A Matter of Time

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Successful treatment of cancer may depend on the accurate timing of chemotherapy or vaccine therapies to match fluctuations in each patient's immune system.

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Not all cancer patients are cured by chemotherapy, biological therapies, radiotherapy or surgery. Some patients can have complete regression of all cancer, while others do not appear to be responding or show some level of clinical response but not enough to overcome the tumour.

This variability has remained unexplained for many decades, and at the end of this week about 800 Australians with cancer will be dead. In the US the numbers will be close to 12,000 per week.

In May 2006, *Science* noted that the US cancer mortality rate had changed very little in 50 years despite the introduction of a multitude of often-expensive drugs. The annual associated cost of cancer treatment and loss to society in personal and economic terms amounts to hundreds of billions of dollars globally.

What Is Cancer?

Cancer is uncontrolled growth and division of genetically altered cells that typically invade other tissues, may have the capacity to spread, and might eventually kill the patient.

Traditional cancer therapies attempt to stop this cell division by poisoning the cancer cells when they are dividing and most vulnerable. But cancer therapy also affects normal cells as they divide, often leading to unwanted collateral toxicities such as nausea, bowel disturbances, hair loss, immune suppression, ulcers, infection and even death.

Cancer cells tend to divide continuously, and that is why chemotherapy and radiotherapy are given over a number of days, weeks or months in various forms and combinations in the hope that the therapy will eventually kill all the cancer cells. Clearly, for most cancer types, this cannot halt the progression of the disease.

The Immune System's Role

The notion of the body's own immune system eliminating cancer cells is not new.

In 1891 William Coley, a New York surgeon, made the remarkable observation that some patients who developed streptococcal infection and fever showed regression of most or all of their cancer. He recorded a series of similar patients, and even inoculated non-infected patients to induce infection. This was truly remarkable in an era long before the introduction of antibiotic therapies!

Coley's daughter and grandson subsequently worked on these early pioneering observations for many years, but the tools required for dissecting the immune system apart to understand the real mechanisms behind these observations remained lacking or rudimentary until the past few decades.

In a series of publications in the 1980s Robert North, an Australian-born immunologist based at the Trudeau Institute in New York, and colleagues were able to induce immune-based tumour regression in mouse cancer models by directing chemotherapy at what was then called "immune suppressor" cells rather than the tumour cells. This was counter-intuitive to the existing paradigm of chemotherapy directed purely at the cancer cells.

But North's therapeutic approach would only work if the chemotherapy was administered as a single dose 14–15 days after the tumour cells had been implanted and had established growth. While an immune response against the tumour cells was generated in the first 10–12 days, it was curtailed at about day 14–15 by the suppressor cells. This immune suppression would allow the tumour to grow and kill the mice some 30 days later.

However, when they were treated at the right time, the tumours would completely regress. The rationale behind the approach was to kill the suppressor cells when they were rapidly dividing and hence vulnerable to typical cancer drugs. In contrast, the activated effector arm of the immune response, which had emerged earlier, was left untouched by the chemotherapy drug and was therefore free to kill the tumour cells.

Interestingly, North also noticed that if the chemotherapy was given at the wrong day and earlier, the tumour would grow faster. Again, this ran counter to the prevailing dogma that the chemotherapy agent was supposed to be active against the tumour – not make it grow faster. This gave the impression that the tumour was resistant to the cytotoxic drug.

Recently this same timing phenomenon was reported by David Klatzmann's group in France. In other papers, radiation therapy seemed to have the same effect.

"the timing of cancer therapy... could be crucial in determining the success of treatment".

Consequently, to achieve a successful treatment outcome for tumour-bearing mice, the therapy had to be applied in an accurate and timely fashion. The mouse immune system behaves almost identically to the human, indicating common immune system mechanisms among mammals.

Why North's work was not fully appreciated at the time is perhaps understandable. In personal communications with North he explained that the work floundered due to a lack of specific markers to readily identify these suppressor/ regulatory cells. Other researchers also doubted their existence due to the difficulty of isolation and assaying. In addition, it was not fully appreciated that these cells are in low numbers and their appearance is short-lived.

North's papers are now commonly cited in other publications, and the assays to detect the numbers and activity of these inhibitory cells – now called T-regulatory cells – are available and more sophisticated.

The implications of these observations are potentially profound, and one could conclude that while chemotherapy and other cancer therapies are therapeutically beneficial, they are actually modulating the cancer patient's immune system, releasing it from regulation rather than directly killing the tumour cells.

Furthermore, a number of researchers have observed that different chemotherapy agents can therapeutically manipulate the immune response in the cancer patient.

Emerging Evidence

Everything in nature exists in a delicate balance. The mammalian immune system has finely tuned opposing forces of immunity and tolerance. This balance can allow vigorous and selective responses to microorganisms and cancer while avoiding damaging responses to normal healthy tissue.

Usually this is a highly efficient physiological process, but if it does get out of balance it can result in diseases such as multiple sclerosis, arthritis, inflammatory bowel disease and cancer.

Evidence gathered over the past few years has made it clear that the immune system is not ignorant of the presence of a tumour. In fact, it can fail to control the disease because the immune system holds itself back, allowing the cancer to kill the host.

Another profound observation is that the immune system, once triggered, works in a very controlled, sequential and time-dependent fashion over several days. That is, it switches "on" and "off". Observations in the mouse and human clinical situation suggest that, in a disease state such as cancer, this "on/off" cycle simply repeats constantly under homeostatic feedback control. In fact, the homeostatic regulation is likely to be the very problem that does not allow the immune system

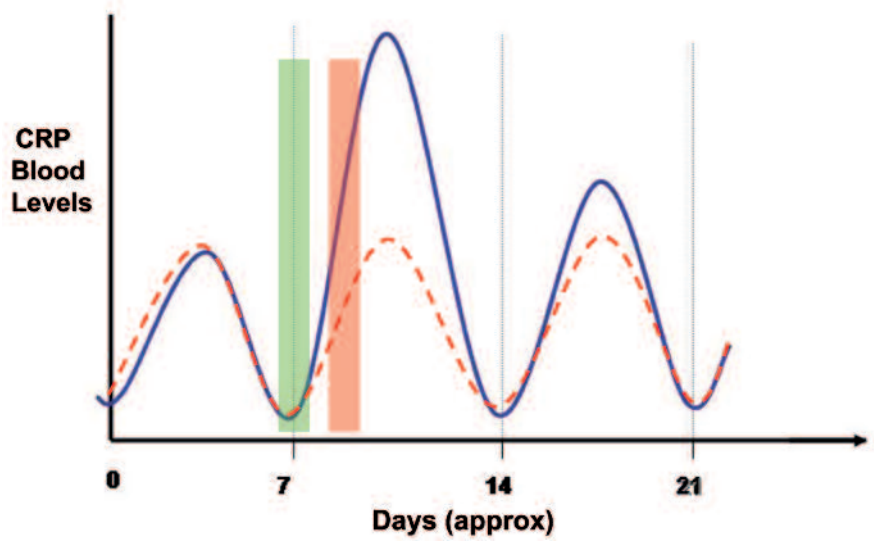

Figure 1. Daily CRP blood levels can be measured and may identify the optimal timing for treatment of cancer with either vaccine (green) or chemotherapy (red) according to variations in the immune cycle (red dashed line) . If these putative "windows of opportunity" are missed, the patient fails to respond to therapy, as described in the mouse experiments.

to gain sufficient momentum to destroy the cancer.

Since the "on-switch" (T-effector cells) and the "off-switch" (T-regulatory cells) divide synchronously over a very short time frame a few days apart, they can be selectively killed with standard cancer drugs by timing the administration to when they are dividing. If the therapy is timed correctly, the "off-switch" cells can be removed, allowing the unregulated immune system to kill the tumour cells. This has been achieved in a number of mouse cancer models.

Timing Treatment

Recently, we and colleagues reported in the *Journal of Translational Medicine* the discovery of homeostatic oscillations in the human immune system in the form of repeating "immune cycles". Using serial (near daily) blood measurements of C-reactive protein (CRP), a commonly used inflammatory marker that rises and falls over several days with the initiation and termination of the immune response, we have been able to observe oscillations in the inflammatory/ immune response in late-stage cancer patients.

These immune cycles most likely represent repeating or cyclical immune activation and suppression against the cancer, with a reproducible periodicity of approximately 6–7 days. The cancer appears to cause the patient's own immune system to switch "on" and then switch "off" against the cancer, perhaps explaining some of the variability in the effectiveness of many cancer treatments. Thus, what North and Klatzmann have described in the mouse model may apply to humans.

Putting these two ideas together – of a persistent regulated immune response cycling "on and off" in cancer patients and a difference in the timing of division for the two opposing immune cell populations controlling this cycle – we have postulated that the timing of cancer therapy with respect to this cycle could be crucial in determining the success of treatment.

By sequentially measuring CRP before and around the time of vaccination or chemotherapy, we were able to establish the position of the patient's underlying immune curve (Fig. 1). Timing with respect to this cycle appears to be critical for modulating the immune system with each intervention, and pivotal to the success of the therapy.

Using these methods we have been able to correlate the timing of vaccination or chemotherapy with the induction of successful clinical responses. More accurately timed delivery of vaccine or chemotherapy approaches might reverse immune suppression in patients with metastatic melanoma, ovarian cancer and cancer more generally.

Conclusions

The implications of our findings could be profound. For a start, reduced amounts of cancer drug, radiotherapy or therapeutic vaccine might be required to successfully treat the cancer patient if the administration is synchronised with each patient's immune cycle. This could result in a dramatic reduction in associated toxicities, with expensive new cancer agents playing a lesser role in cancer treatment. One strong possibility is that the timed therapeutic vaccine approach, with its very low toxicity, might become the best approach.

Furthermore, inexpensive "off-patent" drugs could be used more efficaciously, even at low doses. This could result in a dramatic reduction in the costs of cancer treatments.

We suspect that the unexpected recovery of some advanced cancer patients given standard therapies may have been the result of random, chance or accidental manipulation of the patient's own immune system. By simply being in the clinic on the right day, these patients' inhibitory T-regulatory cells have been ablated, enabling more effective T-effector responses to occur.

Clinical investigations of this phenomenon are underway and, with appropriate funding and trial design, the preliminary findings may be verified in a matter of only weeks rather than the often-quoted 10–15 years.

Time, or rather "timing", will tell.

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