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NATURAL DEFENCE: Killer T-cells can recognise and attack cancer cells

Unleashing the power of the immune system to fight cancer

Recent developments in the field of active cancer immunotherapy foreshadow that the “next big thing” in cancer drugs may be on the way. Yet appropriately designed clinical trials testing combination approaches and continued understanding of the intricacies of the immune system will be needed to maximise benefits for patients, says **Malini Guha**

The question of how to use immunotherapy to unleash the immune system’s known power to fight cancer has mystified researchers for decades. Some apparent successes this year with therapeutic cancer vaccines have now altered the balance between hope and scepticism for what could be a revolutionary approach to treating cancer.

Hopes are at near-fever pitch that in 2010 the FDA will validate this approach by approving the first therapeutic cancer vaccine in the US, Dendreon’s Provenge (sipuleucel-T). Earlier this year, in a Phase III trial in men with late-stage advanced/metastatic prostate cancer, the vaccine extended median survival by about four months.

If approved, Provenge would give a major boost to the whole field; virtually everyone, even Dendreon’s competitors, is cheering for its success.

“For the last few years there have been many clinical trial disappointments, then came Provenge and there are a flood of cancer vaccines behind it ... it is becoming more accepted that the immune system can fight cancer,” says Dr James Hodge, an immunologist at the US National Cancer Institute (NCI). Dr Hodge’s team developed and licensed a promising rival prostate cancer vaccine candidate, Prostavac, to Bavarian Nordic.

Unlike preventative vaccines – which target viruses that can cause an infectious disease or a particular cancer (such as the new HPV vaccines in the case of cervical cancer) – therapeutic vaccines, a form of active immunotherapy, are used instead to treat cancer.

Few areas of cancer drug research have been as controversial as that of cancer immunotherapy, eliciting as much passion from one quarter of the research community as cynicism from the other.

“Success has been too rare for one to be convinced, but too frequent for one to give up,” immunologist Thierry Boon commented more than a decade ago, succinctly summarising the reason for the stark divergence of opinion.

Immunotherapy has resulted in some of the only real cures, or miracles, ever witnessed for small numbers of typically incurable advanced/metastatic cancer patients.

However, until Provenge’s apparent Phase III success, in large trials across a population, no therapeutic vaccine had been shown to be of benefit in any cancer compared with standard treatment; some even seemed to worsen average survival.

Well aware of this fact, and considering the growing number of regulatory reviews it will have to perform for therapeutic cancer vaccines, the FDA recently released draft guidance and held a joint workshop with the NCI relating to improving clinical trial

designs for these agents. Biovest International (a majority owned subsidiary of Accentia Biopharmaceuticals) is also hoping to file next year for accelerated FDA approval of its therapeutic lymphoma vaccine BiovaxID, which was jointly developed with the NCI. In a Phase III trial presented at the biggest session at ASCO, the world's largest cancer conference, BiovaxID prolonged the median time to disease recurrence by more than a year in patients with follicular lymphoma who were in complete remission following chemotherapy.

Meanwhile, Bristol-Myers Squibb believes so strongly in its immunotherapy ipilimumab that it paid \$2.4 billion this year to acquire Medarex, its biotech partner on the drug, Ipilimumab, which is in Phase III trials in advanced melanoma and prostate cancer, provoked dramatic front-page newspaper headlines after a single dose when used in combination with standard agents shrank inoperable prostate tumours in a couple of patients to such a degree that they could be removed completely by surgery.

GlaxoSmithKline, meanwhile, is conducting the largest-ever trial in treating non-small cell lung cancer (NSCLC) with its MAGE-A3 therapeutic cancer vaccine, after promising Phase II results. The vaccine aims to prevent disease recurrence, which is very common in lung cancer after localised tumours have been removed through surgery.

The great hope for cancer patients is that the immune system – if it can be directed to fight cancer with immunotherapy – will prove to be both more effective and less toxic in many cases than any single cancer drug or combination of drugs.

Experts are excited because they foresee much greater benefits than those that have been witnessed in clinical trials so far. This is in part because until now vaccines designed to stimulate the immune response against cancer have not been combined with “modulators of immunosuppression”. These modulators would inhibit the multiple mechanisms that have evolved in the tumour to actively suppress an immune response, and would also inhibit the natural mechanisms the immune system uses to prevent autoimmunity – an aberrant immune reaction against normal tissue.

Designing such combination immunotherapy is an exciting challenge for the researchers; now is the first time in history that they have begun to understand the components of the immune system well enough to be able to properly test the concept.

“We simply didn't know enough before. We now have the tools to begin to properly test the concept of cancer vaccination,” says Dr Lloyd Old, a pioneer of the field and

director of The Cancer Vaccine Collaborative (CVC), a joint programme of the Cancer Research Institute and the Ludwig Institute for Cancer Research.

At the same time, the vastly improved knowledge of the immune system over the past 10-15 years has also led to the sobering realisation that it is incredibly intricate, and stimulating it in the wrong way could lead to disaster.

“Therapeutic intervention breaks down the interaction between the immune system and cancer,” says Dr Vincent Brichard, head of immunotherapeutics at GSK Biologicals. “When you manipulate the immune system, you better know what you're doing,” he cautions.

“It is the first generation of these products and there are a lot of open questions for everyone in the field,” adds Dr Carlos Santos, Biovest's chief science officer of biologics. Ultimately, these can only be answered through well-designed clinical trials, most likely testing combination immunotherapy in appropriate patient populations, as well as through continued understanding of the intricacies of the immune system.

immune system's role in cancer

After decades of research and controversy, it is now accepted that the immune system can recognise and eliminate cancer in the same way that it recognises and destroys infectious agents. Specifically, the immune system's effector T-cells can recognise the antigens (such as chopped up, processed peptides from intracellular, cancer-related proteins) that are presented in a complex on the surface of cancer cells, just as they recognise viral and bacterial antigens. But, if this is true, why does cancer ever arise?

One well-accepted theory called “immunoediting” posits that the immune response actively drives tumour evolution by iteratively killing those cancer cells that present more immunogenic antigens; this leaves behind those cells that do not stimulate an immune response or can evade it through immunosuppressive mechanisms. Paradoxically, this then drives the growth of those tumours most able to evade immune response.

Is there any proof, then, that immunotherapy can summon the immune system to destroy tumours which have developed because they were able to evade it in the first place?

Yes: some of the only real cures that have ever been witnessed for metastatic cancer patients have, in fact, come with the use of high-dose interleukin-2 (IL-2), a natural cytokine that stimulates effector T-cells. This immunotherapy has resulted in cures for about 5% of patients with metastatic melanoma and kidney cancer. Unfortunately,

IL-2 doesn't direct T-cells to target antigens specifically on cancer cells, and as a general immunostimulant, it is quite toxic; it is also unknown how to select which patients will respond to it.

Additionally, “adoptive T-cell therapy”, which involves the removal, amplification and re-infusion of the patient's tumour-specific effector T-cells, has resulted in tumour shrinkage in a high percentage of metastatic melanoma patients, and some long-term remissions, in trials conducted by Dr Steve Rosenberg at the NCI.

The response seen with drugs such as ipilimumab – which block a molecule called CTLA-4 expressed by activated T-cells that limits their expansion – provides additional evidence of the role played by T-cells in fighting cancer.

“Indirect” evidence of the immune system's role in cancer comes from studies of immunosuppressed patients, such as recipients of organ transplants and AIDS patients, who have a higher incidence of cancer than the general population.

Also of note is the observation that the increased presence of effector T-cells in various tumours is strongly correlated with a better outcome for patients.

advantages

Some in the field think that active, specific immunotherapies have the potential to add years of survival to the lives of metastatic cancer patients; the survival benefit seen with chemotherapies and the “targeted” drugs (both small-molecule drugs and monoclonal antibodies) that are the mainstay of cancer drug development today is much more often measured in months in clinical trials, if any benefit is seen at all.

More, perhaps, think that immunotherapy can lower recurrence rates and thereby raise cure rates following surgical removal of a localised tumour (the adjuvant disease setting) – while at the same time resulting in much less toxicity to patients.

The immune system's potential advantages in fighting cancer are its specificity, memory and adaptability.

First, immune cells can be trained to recognise and attack antigens found only on cancer cells – such as those derived from mutated, intracellular cancer genes – so normal cells are not harmed. Drugs primarily inhibit those targets common to both normal and cancer cells, even if over-expressed by cancer cells. This results in various toxicities, which increase with combination therapies.

Second, the immune B- and T-memory cells offer the potential for a lifetime surveillance system against cancer recurrence. Once activated, T-cells and B-cells remain in the body to fight a future recurrence of

cancer cells bearing the tumour antigen which they were trained to target with the immunotherapy, just as they do in the case of foreign bacterial and viral invaders. By contrast, drugs cease to act on the tumour once they are no longer administered.

Third, the dynamic adaptability of the immune system suggests that it has the capacity to evolve with the cancer to continually target newly evolved antigens on constantly mutating cancer cells. There is emerging evidence of an "antigen cascade" effect, whereby a single antigen vaccine can stimulate an immune response against other, unrelated antigens present in the cells in the tumour. For example, T-cells are initially summoned to the tumour to attack the majority of cancer cells with the vaccine-included antigen. The dying tumour cells release other antigens that are picked up by the immune system's dendritic cells, which prime new T-cells to attack these new antigens on remaining tumour cells. Additionally, the genetic "driver" of the tumour need not be known for a cancer vaccine to work.

By contrast, for traditional targeted therapies to be effective, they must target the drivers of the tumour growth at the time the drugs are administered, which are not known in most cases. Also, there could be multiple drivers at any one time in most solid tumours, and the cancer cell can often use another growth pathway if one is blocked with a drug. Even when the correct driving pathways in a tumour are identified and inhibited with combinations of targeted drugs, the tumour's overall composition of heterogeneous and mutating cells can change to develop resistance against these.

"Every tumour cell carries dozens of mutations: these are the bane of targeted therapy, but a goldmine for immunotherapy, with new antigens being generated that are potential targets for T-cell priming," says Dr James Allison of Memorial Sloan-Kettering Cancer Center, who holds the patent on CTLA-4.

biggest challenge

"Vaccines must maximise immune recognition of the cancer and minimise tumour immunosuppression," says Dr Old. He and others in the field cite immunosuppression as the biggest challenge to overcome in developing effective therapeutic cancer vaccines.

"We keep on trying to press on the accelerator of the immune response, but the tumour is applying the brakes, and we need to release those brakes," agrees Dr Louis Weiner, an immunotherapy specialist at Georgetown University Medical Center.

The anti-CTLA-4 agents – ipilimumab and Pfizer's similar drug tremelimumab – have

gained widespread attention in the field as they are among the first agents that are being developed specifically as "modulators of immunosuppression". CTLA-4 (and other immunoregulatory molecules) protects the body against autoimmune destruction, which results from the immune system recognising self constituents of the body as foreign and attacking them. Notably, the tumour has learned how to exploit this natural protective mechanism to its advantage.

Therefore, it follows that in "taking the brakes off" by blocking CTLA-4 and allowing expansion of activated T-cells, careful attention must be paid not to go too far as this could result in uncontrolled autoimmunity. "The lines between anti-tumour response and autoimmunity are right next to each other," says Dr Hodge.

Some autoimmunity has already in fact been seen with anti-CTLA-4 drugs, although this has been manageable, says Dr Allison.

testing combinations

It therefore follows that combination immunotherapy trials would test combinations of a modulator of immunosuppression and a vaccine – usually composed of the tumour antigen and an immune boosting "adjuvant" which trains the immune system to recognise the antigen as dangerous.

Indeed, one reason for tremelimumab's Phase III trial failure in metastatic melanoma last year may have been that it was tested as monotherapy; many in the field would like to test anti-CTLA-4 agents in combination with a vaccine.

Dr Old says that different combination immunotherapy should be tested in parallel in small, Phase I clinical trials (parallel single variable trials) rather than sequentially in large Phase III trials, to speed up the development of the field. For example, the CVC is testing one antigen, called NY-ESO-1 – selected because of its specificity to tumour cells – in combination with various adjuvants and modulators of immunosuppression, to select the most effective combination in a particular tumour type.

However, he recognises that different patents covering individual components of the vaccine poses "one of the greatest" challenges to the industry.

Immunotherapy is likely to also be used alongside traditional cancer modalities rather than replace them, according to many in the field. In the advanced disease setting, it may best be used alongside chemotherapy, radiotherapy or targeted drugs, which can initially more rapidly shrink a tumour, making it easier for T-cells to access.

Some of these traditional agents are known to be immunosuppressive, but others

may be immunostimulatory, in that they release tumour antigens from cells for easier recognition by the immune system.

big pharma's investment

GSK is conducting the largest-ever trial in NSCLC – a 2,270-patient study, testing its MAGE-A3 vaccine in the 35-50% of early-stage patients who express the MAGE-A3 antigen target on the surface of their cancer cells, hoping to observe a similar reduction in disease recurrence as that observed in the earlier Phase II trial. If this result is replicated, it would likely change current practice.

GSK's significant investment in the field – once a preserve of academia and biotech – and that of other big pharma companies, most of which have licensed their products from academia or biotech, is a sign of its maturation.

Other big pharma companies with an interest in this area include BMS with ipilimumab; Pfizer with tremelimumab and a vaccine for brain cancer, CDX-110, both in mid-stage development; and Merck KGaA with the vaccine Stimuvax, in Phase III development in advanced NSCLC and advanced breast cancer. Sanofi-Aventis had licensed rights to the vaccine Trovax from Oxford BioMedica, but returned them to the biotech company this year after a disappointing trial in advanced kidney cancer.

Nevertheless, most companies, large and small, continue to invest far more on developing targeted anticancers, because of their greater success in clinical trials so far. There look to be fewer than a dozen immunotherapies in Phase III trials, although there are significantly larger numbers in Phase I and Phase II development.

who may benefit

There is still some debate over whether immunotherapies will work in the metastatic setting, or only in the adjuvant setting, to reduce the risk of cancer recurrence and increase the chance of a cure by eliminating micrometastases that may be present throughout the body.

Many in the field think that it is in the adjuvant setting that they will make their greatest mark. This is because of their advantages in evoking a long-lasting memory to the cancer antigens and because they are relatively non-toxic – key in a setting in which therapy may need to be administered for years and/or patients may be cured without any drug therapy.

In metastatic disease, there are additional hurdles to overcome, such as larger tumour masses that are difficult for T-cells to penetrate, a much greater number of tumour cells to kill, greater heterogeneity of cells, and the evolution of more tumour

immunosuppressive factors. Additionally, the immune response can take months to develop – longer than patients may have in some types of rapidly progressing cancers, such as pancreatic cancer.

Nevertheless, the success of IL-2 and adoptive T-cell therapy shows that immunotherapy can lead to cures, even in the metastatic setting, for some patients.

It may also be the case that some tumour types are more likely to respond to immunotherapy than others; melanoma and kidney cancer, for example, have been thought to be more likely to respond, in part due to the benefits seen with IL-2 and adoptive T-cell therapy. However, given that few effective vaccines have been developed so far, this is still largely unknown.

It will also be important to identify biomarkers that predict whether an individual will be more or less responsive to immunotherapy, and there are some leads already in this area. For example, in Phase II studies of its MAGE-A3 vaccine, GSK identified a gene signature – reflecting the immune microenvironment in the tumour – that appears to predict which patients will benefit most from the vaccine.

choice of antigen and adjuvants

Heated debates are still occurring in the field over whether it is best to use one, a few or many antigens; the choice of antigen; the antigen form; the method of antigen delivery; and the choice of immunostimulatory adjuvant. These critical choices will influence whether the vaccine will target more or fewer cells in the tumour; its specificity for cancer cells versus normal cells; its applicability to more or fewer patients of a given tumour type; its strength of immune stimulation; and its cost.

Although most vaccines currently in development use a single antigen, the thought among most in the field is to add one or more, to avoid potential “antigen escape”, whereby those cells that do not express the antigen survive the therapy to repopulate the tumour, which then becomes resistant to the vaccine – similar to using a targeted anticancer directed at a single target. However, if an “antigen cascade” effect occurs, even a single antigen would lead to immune attack against other unrelated antigens.

Most antigens found on cancer cells have not by themselves provoked immune attack. Therefore, vaccine “adjuvants” (such as synthetic versions of bacteria or viruses) are usually added to the tumour antigen to help train the immune system’s dendritic cells and T-cells to recognise it as dangerous.

There are, unfortunately, many elements that can impede the final response by

T-cells against the tumour – broadly termed immunosuppression.

First, the tumour cells can potentially downregulate or lose antigen so it is not visible to the activated effector T-cells.

CTLA-4 can prevent expansion of activated effector T-cells.

T-regulatory cells (Tregs), a class of T-cells which also serve to protect the body against autoimmunity and are present in high frequencies in tumours, can affect the priming of effector T-cells or shut them down. There is also evidence that the administration of therapeutic vaccines can actually evoke them.

T-cells may also struggle to get from the blood into tumour tissue, which may be a result of the physical nature of the tumour microenvironment.

Tumour cells fight back with lots of different mechanisms – they have evolved to sneak past the immune system

The tumour also secretes immunosuppressive factors, such as cytokines, which make T-cells defective.

“Tumour cells fight back with lots of different mechanisms, they have evolved to sneak past the immune system,” says Dr Hodge. However, “nothing is insurmountable”, he adds; in many cases already approved drugs can help tackle these.

There is significant research going into finding methods to deplete Tregs. While there are some approved drugs that can accomplish this, they can also deplete effector T-cells. It may be an issue of timing, Dr Hodge suggests, to administer one of these agents just as the Tregs start to shut off the effector T-cell response.

Dr Old warns, however, that the risk of depleting too large a population of Tregs is severe autoimmunity. “The ideal treatment would be to inhibit Tregs that recognise tumour antigens, but not normal tissue antigens.”

But, will each tumour immunosuppressive factor (and there is a growing list) need to be addressed in turn? Dr Allison says that even removing one block, such as CTLA-4, can take the brakes off and send the “car rolling down the hill”, so that T-cells are able to “blast through other things”, and the dynamic immune response can build momentum.

“The odds are that there are a relatively restricted number of dominant mechanisms that tumours develop to evade immune response ... others may be called into play, but it might take a long time for them

to evolve, stretching out the duration of immune control and thus the lives of people afflicted with cancer,” says Dr Weiner.

Dr Old adds: “The key issue is to identify the dominant escape mechanisms, including immunosuppressive pathways, during different phases of tumour growth and devise ways to overcome them.”

Finally, the immune system can adapt and become accustomed to the vaccine, so that an immune response stops being evoked to the antigens included in it with repeated dosing, he says. Therefore, an altered form of the vaccine with different delivery mechanisms, adjuvants or modulators of immunosuppression, may be re-administered in a “prime boost” strategy.

the goal

In summary, the ideal immunotherapy should elicit an immune response that exerts the same sort of selective pressure on the tumour that the natural immune response does, but do so with a more protective response, with the right combinations of antigens and adjuvants. However, any time an immune response is evoked, the body will react to dampen it to prevent dangerous autoimmunity, and the tumour has learned how to take advantage of this natural protective mechanism. This is where the modulators of immunosuppression come into play, as well as the prime boost strategy.

With all the complexity involved in designing combination immunotherapies and walking the fine line between immunostimulation and autoimmunity, what is the realistic goal in the upcoming years for the field?

“Improved survival will depend on how good we are at discovering immune suppressive mechanisms that can be productively and safely disabled in each type of tumour. I suspect this will be a stepwise process, for example, increasing long-term survival from 5% to 10% to 20% in a particular type of advanced cancer; so it will take time,” says Dr Weiner.

“Long-term stabilisation of disease is the goal, with the immune system reaching an equilibrium with the cancer to control it ... This is best measured in terms of survival, in both patients with and without tumours,” says Dr Old, speaking of both the metastatic and adjuvant disease settings. “Immunotherapy could revolutionise the way we think about cancer; treat it, and live with it.” **SCRIP**

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