Paradigm shift in oncology: targeting the immune system rather than cancer cells

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Abstract

The clinical benefits obtained with rituximab in the treatment of CD20⁺ B-cell malignancies and of imatinib in the treatment of Phi⁺ leukaemias have opened a new era in oncology, transforming the concepts of tumour-targeted therapies and personalised medicine into reality. Since then, many tumour-targeted monoclonal antibodies and tyrosine kinase inhibitors have been approved for the treatment of cancers. Compared to conventional chemotherapies, these new drugs have more specificity against cancer cells and less systemic toxicities. However, like conventional chemotherapies, they often provide limited therapeutic benefits with short-lasting tumour responses as the vast majority of cancers become resistant to these drugs over time. Therefore, tumour-targeted therapies are an incremental innovation as compared to historical chemotherapies. Recently, a paradigm shift has been brought to the clinic with drugs targeting immune cells rather than cancer cells with the aim of stimulating the anti-tumour immune response of patients against their own cancer. Immunomodulatory drugs such as anti-CTLA4 and anti-PD-1 have generated long-lasting tumour responses when used as single agent in patients with refractory/relapsing cancers such as metastatic melanomas, renal cell carcinoma or non-small-cell lung carcinoma. These new immune-targeted therapies are therefore a disruptive innovation in cancer treatment: they demonstrate that long-lasting clinical benefits could be obtained by targeting molecules involved in the immune tolerance of cancer cells rather than by targeting oncogenic drivers or antigens expressed by cancer cells.

Introduction

Despite more than a century of dedicated scientific and clinical research, curing cancer remains one of the biggest medical challenges to date. So far, cancer treatments have mainly relied on the combination of surgery, radiotherapy and cytotoxic chemotherapies. None of these strategies is recent. The first report of a radical mastectomy for breast cancer was performed by Bernard Peyrilhe in 1773 and published by the Academy of Science of Lyon, France (1). Its practice became subsequently widely spread, thanks to the work of William Halsted in the USA at the end of the 19th century (2). The first successful use of radiotherapy for cancer treatment was also performed in Lyon, France by Victor Despeignes in 1896 (3). The interest of chemotherapies, such as alkylating agents, was discovered by Paul Ehrlich in the 1930s (4), but their real development in oncology was performed by Alfred Gilman and Louis Goodman, thanks to their work on nitrogen mustard during World War II (5). During the subsequent 70 years or so, a great international collaborative effort has allowed to define the best treatment combinations through randomised clinical trials involving thousands of cancer patients. Thanks to optimised doses and schedules, the overall survival (OS) has dramatically improved for some cancers such as Wilms tumours, paediatric lymphoblastic leukaemias, lymphomas or Hodgkin disease. However, combinations of conventional therapies did not provide much improvement in the survival of other cancers such as high-grade glioblastoma, lung or pancreatic cancers. Moreover,
many of these treatment regimens have shown high toxicity profiles and late side effects (6). Therefore, most of the cancer research efforts of the last 20 years have been focusing on finding drugs with better specificity against tumour cells and less toxicity against the host.

The limits of tumour-targeted therapies
The discovery of imatinib, a tyrosine kinase inhibitor, and its dramatic effect against chronic myeloid leukaemia (CML) bearing the Philadelphia chromosome (bcr-abl gene translocation) has opened a new era in the field of oncology (7). Thanks to the progress made in biochemistry, it is now possible to imagine small molecules which can bind specifically to proteins over-expressed or over-activated in cancer cells and inhibit their proto-oncogenic activity (8). These targeted proteins can be membrane receptors (e.g. erlotinib on the EGFR tyrosine kinase), intracytoplasmic kinases (e.g. everolimus on mammalian target of rapamycin) or intra-nuclear chromatin-associated proteins (e.g. the bromodomain and extra terminal inhibitor GSK525762). At best, they inhibit the single over-activated pathway responsible for the proliferation of the tumour cells and, by doing so, make the disease disappear without too much toxicity for the patient. This situation represents the ideal type of cancer, with a single dominant driver mutation, sensitive to a monotherapy blocking specifically the designated pathway (Table I). Thanks to a small mutational load in these cancers, the patients will rarely develop resistance to the drug. Imatinib represents this ideal clinical situation for patients with CML. More recently, ibritinib might also provide such clinical benefits for patients having B-cell lymphomas relying on the hyper-activation of the Bruton tyrosine kinase (BTK) pathway [although with shorter OR and progression-free survival (PFS)] (9). However, most cancers present with multiple driver mutations and have a large mutational load. These patients would therefore require multigene therapies to control the proliferation of their disease and would be highly susceptible of relapse due to early acquired resistance (Table I).

The validity of the strategy of tumour-targeted therapies also relies on the misinterpreted concept of the clonal origin of cancer (10). Indeed, if cancer cells have a clonal origin, it does not mean that they remain monoclonal over time. We know now that each cancer cell can have an independent genomic evolution over time (11, 12), and that their genome (and therefore the genome of their daughter cells) will acquire new mutations that would not necessarily exist in other tumour cell clones (13). The consequence of this phenomenon is that cancer can be in fact an extremely heterogeneous disease with different mutations found in cancer cells at different sites within the primary tumour and at the metastatic sites (Figure 1) (14). The practical clinical consequences of these results are that:

(i) the identification of a target for therapy based on a single tumour biopsy made at the time of diagnosis might miss other driver mutations present at other sites within the primary tumour or metastases, or which appeared subsequently after the biopsy,

(ii) a targeted therapy directed against one driver mutation will control the burden of the disease only temporarily but will finally allow sub-clones not expressing (or not exclusively depending on) the targeted molecule to finally expand and spread throughout the body.

The relevancy of these conceptual limits has been demonstrated recently in several clinical trials of patients bearing cancers with complex genomics. For instance, metastatic melanoma patients bearing a V600 mutation in the BRAF gene of their tumour cells and treated with a BRAF inhibitor can present dramatic tumour responses (15). However, within a few months, all the responding patients subsequently relapse with a metastatic melanoma sub-clone not sensitive to the BRAF inhibitor, leading to benefits in PFS but few benefits in OS (Figure 2). Similar patterns of transient sensitivity to tumour-targeted therapies followed by a subsequent relapse due to acquired treatment resistance have been described in many tumour types—such as, in patients with metastatic medullloblastoma treated with a hedgehog inhibitor (16) or patients with metastatic lung cancer bearing ROS1 translocations and treated with crizotinib (17).

Interestingly, tumour-targeted monoclonal antibodies (mAbs) can present the same limitations as tumour-targeted small molecules. Thanks to their antigen specificity, these antibodies can destroy selectively antigen-positive tumour cells (e.g. rituximab against CD20+ B-cell lymphoma cells). However, like for small molecules, tumour-targeted mAbs exert a pressure of selection on cancer cells and can eventually favour relapses of antigen negative tumour cells (18, 19).

Therefore, tumour-targeted therapies appear to be an incremental improvement of conventional chemotherapies, with better selectivity and toxicity profile, but like chemotherapies, offering long-term disease control only for a minority of patients and a high level of drug resistance at relapse (Figure 3).

Cancer immunotherapies: what are we talking about?
When people talk about using immunotherapy as a therapeutic strategy in oncology they usually mean ‘to use the immune system to fight cancer’. At the end of the 19th century, some physicians in Europe, such as Robert Koch, Louis Pasteur or Emil von Behring, had recorded observations of erysipelas infection coinciding with cancer regression. Notably, Prof. Busch published, in 1868 in Germany, his successful treatment of neck sarcoma after intra-tumoral inoculation of an extract of erysipela (a cutaneous bacterial infection) taken from another patient (18). Dr William Coley, a surgeon at what would become later the Memorial Sloan Kettering hospital in New York City, turned such observation into a medical practice. He confirmed that intra-tumoral injections of bacteria collected from erysipela could cure some solid tumours (21). Even if the mechanistic was not unravelled at that time, it was clear to them that they were injecting pathogens to their patients, and that the reaction of their body to the pathogens would help to eradicate their tumour. However, at a time where there were no antibiotics, and where radiotherapy showed high rates of reproducible efficacy against tumours, the number of adepts of the Coley therapy vanished over time. After World War II, major scientific discoveries concerning the immune system were done while studying tumour models in mice such as the concept of tumour immunosurveillance, the discovery of the major histocompatibility complex, dendritic cells (DCs), cross-presentation of antigens, etc. (22).
These discoveries led to the development of various strategies of cancer immunotherapy, relying on the different types of effector cells of the immune system. Some of these strategies were considered as passive immunotherapy because they provided directly to the patient the immune effectors needed to fight his cancer (Figure 4). Some were not specific of the cancer antigens such as adoptively transferred lymphokine-activated killer cells, cytokine-induced killer cells, Haplo-identical natural killer (NK) cells, allogeneic hematopoietic stem cell transplantation or donor lymphocyte infusions. Others, such as tumour-targeted mAbs, ex vivo expanded tumour-infiltrating lymphocytes (TILs) and chimeric antigen receptor T cells, were used to passively but specifically target an antigen expressed by the cancer cells. Inversely, active immunotherapy strategies were built to enhance the anti-tumour immune response of the host against his own cancer. One of these nonspecific active immunotherapy strategies that have been widely used in the 1990s is the infusion of immunostimulatory cytokines such as interleukin-2 or interferons (IFNs). Many tumour antigen-based vaccines have been (and still are) tested as tumour-specific active immunotherapies in order to generate an adaptive immune response against cancers. For a comprehensive review on the history of cancer immunotherapy strategies, see Zhao et al. (22).

Reasons of failure of the historical cancer immunotherapies trials

The major breakthrough in cancer immunotherapy happened in 2001 in an academic area very far from oncology. That year, three
teams published back to back in Nature Genetics their discovery of a new gene called FOXP3 (forkhead box P3) which is specifically expressed in a subset of CD4+ T-cell lymphocytes called regulatory T cells (Tregs). The FOXP3 mutation is responsible of a neonatal pan-autoimmune disease called IPEX (Immunodysregulation, Polyendocrinopathy, Enteropathy, X-linked syndrome) (23–25). Rapidly, people understood that the key role played by Tregs in the physiology of immune self-tolerance was also involved in the immune cancer tolerance (26). It is now clear that within the tumour microenvironment, tumour cells, together with cells from the myeloid lineage such as tumour-associated macrophages, DCs and myeloid-derived suppressor cells, sustain the development of Tregs and protect cancer cells from anti-tumour immune effector cells (27). Interestingly, Tregs express high levels of the interleukin-2 receptor α subunit (CD25), and IL-2 therapy results in the stimulation and expansion of Tregs (28). This phenomenon of cancer tolerance enhancement via Treg stimulation mainly explains the failures of the IL-2 immunotherapy strategies developed in the 1990s in cancers such as melanoma and renal cell carcinoma (29–31). Another unexpected immunosuppressive effect on macrophages and DCs might explain why type I IFN cytokine immunotherapy also had little success in the clinic (32). Therefore, it is not surprising to find that these immunosuppressive (or tolerogenic) tumour-infiltrating cells have a bad prognostic value in patients with cancer (33, 34). It also explains why performing a lymphodepletion prior the adoptive transfer of tumour-specific immune cells (CTLS or TILs) greatly enhances their therapeutic efficacy (35).

**mAbs: from incremental to disruptive paradigm in cancer therapy**

mAbs have been the historical milestone of both concepts of targeted therapies and personalised medicine in oncology. Indeed, in 1982, Prof. Ronald Levy at Stanford University, CA showed that a monoclonal antibody could be designed to target specifically the idiotype of each B-cell lymphoma (36). This strategy was tested in patients and resulted in dramatic tumour responses. It opened a large series of blockbuster anti-cancer mAbs over the last 20 years. The understanding of the biology of mAbs efficacy allowed subsequently designing them for specific functions. For instance, mAbs could be designed to have an intrinsic direct pro-apoptotic effect on tumour cells or a cytotoxic effect mediated by immune cells such as NK cells (antibody-dependent cell-mediated cytotoxicity) and macrophages (antibody-dependent cell-mediated phagocytosis). The typical example is anti-CD20 antibodies which have a mode of action that encompasses these different mechanisms. MAbs can also be designed to be antagonistic against a growth hormone receptor such as trastuzumab (anti-HER2). These Mabs turned out to be also versatile platforms for the local delivery of cytotoxic molecules such as chemotherapies and radioactive particles (37). In terms of therapeutic paradigm, these different types of Mabs were an incremental innovation in cancer therapy, providing drugs that are more specific to tumour cells, but less toxic against the healthy ones.

Over the last 15 years, it has been increasingly clear in pre-clinical tumour models that very significant anti-tumour efficacy could be obtained when mAbs are designed to target co-stimulatory or co-inhibitory molecules expressed on the surface of immune cells (38, 39). As a matter of facts, these either agonistic or antagonistic Mabs resulted in breaking the tumour tolerance and/or boost the anti-tumour immune effectors. These so called ‘immunomodulatory antibodies’ capable of ‘immune checkpoint blockade’ were then translated to the clinic. In 2010, one of them called ipilimumab, directed against the immunosuppressive CTLA4 (cytotoxic T lymphocyte antigen 4) molecule expressed by CD4 T cells (notably Tregs), showed in a randomised Phase III monotherapy clinical trial to improve the survival of patients with relapsed/refractory metastatic melanoma (40). Ipilimumab therapy resulted in long-term tumour responses with benefits in OS in about one patient out of five (20%). The proof of concept that immunomodulatory mAbs could be of interest in oncology was subsequently confirmed with another checkpoint blockade antibody directed against PD-1 (programmed death receptor-1), a molecule also expressed by T cells. A monotherapy Phase I trial showed long-term tumour responses upon nivolumab (anti-PD-1 mAb) therapy in one third of patients with metastatic melanoma and non-small-cell lung carcinoma (41). Interestingly, concomitant combinations of anti-CTLA4 with anti-PD-1 seem very synergistic with more than two third of melanoma patients developing durable tumour responses (42).

Immunomodulatory antibodies are disruptive by design. Indeed, these molecules are not designed to target the tumour cells but to target the immune system in order to break the cancer tolerance and boost the anti-tumour immune response (Figure 5). As opposed to tumour-targeted therapies, this paradigm shift offers tumour
immune effectors such as antigen-presenting cells (APCs), CD8 and CD4 effector T cells, or a direct dampening of Tregs function (44).

The demonstration of the ICD phenomenon and of the immune effects of conventional therapies is in striking contrast to the historical view that the clinical efficacy of anti-cancer drugs relies only on tumour cells via a direct cytotoxic effect. Taking into account, these results should improve the efficacy of combination therapies. Indeed, the choice of drug regimen should focus on their ability to generate an ICD and improve the cross-talk between the dying cells and the immune system.

In accordance with this consideration, some teams have recently shown that the anti-tumour effects of tumour-targeted therapies such as imatinib, dasatinib or radiotherapy synergise with immunomodulatory mAbs such as anti-CTLA4, anti-OX40 or anti-PD-L1 to generate long-term tumour responses in mice (46–49). Therefore, combination of ICD-inducing tumour-targeted therapies with immune-targeted therapies seems a promising strategy in oncology (50).

From Coley’s toxins to the 2011 Nobel prize: rationale for the use of pattern recognition receptor agonists as adjuvants for cancer immunotherapy

The 2011 Nobel Prize of medicine rewarded J. Hoffman, B. Beutler and R. Steinman for their work on the role of pattern recognition receptors (PRRs) to activate the innate and adaptive immune systems. PRR agonists are made of pathogen-associated molecular pattern molecules (PAMPs) and DAMPs (also known as danger-associated molecular pattern molecules). Within the PAMPs, TLR agonists have been widely used in clinical trials with the idea of reproducing William Coley’s work (51). We understand now that their therapeutic effect is probably mediated by the activation of APCs switching from a tolerogenic to an immunogenic phenotype upon TLR stimulation (52).

Enhancing anti-tumour efficacy via the combinations of immunomodulatory drugs

The abscopal effect is a very rare physiological phenomenon where an irradiation of a tumour site has a bystander effect on other distant, non-irradiated, tumour sites. Recently, two teams have reported that a local irradiation resulted in tumour responses on distant sites (abscopal effect) upon combination with a systemic anti-CTLA4 therapy in patients with metastatic melanoma (53, 54).

Interestingly, the team of Prof. Ronald Levy at Stanford University showed recently in a Phase I trial of patients with metastatic lymphoma that local irradiation of a single lymphoma site could trigger a systemic anti-tumour immune response when combined to intra-tumoral injections of CpG (a TLR-9 agonist) into the same irradiated site (55). This result illustrates in humans the above-mentioned synergy between a conventional anti-tumour therapy (irradiation) with an immunomodulatory drug (CpG). Notably, in this synergistic strategy, both therapies were delivered locally at the same tumour site, suggesting that the ignition of an anti-tumour immune response at a single site might be sufficient to trigger a systemic tumour response. However, this systemic anti-tumour response seemed to be limited by the expansion of Tregs (55). The same team showed in a pre-clinical murine model of lymphoma that, like in humans, intra-tumoral CpG monotherapy triggers an anti-tumour immune response eradicating mainly the injected tumour site but had little effect.
on the growth of a distant, non-injected, tumour site (56, 57). Surprisingly, the combination of intra-tumoral CpG with immunomodulatory mAbs (such as anti-CTLA4, anti-OX40, anti-FR4 or anti-GITR) allowed the generation of a systemic anti-tumour immune response able to eradicate the distant (non-injected) tumour site (57). Interestingly, the anti-tumour effect of these immunomodulatory mAbs seems to be mediated by the intra-tumoral depletion of tumour-specific Tregs (58–60). Notably, better systemic anti-tumour efficacy can be obtained when injecting low doses of mAbs directly into one tumour site, while preventing their systemic toxicity (61, 62).

In accordance with these pre-clinical results, intra-tumoral delivery of immunomodulatory mAbs directly into tumour sites is currently sought as an alternative way of using these new drugs in order to maintain their therapeutic benefits but prevent their systemic, off-target, toxicity (63).

Conclusion
Tumour-targeted therapies are still the main focus of drug development in oncology these days. However, immune-targeted therapies aimed at boosting the anti-tumour immune response in cancer patients are now a game changer in the field and many immunomodulatory mAbs are currently in development in the clinic. There is a strong scientific rationale to believe that combinations of ICD-inducing tumour-targeting drugs should synergise with immune-targeted mAbs. However, the doses, schedules and ways of administrations of these drugs remain to be specified for each cancer type in order to obtain gains in survival with less toxicity. The whole oncology practice should therefore be completely transformed over the next decades.

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References


