Is cancer chemotherapy dying?

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Traditionally, cancer is treated by surgery, radiotherapy and chemotherapy. Chemotherapy has its genesis from gases that were used during second world war in 1942.[1] Chemotherapy has cured many cancers which would have been otherwise fatal e.g., childhood acute lymphoblastic leukaemia, Hodgkin lymphoma, testicular malignancies and so on. Similarly, there have been significant extension of fruitful life in various diseases such as high grade non-Hodgkin lymphomas, multiple myeloma and so on. Problem with chemotherapy is that it is non-specific. Besides killing the cancer cell by apoptosis or other mechanisms, it also causes wide-spread damage to other tissues especially bone marrow leading to morbidity and even mortality.

During last two decades, there have been various novel methods of treating cancer. These include:

1. Immunotherapy
2. Targeted therapy
3. Drugs acting cell signal pathways
4. Anti-angiogenesis
5. Anti-microbial agents.

We will discuss these at greater length today.

Immunotherapy

What exactly is immunotherapy? Immunotherapy is a therapeutic approach that uses humoral and/or cellular elements of the immune system to fight a disease. One could give immune cells from outside or boost body's own immune cells to attack cancer. Figure 1 depicts various aspects of innate and acquired immunity.[2] Innate immune system can be activated by using safe adjuvants which can be used *in vivo*. The whole concept of cancer vaccines is to activate tumour antigen-specific immunity [Figure 2]. These cancer vaccines include:

1. Dendritic cell vaccine[3]
2. Antigen vaccine[4]
3. Anti-idiotype vaccine[5]
4. DNA vaccine[6]
5. Tumour cell vaccine.[7]

Recently, cancer immunotherapy got a booster with a development of certain exciting technologies. These include:

1. Monoclonal antibodies - conventional
2. Monoclonal antibodies - engineered
3. Checkpoint inhibitors
4. Adoptive immunotherapy.

These can be used singly or in various combinations (multi-prong attack). Classical example of conventional monoclonal antibodies is anti CD20 antibody i.e., Rituximab.[8] Bispecific T-cell engagers i.e., BiTEs is an example of engineered monoclonal antibody.[9] Checkpoint inhibitors include certain other monoclonal antibodies and pharmaceutical drugs that block inhibitory T-cell pathways i.e., PD-1 and CTLA-4.[10] CART (Chimeric Antigen Receptor Therapy) is an example of adoptive immunotherapy.[11]

Paul Ehrlich [Figure 3] was a great genius who had conceptualized immunotherapy more than a century ago. However, it was the vision and dedicated work of George Kohler from Basel Institute for Immunology (Switzerland) and Cesar Milstein from MRC Laboratory of Molecular Biology (Cambridge, UK) that lead to development of monoclonal antibodies from hybridoma technique in 1975.[12] For this they received Nobel prize in 1984 [Figure 4]. It must be appreciated that for the benefit of mankind, both these scientists decided not to patent this technique. They need to be applauded for this vision. It was quite some time later i.e., 1997 when US-FDA approved the first MAB (Monoclonal Antibody) i.e., anti CD20 antibody - Rituximab for treatment of lymphoma.[8] This changed medicine especially haematology and oncology.[8] Figure 5 shows what a MAB means while Figure 6 shows that these MABs could be of various types[8] i.e.:

1. Fully humanized MABs
2. Humanized MABs
3. Chimeric MABs
4. Mouse MABs.

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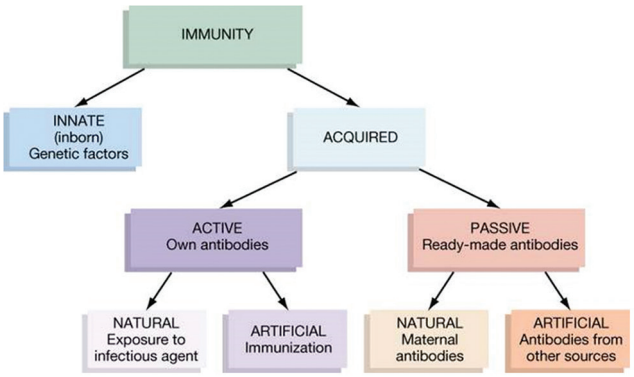

Figure 1: Details of body immune system and immunotherapy

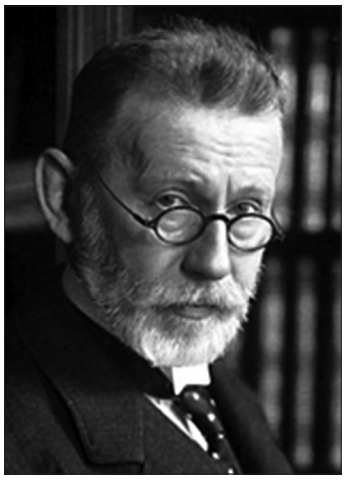

Figure 3: Paul Ehrlich (1854–1950)

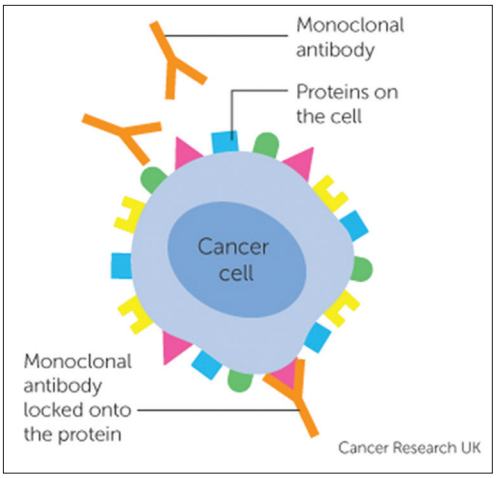

Figure 5: Monoclonal antibody (MAB)

Rituximab was the first generation MAB. Today, we have advanced to second generation MABs against CD20 and these include ofatumumab and obinutuzumab.[13,14] Besides CD20, various other antigens have been used to produce MABs. Alemtuzumab is a MAB against CD56 which is expressed in almost all lymphocytes.[15]

Not only that, antibody-drug conjugates (ADC) have been produced where a MAB is linked to cytotoxic molecule [Figure 7].[16]

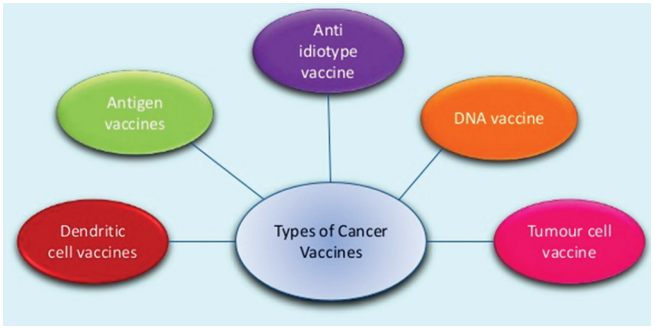

Figure 2: Development of cancer vaccine and its various types

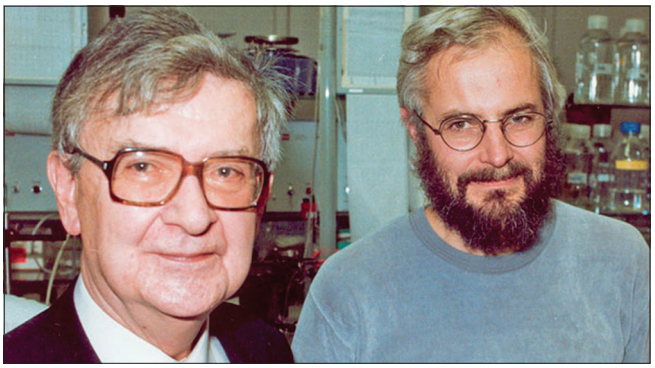

Figure 4: George Kohler and Cesar Milstein (Nobel prize winners in 1984 for developing hybridoma technique leading to production of monoclonal antibodies)

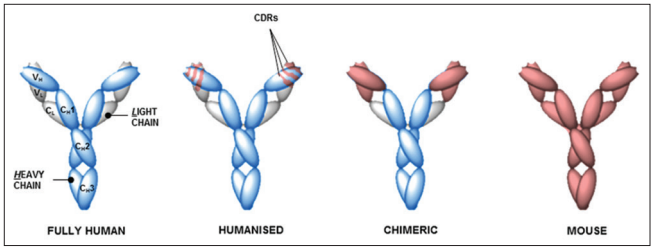

Figure 6: Various types of monoclonal antibodies (MABs)

ADC technology allows for targeted delivery of highly toxic agents resulting in increased efficacy against malignant cells and less damage to normal tissues. These effector agents could be small molecules, radioisotopes, proteins or bacterially derived toxins. These agents are otherwise too toxic for systemic use. Classical examples of ADC include GO (Gemtuzumab Ozogamicin) which is anti CD33 antibody carrying ozogamicin - the chemical agent used in the treatment of acute myeloid leukaemia.[17] Brentuximab vedotin is another antibody against CD30 antigen carrying a chemical agent useful in the treatment of relapsed/refractory Hodgkin lymphoma and CD30 positive lymphomas such as ALCL (Anaplastic Large Cell Lymphoma).[18]

Further manipulations have enhanced the utility of MABs. The Bevan group, in 1975, had synthesized hybrid antibodies i.e., bispecific antibodies.[9] These antibodies bring about an attack on cancer cell by auto T-cells [Figure 8]. Today, after 40 years, we have therapeutically used bispecific antibodies that harness T-cell mediated anti-tumour response. BiTEs (Bispecific T-cell engagers) is an example of this group.[9] BiTEs cross links T-cells with tumours. These are against CD3 complex of host T-cells leading

to homing of cytotoxic T-lymphocytes to cancer cell. Fortunately, these antibodies do not create T-cell mediated autoimmune disorders.[9] Blinatumomab is an example of first BiTE antibody in clinical use. It is a bispecific CD3/CD19 construct that tethers the resting T-cells to tumour cells.[9]

Less we forget, let me remind you that allo haematopoietic stem cell therapy (HSCT) was the first example of cancer immune therapy.[19] This was developed more than 50 years ago. Initially, it was thought to act by allowing delivery of high doses of radiation and chemotherapy, enabling higher tumour kill at the expense of permanent bone marrow suppression. Donor HSCs engrafted and repopulated haematopoietic system. It was much later that one realized the ability of reconstituted donor immune cells playing a critical role in eliminating recipient tumour cells (the graft vs. leukaemia effect).[19] Donor lymphocyte infusion (DLI) is commonly used in haematopoietic malignancies for relapses after allo HSCT.[20]

CART which was touched upon earlier, is an example of auto-T-cell therapy.[11] Scope of this oration will not permit me to discuss CART at length. However, Figure 9 gives the essence of this treatment. Landmark Clinical Trial conducted by Carl June at University of Pennsylvania in children with refractory ALL showed the success of this unique treatment. One of the two children treated using this technology is today free from leukaemia for over 2 years. This feet was subsequently repeated at MSKCC (Memorial Sloan Kettering Cancer Centre), New York. Both children and adults have been treated. The approach has quickly gained momentum and today several centres are using this technique. Further developments have lead to second and third generations CARs [Figure 10].[11]

We now come to checkpoint inhibitors.[10] Cancer cell has ability to stimulate inhibitory receptors [Figure 11] on T-cells leading to their self survival. CTLA-4 and PD-1 are the most relevant inhibitory receptors used in clinical practice. Ipilimumab is CTLA-4 inhibitor while Nivolumab is PD-1 inhibitor. These agents have already been US-FDA approved for clinical use in human cancer.[10]

I can only make passing reference to dendritic cell [Figure 12] and regulatory T cells i.e., Treg [Figure 13] regarding the importance in treating cancer through immunotherapy.[3,21] Once again, the scope of this write up will not permit detailed discussion on these two entities.

Targeted Therapy

The concept of targeted therapy is also not new. The word is self-explanatory. Chemotherapy is non-specific. It does not target cancer cell alone but even the normal tissues as stated earlier. Targeted therapy directly attacks the cancer cell avoiding normal tissues. This is a great achievement of translational research. Discovery of various molecular events have lead to

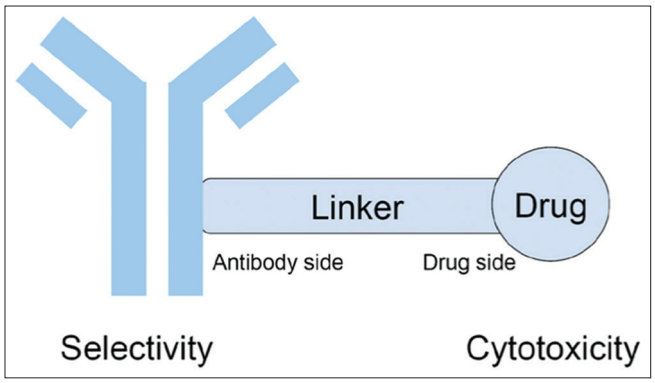

Figure 7: Antibody-drug conjugate (ADC)

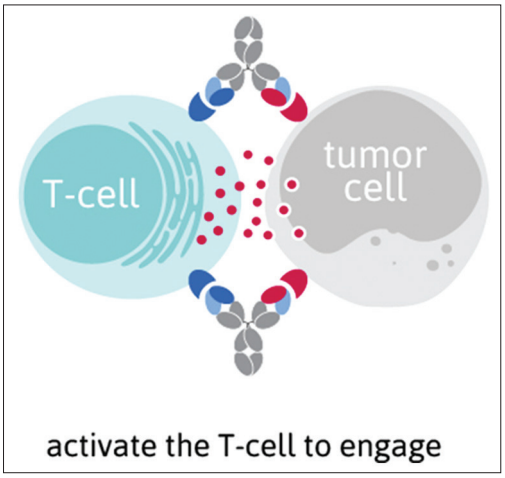

Figure 8: Bispecific antibodies

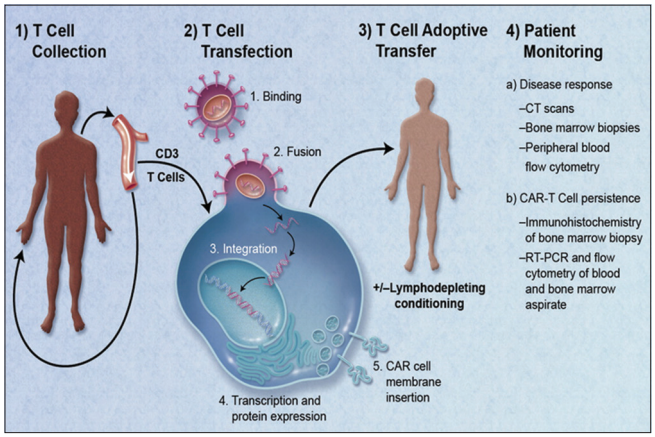

Figure 9: Steps of CART (Chimeric Antigen Receptor Therapy)

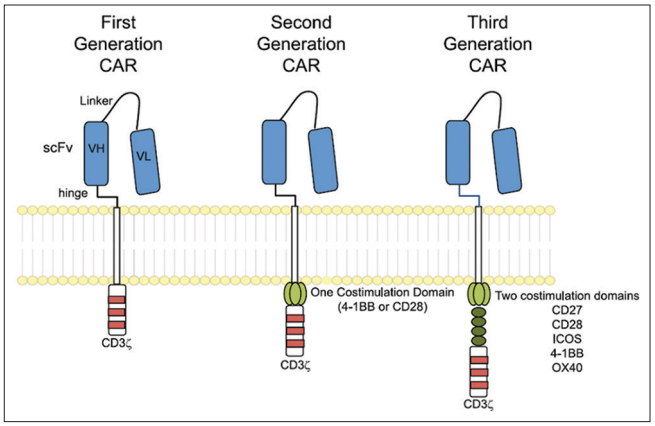

Figure 10: First, second and third generation CARs

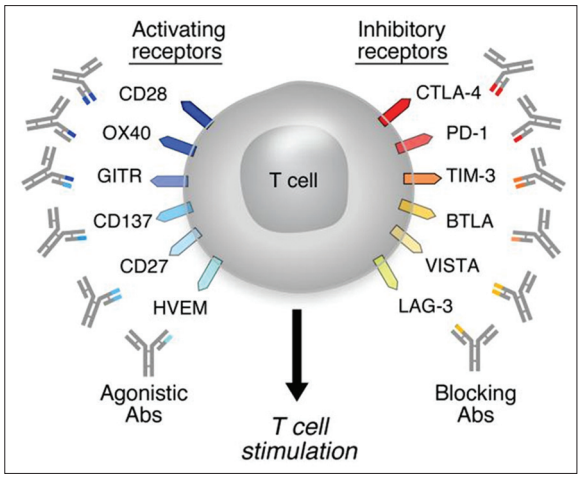

Figure 11: Activating an inhibitory receptors on T-cells. CTLA-4 and PD-1 are widely used in treatment of cancer

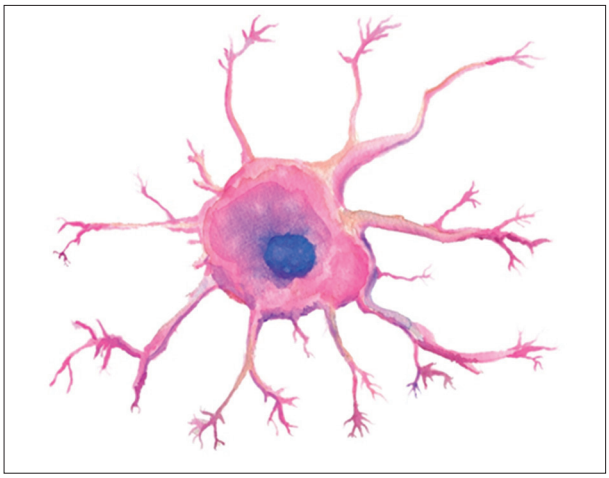

Figure 12: Dendritic cell

Figure 13: Regulatory T-cells (Treg)

molecular targets for treating cancer. Figure 14 gives a bird's eye view of such biomarkers that have been used for developing targeted therapies for treating cancer.[22] The story of tyrosine kinase inhibitors (TKI) i.e., Imatinib, Nilotinib and Dasatinib in treatment of chronic myeloid leukaemia is too well known to elaborate [Figure 15].[23] Same is the story of Ruxolitinib, the JAK inhibitor [Figure 16] for treating myelofibrosis and other bcr abl negative myeloproliferative neoplasms (MPNs).[23] More recently, Bruton's tyrosine kinase (BTK) inhibitors such as Ibrutinib is used for treating chronic lymphocytic leukaemia and mantle cell lymphoma [Figure 17].[23]

Cell signaling pathways [Figures 18 and 19] are the latest under targeted therapy.[24] Failure of apoptosis (programme cell death) underpins the development of many cancers and often enders them resistant to cancer therapies. In haematological cancers, impaired apoptosis is often caused by over expression of the pro-survival protein bcl 2. Attacking or targeting bcl 2 is another success story. Venetoclax (ABT-199) is effective in 100% of patients with relapsed/refractory CLL and many non-Hodgkin lymphomas.[25]

p53 is the guardian of genome [Figure 20].[26] It is located on chromosome 17p. It is the first tumour suppressor gene to be identified. This was way back in 1979. Job of p53 is to eliminate abnormal cells and thus prevent tumorogenesis [Figure 21]. p53 is lost in 50% of cancers by mutation or deletion. Both chronic lymphocytic leukaemia (CLL) and multiple myeloma (MM) are the classical examples. Such patients have aggressive disease. As chemotherapy works via apoptosis, it requires intact p53 for its efficacy.[26]

In cancer therapy, differentiating agents play a great role in curing certain specific conditions. Here, I will like to quote two disorders and their treatment.

1. Using all trans retinoic acid (ATRA) and arsenic trioxide (As2O3) for treating acute promyelocytic leukaemia (APL)
2. Using hypomethylating agents (HMA) e.g. Azacitidine and Decitabine for treating high risk myelodysplastic syndromes (MDS).

Targeting protein-protein interactions is another great opportunity for future therapy of cancer.

Tumour Microenvironment

Besides hitting the cancer cell, another approach for controlling cancer is to alter the environment in which the cancer cell is thriving. A glorious example of this approach in haematological malignancies is use of lenalidomide in the treatment of chronic lymphocytic leukaemia and follicular lymphoma.[27] Lenalidomide and other IMiDs are effective in treatment of multiple myeloma by various mechanisms including altering the tumour microenvironment.[27]

Tumour Angiogenesis

Judah Folkman is considered as the father of cancer angiogenesis and development of anti-angiogenesis drugs for treating cancer. It was way back in 1971, when he conceptualized that all cancers are angiogenesis dependent. It was not readily accepted at that time. However, a decade later, people recognized a close relationship between tumour and angiogenesis. This has now lead to development

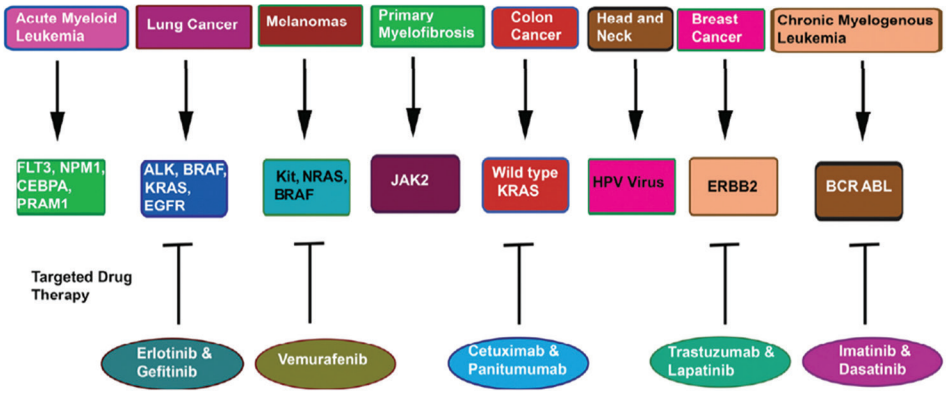

Figure 14: Novel diagnostic biomarkers in cancer which are used for targeted drug therapy

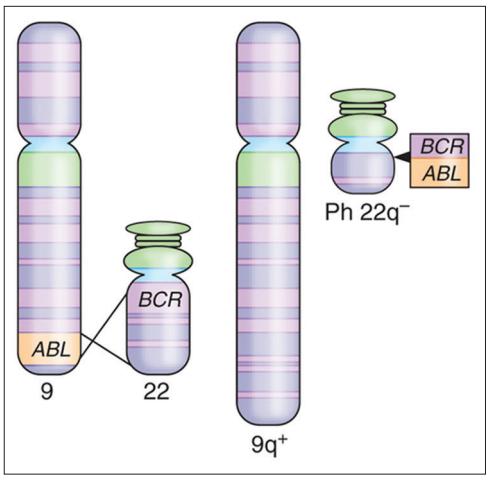

Figure 15: Bcr Abl fusion gene in CML. Tyrosine kinase inhibitors are used to nullify this event

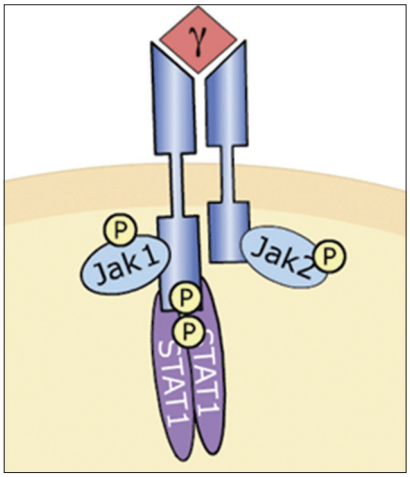

Figure 16: JAK STAT pathway. Ruxolitinib acts on this pathway for treating myeloproliferative neoplasms especially primary myelofibrosis

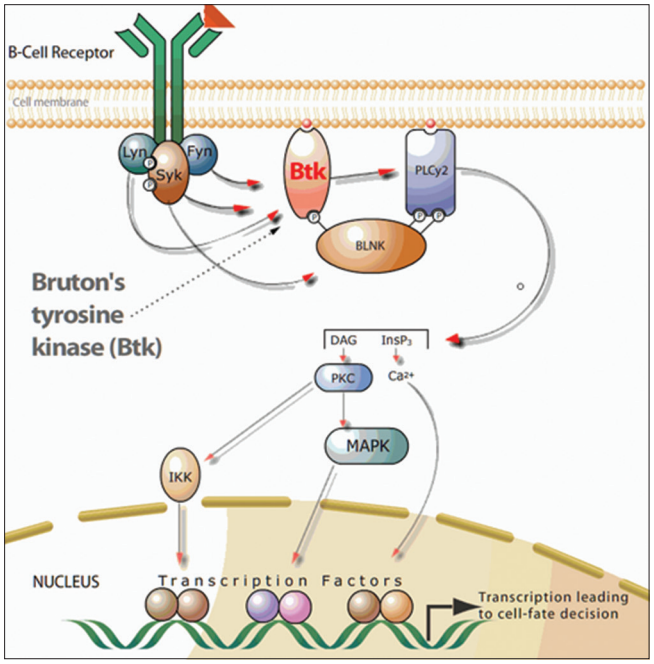

Figure 17: BTK (Bruton's tyrosine kinase) is blocked by Ibrutinib for treating chronic lymphocytic leukaemia

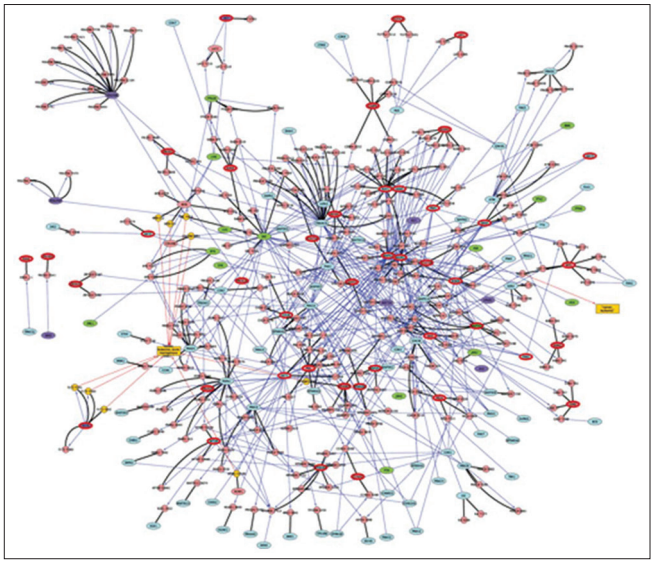

Figure 18: Cell signaling pathways

of a new modality of treatment. It has been shown that tumour cells secret angiogenic cytokines. The most important of these cytokine is vascular endothelial growth factor (VEGF).[28] These lead to

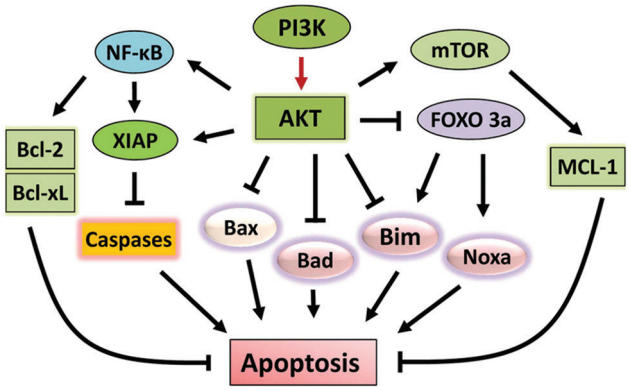

Figure 19: Cell signaling pathways

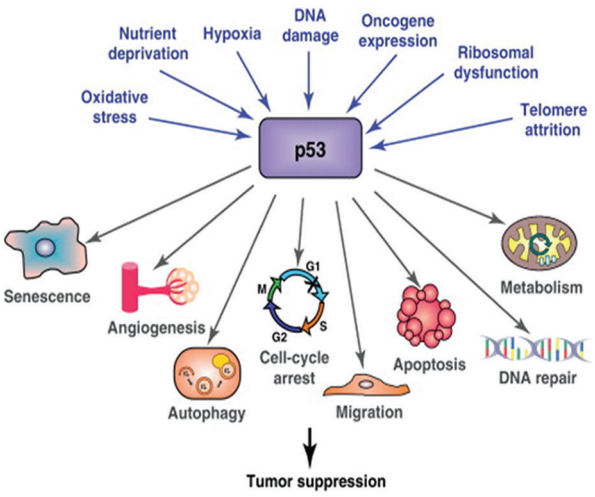

Figure 20: p53 - The guardian of genome

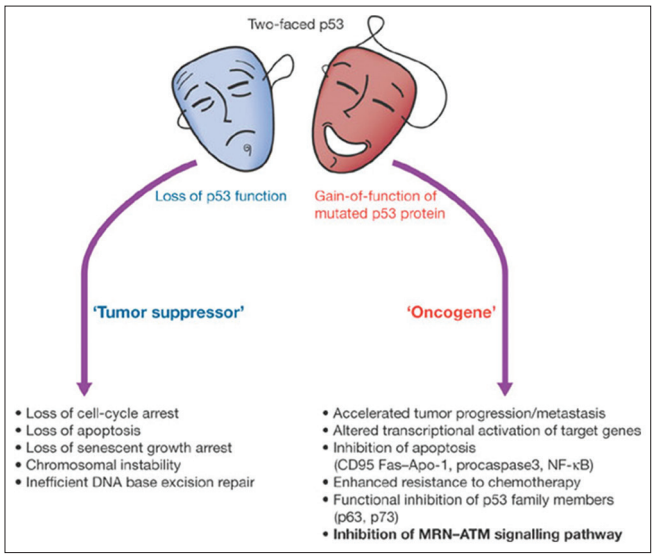

Figure 21: p53 and its function

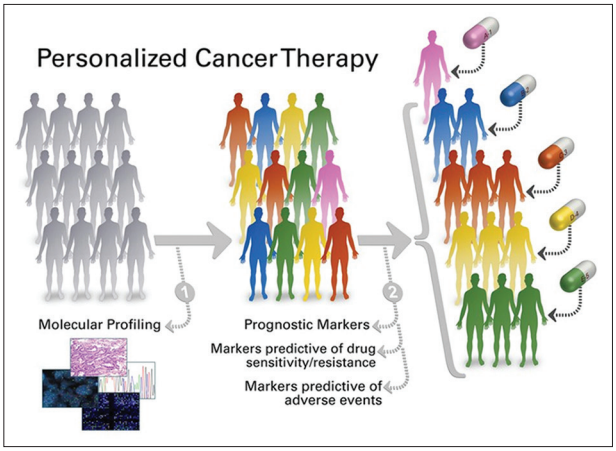

Figure 22: Personalised cancer therapy and its basis

Table 1: A list of all FDA-approved antiangiogenic therapies (2014)

Compound	Target	Indication
Antibody-based therapies		
Bevacizumab (Avastin)	Anti-VEGF antibody	Glioblastoma, metastatic colorectal cancer, metastatic RCC, some non-small cell lung cancers
Aflibercept (Eylea)	VEGF-trap recombinant fusion protein of VEGF-binding domains from VEGFR	Metastatic colorectal cancer
Ramucirumab (Cyrazma)	Human monoclonal VEGFR2 antibody inhibits VEGF binding	Advanced gastric or gastro-oesophageal junction adenocarcinoma
Small molecular inhibitors		
Axitinib (Inlyta)	VEGFR1-3, PDGFRβ, and c-KIT	Advanced RCC
Cabozantinib (Cometriq)	VEGFR1-3, MET	Metastatic medullary thyroid cancer
Everolimus (Afinitor)	mTOR	RCC, neuroendocrine tumours
Pazopanib (Votrient)	VEGFR1-3, PDGFR, c-KIT	RCC
Regorafanib (Stivarga)	VEGFR1-3, PDGFRβ, TIE2	Metastatic colorectal cancer
Sorafenib (Nexavar)	VEGFR1-3, PDGFR, RAF	Hepatocellular carcinoma, RCC
Sunitinib (Sutent)	VEGFR1-3, PDGFR, c-KIT, FLT3, RET, CSF-1R	RCC, neuroendocrine tumours
Vendatanib (Caprelsa)	VEGFR1-3, EGFR, RET	Medullary thyroid cancer in patients with unrespectable locally advanced or metastatic disease

RCC, renal cell carcinoma

neo-angiogenesis. Cancer has increased micro-basal density (MBD). Drugs have been developed against angiogenesis. Bevacizumab is one such example having anti-VEGF activity. Table 1 gives a list of various FDA-approved anti-angiogenic therapies.[28]

Antimicrobial Agents

Majority of cancers are not known for having a microbe in its etiopathogenesis. However, certain malignancies do show such

correlation. There are various types of non Hodgkin lymphoma which fall in this category. Gastric maltoma is associated with H. pylori and eradication of H. pylori is standard treatment for early stage localized gastric maltoma. Today we even have molecular and biological markers predicting H. pylori dependency of gastric maltoma.[29] CagA positivity is seen more often in patients of east Asian origin and these are the patients who show higher response to eradication of H. pylori infection for curing gastric maltoma.[29]

Conclusion

Today, we are moving towards non-chemotherapeutic drug therapy of malignancy. Also, today we are moving from protocol based treatment to personalized therapy based on prognostic markers, markers predictive of drug sensitivity/resistance, markers predictive of adverse events and molecular profiling [Figure 22]. I have no hesitation in predicting that very soon, chemotherapy may play a very small role in the cure of cancer.

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Conflicts of interest

There are no conflicts of interest.

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