

**IMMUNOTHERAPY OF MELANOMA**

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**Why?**

Melanoma is a cruel disease. The most recent Australian figures indicate that over 8000 cases of melanoma were reported in 1997 and that approximately 900 people died of the disease that year. Overall, because most melanomas are diagnosed early, the five-year survival for melanoma is more than 90% and Australia in fact leads the world in this respect. However, for the sub-groups of patients with high-risk primary disease or metastatic disease, the outlook is very poor. The one-year survival of metastatic melanoma is 41-59% and the median survival is approximately 7.5 months, although this varies according to the site of metastasis. No intervention has been shown to improve the outcome of patients with metastatic disease. Clearly, better treatment approaches are required.

There is tantalising evidence that immune responses may alter the outcome of patients with melanoma. Many of these patients have circulating antibodies or T cells specific for particular tumour antigens. This does not prove a cause and effect relationship, since it is possible that these patients simply have indolent melanomas and that the immune response is an epiphenomenon. However, it is a consistent observation and the hypothesis that immune responses help to control some cancers is reasonable.

Interleukin-2 (IL-2) is approved for use for patients with metastatic melanoma in the USA but not in Australia. Although responses are infrequent and toxicity is high, the small proportion (about 6%) of patients who achieve a complete response to IL-2 have a high probability of long-term complete remission and presumed cure. This is very rare with conventional chemotherapy and indicates an important qualitative difference in the mechanism of action of this agent — induction of immune memory. Many of these patients develop vitiligo due to T cell-mediated killing of normal melanocytes, indicating that the immune response is specific for antigens in cells of the melanocyte lineage. The development of vitiligo in these patients indicates a higher probability of response to immunotherapy. High dose IL-2 is both expensive and very toxic. Current work is concentrating on approaches that may be less toxic, more effective and based on known antigens specific for particular tumour types. Taken together, these observations indicate that melanoma is capable of being controlled by immunological responses. The best way of eliciting these responses is not yet known.

**What?**

Many approaches have been used for immunotherapy of melanoma. This very fact is a strong indicator that none of these approaches have been particularly successful thus far. Initial work concentrated on using non-specific immunostimulants such as BCG or sources of undefined antigens such as tumour cell extracts or lysates. Since the first human cancer antigens that could be recognised by T cells were defined, the field has advanced rapidly. Numerous potential vaccine targets are now available, and there are also many new adjuvants that can predispose towards the T cell responses that are required to kill cells expressing these intracellular antigens.

In the case of melanoma, most work involving defined melanoma antigens has used either antigens specific for cells of the melanocyte lineage (and therefore expressed also in normal melanocytes), or antigens that are relatively specific for cancer cells and not expressed by normal cells (“cancer-tests” or CT antigens). The latter group is particularly appealing since the proteins in this family are expressed by a broad range of cancers. Expression in normal tissues is restricted to cells such as spermatogonia, which do not express HLA class I molecules and are not subject to T cell killing.

One antigen of particular interest is the CT antigen NY-ESO-1, initially identified from a patient with oesophageal cancer who had circulating antibodies specific for this protein. NY-ESO-1 is expressed in a wide variety of cancers and is very immunogenic: spontaneous immune responses to NY-ESO-1 occur in 50% of patients whose tumours express this antigen. Both antibody and T cell responses are seen de novo, and patients treated with NY-ESO-1 peptides commonly develop T cell responses. Our group and others are investigating various ways of using NY-ESO-1, including peptide-based approaches as well as using the recombinant protein.

In view of the fact that immune responses may take several months to become apparent, it was logical to combine immunological approaches with conventional cytotoxic chemotherapy in order to achieve an early cytoreductive effect while awaiting a longer term immunological effect. Although there is a general belief that chemotherapy impairs immune responses, the immunosuppression seen after most cytotoxic treatments is primarily related to neutropenia. There is little evidence that memory responses to viral antigens are impaired unless immunosuppressants such as corticosteroids are used. Responses to cancer antigens are similar to those against viral antigens in that most cancer antigens are intracellular and hence only able to be recognised by T cells. Various regimens combining chemotherapy and immunotherapy (“biochemotherapy”) have been tried and these have been reviewed recently. Single arm studies indicated good response rates although, interestingly, this was schedule dependent – ie responses when the two modalities were given concurrently were superior to those in which the immunotherapy preceded the chemotherapy. Perhaps the cell death induced by the cytotoxic agents then provides a larger pool of antigens that can then stimulate a subsequent immune response that is more effective.

A recent phase III trial comparing biochemotherapy with conventional chemotherapy was disappointing. Although the experimental arm had an improved response rate and a significant although minor benefit in terms of progression free survival, overall survival was not significantly prolonged. The highly selected study population had substantial toxicity in the experimental arm. However, long term responders have been described and this regimen can act as a basis for future work, having proven the principle.

How?

Much of the work to date in melanoma immunotherapy has been empirical. Observations made in vitro or in animal models have been extrapolated to humans and high hopes have been held for useful anti-tumour responses. However, with few exceptions, the results of these approaches have been disappointing. Obviously, the immune system is capable of rejecting large volumes of tissue – this is the bane of the transplanters. The difficulty is that cancers arise from the cells of the host and are not allogeneic. Although they are not normal cells, they are insufficiently abnormal to trigger a potent rejection response. It is this deficiency that must be addressed if these approaches are to be successful.

Tumours have evolved to down-regulate or evade immune responses, but this can be overcome. If it is possible to elicit an inflammatory response in a cancer, anti-tumour responses can often be observed. This is probably the mechanism of action of BCG in bladder tumours. Similar effects have been seen in melanoma, which will often regress when injected with cytokines such as GM-CSF or interferon-α. In the case of high dose IL-2, it is possible that its pharmacological toxicity may be an important part of its effect, rather than direct effects on cells of the immune system, since interventions to decrease the toxicity of IL-2 also abrogate its efficacy.

It is logical to assume that a vaccine delivered in such a fashion as to cause an appropriate “danger” signal is the one most likely to elicit a useful immune response. Such signals might be delivered in vivo using appropriate adjuvants. Alternatively, cellular effectors such as T cells or DC might be manipulated ex vivo so as to allow optimisation of both antigen presentation and of functional activation. The area of DC biology is reviewed elsewhere in this issue.

Who and when?

So far, most work in cancer immunotherapy has involved patients with advanced disease. Although these patients offer the opportunity to observe tumour responses if they can be induced, they are probably the worst group to study if the aim is to optimise the vaccination approach. Patients with advanced cancer are often inherently immunosuppressed due to their disease, their poor nutrition or in some cases their treatment. Their cancers are usually progressive, sometimes rapidly. Because an immune response can take weeks to months to become apparent (assuming that it will become apparent – a risky assumption), it is likely that these patients will encounter problems due to their progressing cancers before an immune response can be elicited. The short median survival of patients with metastatic melanoma means that if a course of vaccination lasts for three months, many patients will not be able to complete it. In one sense, it is surprising that clinical effects of immunotherapy have ever been seen in this population.

Early immunotherapy studies in melanoma used approaches that were thought to be good ideas but had not been validated in humans. Clinical responses were rare, but significant toxicity was also relatively uncommon. Because of the infrequency and unpredictability of clinical responses to treatment, valid immunological surrogate endpoints were required. Until recently these assays were not available. Newer assays are now available that are much more reproducible and sensitive (reviewed in reference 16). For the first time, immunological responses can now be characterised and measured, finally raising the possibility of optimisation of vaccine protocols.

For this reason, several investigators including our group are now turning to patients with earlier stages of disease. We are performing a series of small studies involving patients who have had cancers that express the antigen of interest but which have been removed. These patients are eligible if they arbitrarily have a risk of relapse of at least 25% over five years. For melanoma, this means patients with a primary melanoma of ≥1.5 mm, or ≥1.0 mm if ulcerated. Patients with resected nodal disease or resected distant metastases have a higher risk of recurrence and are also eligible. Depending on the nature of the study, it is sometimes necessary to limit eligibility to patients of a particular HLA type. Patients in these studies are usually able to finish a three-month course of vaccination without a significant risk of relapse of their melanoma. This then provides the opportunity to determine whether a vaccination strategy that seemed a good idea on paper is in fact able to elicit measurable immunological responses. The underlying assumption is that only if an immune response is measurable will it be able to mediate an anti-tumour response. This assumption has never been proven, but it provides a reasonable starting point.

Where to now?

As a result of these observations at both the preclinical and clinical level, it is possible to conceive of a strategy that is most likely to be effective. It is important to identify antigens that are widely expressed and are important to the malignant phenotype so that tumours are not easily able to down regulate their expression. These antigens then need to be delivered in such a way that effective antigen presentation can take place and a vigorous immunological response can be elicited. Our understanding of the basic biology of the process suggests that this will best be done in a context that provides an inflammatory or “dangerous” microenvironment in the region of the antigen. Once an immune response is elicited, it will then be important to sustain it so that effector T cells continue to traffic through the tissues and are capable of recognising and killing any residual or recurrent tumour cells. At the same time, consideration must also be given to non-T cell approaches so as to capture the inevitable “escape” mutants.

These approaches may also need to be considered in the context of other treatment modalities, such as chemotherapy, radiotherapy, or in combination with newer biological agents such as inhibitors of tumour angiogenesis, receptor tyrosine kinase inhibitors, cell cycle inhibitors and monoclonal antibodies. Once an optimal vaccination strategy has been identified and validated using immunological surrogate measures, it will then be important to test these approaches once again in patients with advanced disease. For patients whose disease is progressing rapidly, it will probably be necessary to combine these treatments with some other intervention in order to change the kinetics of the tumour growth so as to allow time for an immune response to develop. However, it is also likely that one of the most useful applications of immunotherapy will be in the adjuvant setting, when the burden of disease is at its lowest ebb. Trials in this clinical setting can only be justified once the optimal method of vaccination has been determined.

References


