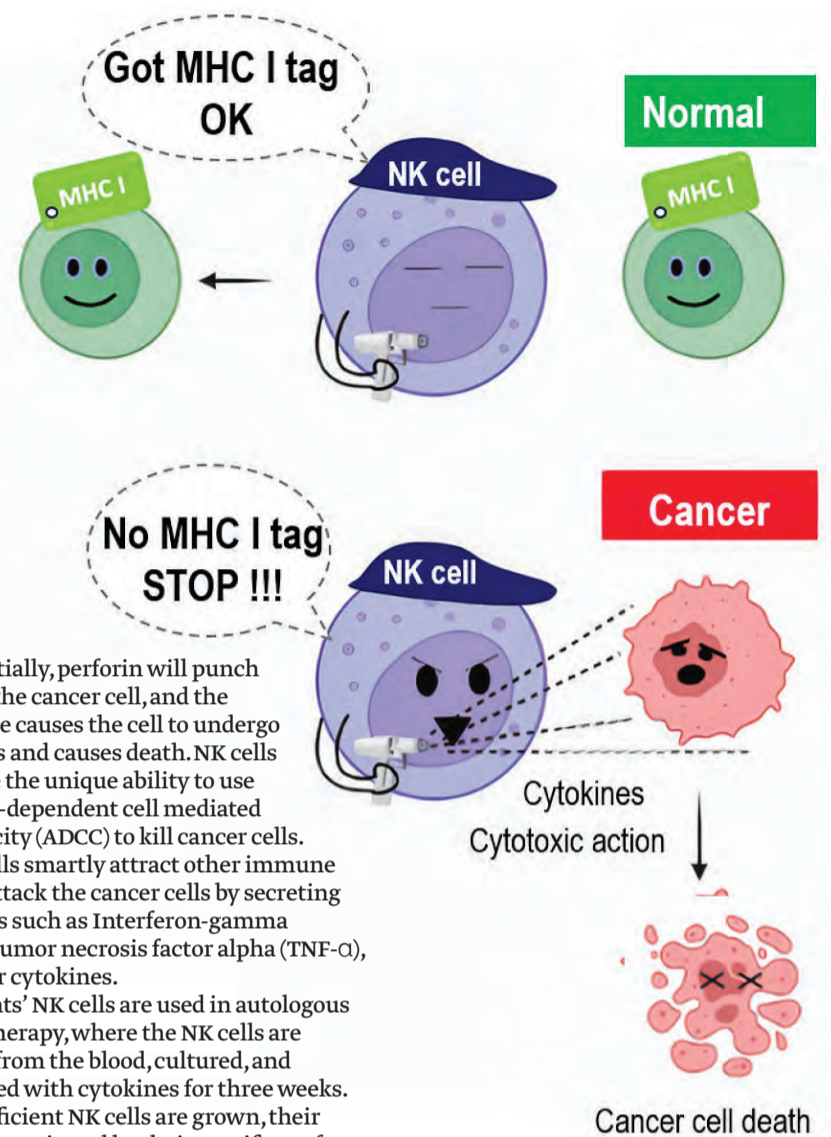
Our immune system regularly monitors and eliminates these cancer cells by utilising NK cells and other mechanisms. When an individual's immune system is compromised, it can lead to the rapid growth and spread of cancer cells.

NK cells are white blood cells with unique CD markers, including CD16 and CD56, and do not have the CD3 marker. The NK cells play a significant role in eliminating cancer cells and virus-infected cells. The mechanism is intriguing, like army personnel who eliminate any intruding enemies.

## NK CELLS HAVE A UNIQUE ABILITY

Major histocompatibility complex type 1 (MHC class I) molecules are present in every nucleated cell of our body as "self tag". Cancer and virus-infected cells often lose these MHC class I "self tags". When an NK cell comes across virus-infected or cancerous cells that do not have MHC class I tags, it will promptly kill and eliminate them.

NK cells can exert a direct cytotoxicity effect against cancer or virus-infected cells that lack the MHC class I molecule. It is through the release of granules containing perforin and granzyme.



Essentially, perforin will punch holes in the cancer cell, and the granzyme causes the cell to undergo apoptosis and causes death. NK cells also have the unique ability to use antibody-dependent cell mediated cytotoxicity (ADCC) to kill cancer cells.

NK cells smartly attract other immune cells to attack the cancer cells by secreting cytokines such as Interferon-gamma (IFN- $\gamma$ ), Tumor necrosis factor alpha (TNF- $\alpha$ ), and other cytokines.

Patients' NK cells are used in autologous NK cell therapy, where the NK cells are purified from the blood, cultured, and stimulated with cytokines for three weeks. Once sufficient NK cells are grown, their purity is monitored by their specific surface markers (CD16 & CD56) by flow cytometry analysis.

Quality control tests such as endotoxin, bacterial, fungal, and mycoplasma tests are conducted to ensure the cultured NK cells' safety before they are infused back into the patients. The infused activated NK-cells seek and eliminate the cancer cells and boost the patient's immune system.

Combining NK cell therapy with surgery, radio or chemotherapy, and checkpoint inhibitor immunotherapy is essential to achieve the best outcomes in cancer therapy. Although autologous NK cell therapy has shown potential in fighting solid tumours, it is not advisable for liquid tumours like lymphoma.

However, allogenic NK cells have been used in liquid tumours such as lymphoma and myelomas. Autologous NK cell therapy has been used in the following cancers: Ovarian, Kidney, Bladder, Colorectal cancer, Neuroblastoma, glioblastoma, hepatocellular carcinoma and non-small cell lung carcinoma (NSCLC).

## A SAFE ADJUNCT CELL THERAPY

The advantage of NK cell therapy is that it is safe with minimal side effects, unlike chemo and radiotherapy. It does not cause cytokine release syndrome (CRS), Immune effector cell-associated neurotoxicity syndrome (ICANS) and improves the quality of life of cancer patients. One attractive feature of NK cells is that they can kill cancer stem cells. Overall it's a safe adjunct cell therapy for cancer.

Several adoptive immunotherapies are available such as Dendritic cell therapy, Dendritic cell vaccine, Cytokine-induced killer cell (CIK) therapy and Natural Killer T (NKT) therapy. Some of these therapies have been tried in various combinations of cells to treat cancer.

Chimeric antigen T cell therapy, commonly known as CAR-T therapy, has recently gained popularity. In this method, patients' T-cells are genetically engineered

in a cGMP lab with a receptor for cancer cells akin to "GPS tags" that locate and kill the cancer cells. Licensed products are now available for treating liquid tumours such as lymphomas; however, this therapy has side effects such as CRS and ICANS though the efficacy is very good.

Another advancement in NK therapy is Chimeric antigen NK cell (CAR-NK) therapy, similar to CAR-T cell therapy. This method will be more effective in killing solid and liquid tumors and will not have CRS and ICANS side effects. Researchers are considering the possibility of using CAR NK as a potential treatment option for triple-negative breast cancer, which has a poor prognosis and for many other solid tumours.

As the number of senior citizens increases globally, many are looking for ways to slow the ageing process. Ageing can negatively affect the body, such as reducing the functional capability of NK cells and circulating senescent cells.

During ageing, our bodies undergo a process of biological ageing, also known as senescence. During this process, 'zombie' cells, also known as senescent cells, begin to accumulate and refuse to die.

These cells release chemicals that can harm surrounding cells, affecting their ability to survive and repair themselves. NK cell therapy effectively improves immune system function and safeguards elderly individuals from the detrimental effects of circulating senescent cells.

Studies have demonstrated the ability of NK cells to eliminate senescent cells. Therefore, NK cell therapy provides hope for the elderly population to combat senescence and boost immunity against cancer and viral infection. - *The Health*

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