

[OPINION] Cancer – Contemporary Treatment Options

In the introductory segment of our Cancer series, we touched upon the broad categories of factors that drive cell mutation and cancer – hereditary mutations, environmental exposure, and replicative errors.

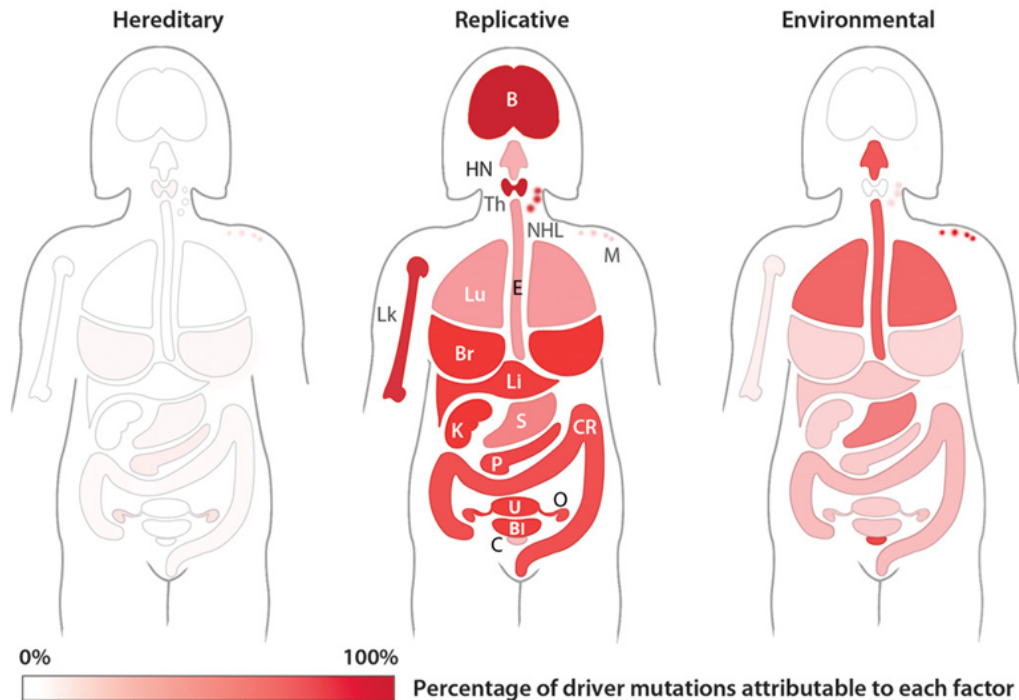
In the second part of the same series, we briefly shared the external factors that possibly collaborate to increase the incidence of one contracting cancer. Reading these scary facts would sufficiently motivate concerned readers to adjust their lifestyles and habits to minimise these unnecessary risks.

In 2015, Tomasetti and Vogelstein rocked the medical world when they announced that only a third of all cancers are attributable to environmental factors or inherited predispositions. Instead, the majority of cancers are associated with “bad luck,” or random mutations arising during DNA replication in normal, non-cancerous stem cells. These findings were further validated in 2017 with 32 cancer types.

From a theoretical perspective, the “bad luck” model of cancer risk is based on the somatic mutation theory of cancer, which argues that cancer is limited by the occurrence of oncogenic mutations. Most cancers, therefore, develop because of a combination of environmental factors and random, replicative errors that are potentially responsible for the progression of a tumor from initiation to clinical detection, rather than having inherited a specific faulty cancer gene.

Accordingly, cancers due to inherited faulty genes are much less common than cancers due to gene changes resulting from aging or other factors.

And how much did the research attribute to these three factors that caused cancer-promoting mutations? Ultimately, the researchers concluded that, across 32 cancer types, 66% of cancer-promoting mutations arise randomly during cell division in various organs throughout life, 29% are traced to environmental causes, and 5% are inherited. So much for making corrective efforts to maintain a clean living that may not be fully rewarded.



Credit: C. Tomasetti et al, Science (2017)

Make no mistake, the research did not advocate the renunciation of preventive measures but instead sought to prioritise early detection and effective treatment as future strategies against cancer as the disease seemingly appears to be inevitable. It is therefore important to know what treatment is currently available, understand when these should be applied and what are their adverse effects.

Surgical Oncology

Historically, surgery was the exclusive cancer treatment, and only in the last century did non-surgical means provide an adjunct or a rare alternative to surgery. Today, surgical oncology remains one of the three pillars on which the treatment of solid malignancies rests. And perhaps the only modality with the potential to cure most solid cancers before metastasis sets in.

Over the years, despite significant advances in overall cancer care, the stature of surgical oncology remains sharp by incorporating cutting-edge technologies including robotics.

Surgery is often deployed for the diagnosis and staging of cancers, radical removal of a tumor with appropriate resection margins, and if only part of the cancer can be removed feasibly, a debulking surgery. Post-operatively, reconstructive surgery may be performed to restore as much as possible the body's condition as in breast oncoplastic or colostomy closure.

In the advanced stage of the disease, palliative surgery may be performed to ease symptoms caused by the cancer. Yet another situation when surgery may be prophylactically deployed is the prevention of disease occurrence as in Angelica Jolie's double mastectomy and bilateral salpingo-oophorectomy for defective BRCA genes.

Because of the breadth and diversity of the disease, it is hardly possible for a single surgeon to have the expertise to perform the full range of oncological procedures, from head to toe. Like any surgery, surgical oncology carries similar risks of post-surgical pain, infection, healing complications, and internal bleeding.

Radiation Oncology

As one of the primary modalities for treating malignant diseases, radiotherapy is deployed in both curative and palliative settings for almost all solid cancers. Commonly combined with surgery, chemotherapy, and other treatment modalities, radiotherapy is deployed as first-line treatment in more than 30% of cancer cases, and about half of cancer patients receive radiotherapy sometime during their treatment regime. At times, where the knife cannot reach, radiation could be an option.

Depending on the tumor location, radiotherapy may be administered in any of three ways, external beam (EBRT), internal radiation (brachytherapy), or radioactive drugs (radiopharmaceuticals).

The main objective of radiotherapy is to deprive cancer cells of their proliferation potential. Radiation is an energized stream of ionized particles that deposits its energy load in the tissue cells it passes, and in so doing damage the genes in cells. Without going into the intricacies of the cell-division cycle, radiation affects actively dividing cells more readily, and thus rapidly dividing cancer cells and frequently renewing cells of normal tissues are equally susceptible to destruction by radiation.

Thus, the goal of radiation therapy is to maximise the radiation dosing to cancer cells while minimising exposure to normal cells, which are adjacent to cancer cells or in the path of radiation. Even when normal cells can repair themselves faster and resume normal function sooner than cancer cells, the treatment gives rise to adverse effects or radiation-associated toxicities that may manifest during or even long after treatment.

These adverse effects are location-dependent and include fatigue, alopecia, nausea, vomiting, taste change, mucositis, pruritus, dysphagia, edema, diarrhea, headache, sexual/fertility issues, cognitive issues, and visual disturbance. There is also a possibility of contracting a second cancer after treatment. Notwithstanding, radiotherapy techniques have improved over the years

with precision targeting of cancer locations as well as more calibrated radiation dosing, thereby reducing both radiotoxicity and second cancer risks.

Medical Oncology

Surgical oncology and radiotherapy are localized treatments effective if the cancer remains in situ or has invaded surrounding tissues only. They are also primarily deployed for solid malignancies. Chemotherapy is a systemic treatment in which the drugs administered course throughout the body and in so doing, kill cancer cells that have metastasized to distal regions in addition to those at the primary site.

The goal of chemotherapy is to inhibit cell proliferation and tumor multiplication, thus avoiding invasion and metastasis. Inhibition of tumor growth can be targeted at several levels within the cell and its environment. Chemotherapy drugs that kill cancer cells while they are dividing are cell-cycle specific whereas those that kill cancer cells when they are at rest are cell-cycle non-specific. Alkylating agents like cisplatin and cyclophosphamide are examples of cell-cycle non-specific drugs oftentimes used in conjunction with cell-cycle specific drugs to achieve higher levels of therapeutic efficacy.

When administered before the primary treatment, neoadjuvant chemotherapy facilitates surgery conservation as well as arrest of micro-metastasis, while adjuvant chemotherapy performed after the initial treatment is prevention against disease relapse. Administered with little curative intent during the advanced stage of cancer, palliative chemotherapy aims to decrease tumor load to relieve discomfort, improve quality of life, and extend life expectancy.

However, chemotherapy is not without limitations. Its pervasive, non-selective cytotoxic effects bearing upon fast-growing normal cells are major concerns for early dose-limiting events leading to indefinite postponement of treatment. In rare situations, its cytotoxic properties may promote and accelerate malignancy by altering the tumor microenvironment. As adjuvant therapy, it imposes a narrow time window of application dictated by tumor burden characterized by the Gompertzian model.

Chemotherapy may also cause tumor genetic changes leading to chemo-resistance, which rapidly causes drug monotherapy to lose therapeutic efficacies; hence the use of combo regimes or cocktails. Notwithstanding, chemotherapy is an effective enhancing agent to other cancer treatments.

Adverse effects of chemotherapy are a reflection of their mechanism of action affecting normal rapidly dividing cells that constitute hair follicles, skin, bone marrow, and lining of the digestive tract. Common toxicities induced by chemotherapy include myelosuppression, mucositis,

nausea, vomiting, diarrhea, alopecia, fatigue, sterility, infertility, and infusion reactions. There is an increased risk of infections due to immunosuppression.

There are, of course, other more sophisticated therapies that have developed over time mainly to address the shortcomings of the existing treatment modalities. These include targeted therapy, immunotherapy, and even CRISPR, the understanding of their mechanisms of action requires a background in cell biology and molecular sciences.

Unlike chemotherapy which kills any fast-dividing cell, targeted therapy limits damage to healthy cells by interfering with specific proteins and signal pathways that promote tumor proliferation and metastasis throughout the body. They include EGFR inhibitors, PARP inhibitors, mTOR inhibitors, and anti-angiogenics. Targeted therapy drugs often have to be taken for an extended period.

Targeted therapy is not without adverse effects. The treatment generally elicits a high response rate that lacks therapeutic resilience and sustainability.

Conversely, treatment with immunotherapy has a lower response rate but offers better long-term responses. Immunotherapy aims to harness and tweak the host's adaptive and innate immune response to effectuate the long-term elimination of diseased cells. The most commonly known immunotherapy is Keytruda (Pembrolizumab), an immune checkpoint inhibitor. As indicated by its name, it acts on the immune system(Ii) and is a humanized (zu) monoclonal antibody (mab) that is administered intravenously in cycles until disease progression or unacceptable toxicity.

There is yet a more elaborate, truly personalized, and dramatic side of immunotherapy. CAR-T involves harvesting T cells from the patient and re-engineering them in the laboratory to produce on the cell surface, chimeric antigen receptors or CARs that recognize and bind to the surface antigen of cancer cells. The revamped T cells are “expanded” by the millions in the laboratory before being re-infused into the patient after which CAR-T cells continue to multiply in the patient and, guided by their engineered receptor, identify and eradicate cancer cells that bear the target antigen on their surface.

CAR-T therapy has a distinct advantage over many modalities in that it is a “living solution” given that the re-engineered T cells continue to thrive in the body to provide a truly long-term solution. An added advantage is the stable development of a critical mass of re-engineered T cells is performed in vitro without interference by the cancer environment.

As a radical treatment, immunotherapy carries potentially severe adverse effect risks. In particular, CAR T therapies may cause potentially serious or even life-threatening side effects, the most frequent being cytokine release syndrome.

Gene Therapy

The last treatment option on the table that is still being heavily researched is CRISPR, a gene editing technology that made global headlines when a China scientist was prosecuted for creating the world's first genetically edited babies using this know-how. In essence, the technology permits the most versatile and precise editing and manipulation of the genome.

Remember that mutations are caused by changes in the base sequencing of genes, this CRISPR “molecular scissor” can rewrite the defective genetic code to its originally intended form, thus providing a new dimension in the way healing is performed in the medical world and a promise of almost unlimited solutions to previously untreatable genetic conditions, including cancer. In fact, the re-engineering of T-cells in CAR-T therapy is predicated on this technology too.

All told, contemporary medicine's powerful therapeutic options when deployed under appropriate conditions, doubtlessly yield positive outcomes albeit with limited success. Disease remission is therefore never guaranteed and requires the qualification of having disease-free survival over a defined period.

Moreover, the treatment characteristics demonstrate that cancer was never a localized disease that given time, may invade surrounding and distal regions of the body. And this is the major thrust of all treatment options. To stem replicative potential and uncontrolled proliferation of cancer cells – an elusive goal that has yet to be achieved.

The disease per se is not deadly as mutant cells merely outpace normal cells in growth, outstrip normal cells in energy requirement, and violate contact inhibition to advance their proliferation agenda that allows cancer cells to usurp the rightful places of normal cells. This is how cancer undermines and impairs the functions of any organ it afflicts to the point where the organ can no longer perform life-supporting processes.

Thus, the cause of death arising from such afflictions is likely to be driven by invasion and metastasis rather than the cancer itself, which results in aggravating medical complications.

In the next and concluding chapter of our Cancer series, we shall discuss the conceptual issues associated with treating this elusive disease and how TCM may assist in and complement orthodox treatment options to provide a holistic therapeutic regime for the benefit of the patient.

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