From History to Future in Cancer Treatment

History

At the beginning of the 20th century, the only two options doctors had available to treat cancer were surgery and/or radiation therapy. At that time, cancers that couldn't be removed or irradiated, because of their position or because they involved blood cells, were deemed untreatable.

Serendipity during World War II

During the Second World War, people exposed to mustard gas were found to die because of complications due to bone marrow toxicity. This nitrogen mustard agent, inducing DNA lesions, was further studied at Yale University (USA) on organisms affected by certain types of cancer. Following clinical studies results, the first chemotherapeutic medicine to treat cancer was born.

The advent of chemotherapy

The discovery of chemotherapeutic medicine eventually started a wave of investments in further research for new treatments, paving the way for chemotherapy to become the mainstay of cancer treatment, which it still is today in a number of cancer types. This first generation of nitrogen mustards are no longer used today because of their toxicity to our body and the development of resistance mechanisms against this therapy by tumor cells.

Several other chemotherapies were developed, such as metal salts (cisplatin, carboplatin and others), which are still widely used in the treatment of various tumors. Another important category of molecules discovered after the Second World War was antimetabolites, which indirectly lead to cancer cell death. This medicine class (including methotrexate), proved to be effective in limiting tumor growth of

numerous solid tumors such as breast or ovarian cancer, whereas other medicine classes (including medicines such as fluorouracil) instead revolutionized the treatment of gastrointestinal tumors, in particular colorectal cancer.

Medicines slowing down cell proliferation were discovered in the late 1950's, derived from plants and tree extracts. These medicines of natural origins, belonging to different classes, such as docetaxel or irinotecan, improved the treatment of several cancers, such as metastatic breast cancer or colorectal carcinoma.

The multiple chemotherapeutic treatments that were eventually developed and approved led to treatment combinations in the 1960's and 70's. The use of combined chemotherapeutic treatments allowed greater therapeutic efficacy compared to monotherapies, by killing a larger number of tumor cells and guaranteeing a wider range of interactions between medicines and cancer cells with different genetic profiles. It also prevented and/or slowed down a potential resistance against a specific treatment.

The move towards targeted therapies

With the analyses of human DNA structure and the development of new technologies to develop medicines, specific targeted treatments were synthesized. Unlike the classic chemotherapy approach, which might kill both normal cells and cancer cells, targeted therapies intervene mainly with cells of a specific tumor and therefore are expected to have less frequent and less severe side effects. In this category, one can outline monoclonal antibodies as well as tyrosine kinase inhibitors.

Monoclonal antibodies are acting by inducing cell death through direct and indirect mechanisms. The first effective therapies with monoclonal antibodies became available in the 1990's. The first one called Rituximab was eventually used in combination with chemotherapies which achieved significant outcome improvement for patients affected by Non-Hodgkin lymphomas (cancer that affects the immune system). Soon after, many other antibodies were approved, and they are still widely used in various cancer types today.

In the same decade, the first treatments for specific targets known to be involved in the development of cancer and called tyrosine kinase inhibitors were born. Different classes in this category eventually led to improvement of prognosis for patients in a wide range of cancer types.

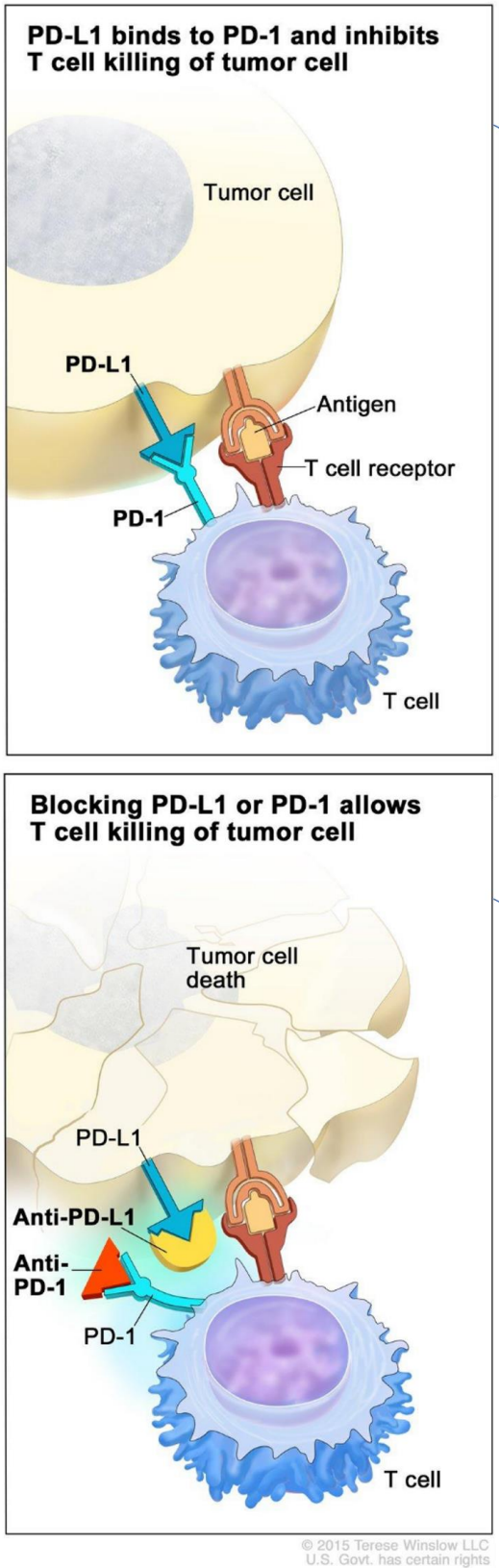
Present

Immuno-oncology

1/ Checkpoint inhibition

The treatment of cancer has experienced remarkable advances in recent years with the development of new antibodies, defined as immune checkpoint inhibitors. Broadly speaking, they act by inducing or augmenting the anti-cancer response of our own immune system. Cancer cells are trying to trick the immune system into thinking they are normal cells and checkpoint inhibitors are preventing immune cells that try to kill cancer cells from falling into this trap.

Recent medicine approvals in this field are mainly focused on two targets, namely CTLA4 and PD-1/PD-L1. In this area, the most successful medicine is called Keytruda®, which sales reached $14.4 bn in 2020. It is an anti-PD-1 checkpoint inhibitor developed by Merck & Co, one of Aescap Life Sciences' portfolio companies. It already showed its efficacy across a wide range of cancers, and we believe it will keep contributing greatly to patients' health for many years to come. Going into more details in the mechanism of action of this medicine, one needs to understand the role of T cells in our immune system's fight against cancer.



This drawing illustrates how cancer cells escape killing from immune cells because of PD-1/PD-L1 interaction

This drawing illustrates how cancer cells are prevented from escaping killing by immune cells, through anti PD-1/PD-L1 treatment

Figure 1 - Mechanism of action of PD-1/PD-L1 inhibitors – US National Cancer Institute

T cells are responsible for the immune system response in our body, and, if properly activated, can recognize tumor cells and help their destruction.

PD-1-targeting antibodies such as Keytruda® play a key role in re-activating T-cells to execute their work of killing tumor cells. Beyond the two targets (PD-1/PD-L1 and CTLA4) that we mentioned earlier as part of the immune checkpoint inhibition strategy using antibodies to target cancer, several other targets are being explored by companies with different technologies ranging from antibodies to fusion proteins.
The usefulness of antibodies, such as Keytruda®, goes beyond what we just described as they can also be used as a cargo to refine targeting of cancer cells with cytotoxic agents. These so-called 'antibody-drug conjugates' allow for a more precise delivery of anticancer drugs by using the targeting property of antibodies towards cancer cells. More than 10 different antibody-drug conjugates have already been approved to date.

2/ Cell Therapy

The cell-therapy field is another area which saw significant advances with regards to its potential in the treatment of cancer. What is called CAR-T (Chimeric Antigen Receptor) cell therapy basically consists of engineering T cells so that they are able to recognize cancer cells to a higher degree than they would normally do. The currently approved CAR-Ts, often referred to as autologous, require T-cells to be harvested from the patient before being genetically modified and reinfused to obtain the therapeutic effect. The efficacy of such treatments has been strong, with a 60% rate of complete remission and 31% rate of partial remission achieved in clinical trials with Yescarta®, in patients who had a specific lymphoma sub-type. This is quite impressive considering that the patients failed on other previous treatments or relapsed. As a drawback, such therapies can include systemic reactions to the treatment or neurotoxicity which can be severe. Further development is ongoing to try to limit these side-effects in subsequent cell-therapy generations.

Future

As we highlight the autologous form of CAR-T therapies, it is important to outline that several companies are working on so-called allogeneic CAR-T therapies. These can be manufactured through harvesting of cells from any healthy donor and preserved like other therapies are, for on-demand use. This should give an advantage in time between diagnosis and infusion of the therapy to patients, as these allogeneic therapies would be available at any moment.

Gene & RNA Therapy

Another class of treatments currently investigated in a number of clinical trials is gene therapy. Different strategies are contemplated here, such as 1) administering genes that cause cancer cell death or sensitize cells to chemotherapy, 2) expression of genes able to induce specific antitumor response and 3) silencing of genes closely linked to tumor growth. In our last Fact & Figures, we discussed RNA and, more specifically, RNA interference and antisense technologies which can also be used to induce targeted gene silencing. Several companies are developing potential treatments to silence genes linked to cancer. Aescap Life Sciences' portfolio company Arrowhead is developing such technologies and is currently conducting a clinical study in kidney cancer.

Therapeutic Vaccines

Another approach currently being investigated, while not completely new considering the first treatment in this category was approved by the FDA 10 years ago, is therapeutic cancer vaccines. The aim of such vaccines is to stimulate the patient's immune system to regain control over tumor growth and induce the death of established tumors. Due to a better understanding of the tumor environment and of cancer immune responses, development of therapeutic vaccines targeting cancer restarted after some failures in the field.

Outlook

Of the utmost importance is that all the progress made on the front of cancer treatments eventually contributes to improvement in survival and quality of life for patients. In the US, the death rate from cancer declined by 29% from 1991 to 2017. This translates to more than 2.9 million deaths avoided since 1991 in this country only, should 1991 death rates have persisted.

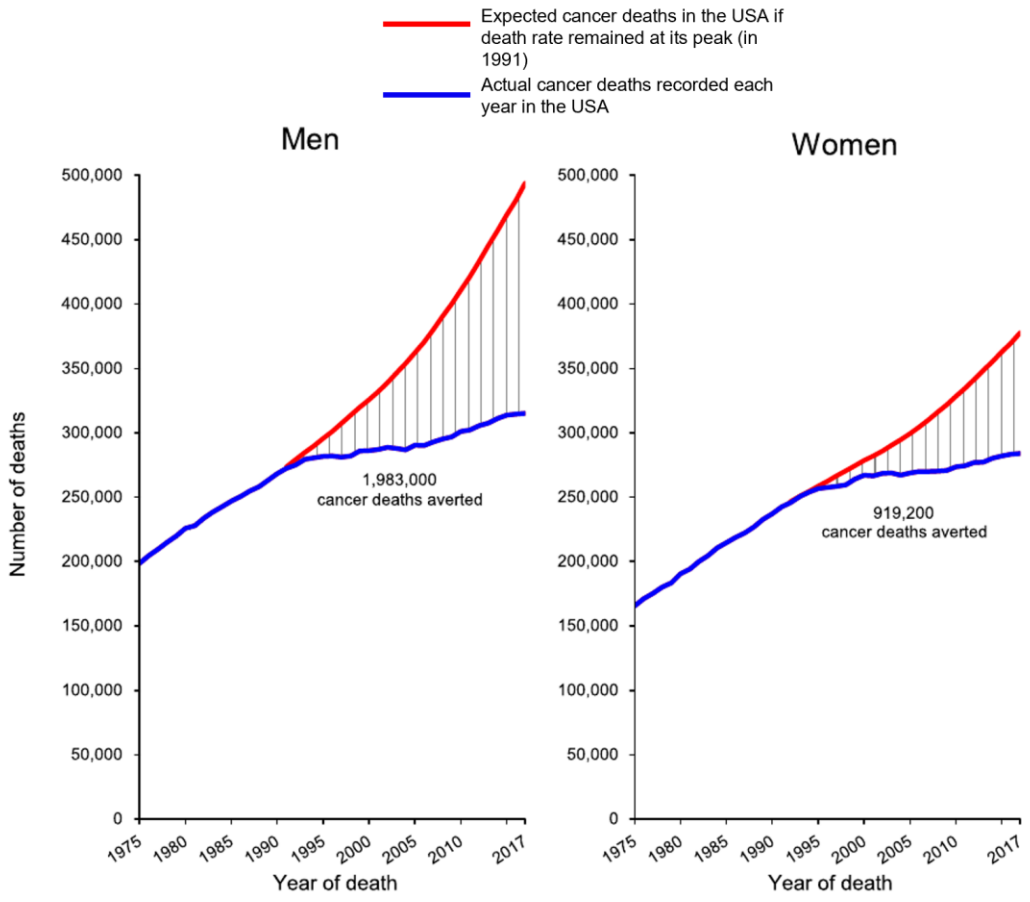


Figure 2 - Total Number of Cancer Deaths Averted From 1991 to 2017 in Men and From 1992 to 2017 in Women, United States.

Beyond significant progress in the treatment of cancer, action on prevention of cancer as well as earlier time of diagnosis also contribute to lower occurrence of cancer and improvement of cancer outcomes.

Interestingly, even at the country level in the USA, disparities in prevention action and medical detection practices lead to important differences in terms of occurrence of specific cancer types. Cancer occurrence also varies considerably between sex and between ethnic groups. Looking at kidney cancer, a 30-year analysis showed that it constantly stayed at least twice as more incident in males than in females over that period, thus making this sex-difference unlikely driven by changing lifestyle habits, such as smoking habits which evolved differently between males and females over the same time-period.Wealth inequalities in the US are largely driving cancer incidence and mortality disparities between ethnicities. Looking at breast cancer more specifically, despite having similar incidence rates, Black/African-American women are more likely to die from the disease than other population groups

In terms of geographical disparities, it's interesting to note that important differences in terms of occurrence of specific cancer types can arise between populations, which can be due to environmental factors or lifestyle habits. Looking at China, one can see that the country has around 40% higher cancer mortality than the USA, among which around 36% of the cancer-related deaths were caused by stomach, liver and esophagus cancers. In comparison, these same cancers only took up less than 5% of the total cancer deaths in the USA. On the other hand, breast cancer is two times more incident (age-standardized incidence rate) in USA than in China, even though incidence is rising steadily in China. A number of hypotheses are brought forward to explain this difference, like excess in body weight and physical inactivity. Similarly, owing to a growing "Westernized" lifestyle, China saw a rising incidence of cancers such as prostate cancer. With China transitioning from developing to a developed country and with the Chinese Communist Party's policies looking at improving health of the population, achieving better cancer care is of the essence. Zai Lab, one of our portfolio companies, is at the forefront of this effort and already brought several therapies to the Chinese market.

Despite the substantial improvement in last decades in the treatment of cancer, there is still a high unmet medical need in the treatment of many different types of cancer. Several new technologies and discoveries are still in development to further improve the way cancer is currently addressed. At Aescap we monitor these developments closely and we would only invest in companies which products show solid human clinical data because oncology is the most crowded space in the biotech industry. New approaches are currently developed at a high pace, which is valuable for patients in need of better treatments. One should realize it is unlikely that a one cure for all types of cancer will be found, as tumor cells are very smart to defend themselves against the body's immune system trying to destroy them. Cancerous cells can even become immune to a therapy or combination of therapies. To control cancer as much as possible, many better treatments for different types of cancer will need to be developed and therefore financed.

Best regards on behalf of the Aescap team,

Patrick J. H. Krol
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About Aescap Life Sciences

Aescap Life Sciences is an open-end fund investing in public biotech companies that develop and market next generation medical treatments. Within its focused portfolio of around 20 companies it diversifies over different diseases, development phases and geographies. Companies are selected for their growth potential ('earning power') and limited risk (technological and financial). Investors can enter and exit the fund twice per month.

The selection of companies in our portfolio is based on 'high conviction' - extensive fundamental analyses combined with intense interaction with management and relevant experts. The fund's performance is fueled by stock picking and an active buy and sell discipline. Biotech stocks are known for their very low correlation and high volatility, caused by media, macro-events and short-term speculative investors. This creates an ideal setting for a high conviction fund manager to invest in undervalued companies with a great mid- and long-term earning power. The fund has an average annual net performance target of 20% over the mid-term (4-5 years)

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