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Cell transfer immunotherapy for metastatic solid cancer—what clinicians need to know

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Abstract

Cancer immunotherapy using the adoptive transfer of autologous tumor-infiltrating lymphocytes results in objective cancer regression in 49–72% of patients with metastatic melanoma. In a pilot trial combining cell transfer with a maximum lymphodepleting regimen, complete durable responses were seen in 40% of patients, with complete responses ongoing beyond 3 to 7 years. Current approaches to cell transfer therapy using autologous cells genetically engineered to express conventional or chimeric T-cell receptors have mediated cancer regression in patients with metastatic melanoma, synovial sarcoma, neuroblastoma and refractory lymphoma. Adoptive cell transfer immunotherapy is a rapidly developing new approach to the therapy of metastatic cancer in humans. This Review will emphasize the current available applications of cell transfer immunotherapy for patients with cancer.

Introduction

Attempts to develop effective immunotherapies for the treatment of patients with metastatic cancer fall into three major categories: nonspecific stimulation of the immune system, active immunization using cancer vaccines, and adoptive cell transfer immunotherapy. Nonspecific approaches include the upregulation of immune reactivity either by general immune stimulation (such as the administration of interleukin [IL]-2) or the blockade of inhibitory influences (such as the use of an anti-CTLA4 antibody).[1] These approaches can mediate tumor regression in about 10–15% of patients with metastatic melanoma and renal cell carcinoma,[2] these tumors seem to be responsive because of their ability to naturally give rise to high levels of antitumor T cells that can be stimulated by these immune modulators. Active immunization with cancer vaccines is an attractive therapy approach because of its ease of administration and lack of toxi city; however, no approach has yet been developed that can reproducibly mediate the regression of metastatic cancers at clinically meaningful levels. Adoptive cell transfer immunotherapy is the most effective form of immunotherapy and involves the transfer of immune cells with antitumor activity into cancer patients. It has been shown to mediate the objective regression of metastatic melanoma in up to 72% of patients, including the induction of up to 40% of complete durable responses.[3] Recent developments involving the introduction of genes encoding antitumor T-cell receptors

Competing interests

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(TCRs) into lymphocytes have provided immune cells capable of mediating cancer regressions in patients with several different cancer types and this approach is under vigorous development at a variety of academic centers. In this Review, I present a brief history of the development of immunotherapy for patients with metastatic cancer and describe the current state of development of adoptive cell transfer immunotherapy.

A very brief history of cancer immunotherapy

Following the first quantitative descriptions of antibodies in the 1880s, studies of the humoral arm of the immune system dominated immunology until the 1960s. The importance of the cellular arm of the immune system was not known and the word 'lymphocyte' was not listed in the index of the 1958 issue of the *Journal of Immunology*. Two advances in the 1940s were harbingers of the future development of cellular and cancer immunology. In 1942, Landsteiner and Chase demonstrated that delayed hyper sensitivity could be transferred between mice using immune cells obtained from sensitized donors,[4] and a year later Gross showed that syngeneic mice immunized against tumors in the same inbred strain could reject a subsequent tumor challenge.[5] This work, however, received little attention until the 1960s when many studies demonstrated the importance of cellular immunology as a mediator of allograft rejection as well as protection against the transfer of mouse tumors. Studies were hindered by the inability to manipulate lymphocytes and sustain their survival outside the body. The identification of a T-cell growth factor (IL-2) in 1976[6] provided, for the first time, a means to grow T lymphocytes *in vitro*, although the tiny amounts of IL-2 available from *in vitro* cell lines severely limited its application to cancer immunotherapy. The identification of the DNA sequence of the gene encoding IL-2 in 1983,[7] and the expression of this gene in *Escherichia coli* and biological characterization of recombinant IL-2 a year later[8] provided new opportunities for therapy in humans.

The demonstration in 1985 that the administration of IL-2 to patients could mediate the regression of large, established, invasive human cancers[9] represented the first demonstration that manipulation of the human immune system could reproducibly lead to tumor regression. These data ultimately led to the FDA approval of IL-2 for the treatment of patients with metastatic renal cell carcinoma in 1992 and for metastatic melanoma in 1998. Durable complete responses of metastatic disease in 5% to 10% of patients have been observed more than 20 years after IL-2 administration.[10] Other nonspecific immunotherapy approaches, such as the administration of the monoclonal antibody ipilimumab that can block inhibitory influences (for example CTLA-4 engagement on lymphocytes), have also been shown to lead to tumor regression in patients with melanoma.[11]

The ability of IL-2 to support the growth of human lymphocytes in the laboratory with maintenance of their immunologic activity led to the molecular characterization of the first human cancer antigen in 1991.[12] In the next two decades, hundreds of antigens and antigenic epitopes expressed on cancer cells recognized by the immune system were described,[13,14] which led to a myriad of clinical trials assessing immunization with peptides, proteins, dendritic cells, recombinant viruses, whole cells, and plasmid DNA. With very few exceptions these trials have failed to demonstrate a clinical benefit. Recently, a dendritic cell vaccine was reported to prolong the survival of patients with prostate cancer by about 4

months, though there were no tumor regressions or prolongation of progression-free survival in treated patients.[15] There are many difficulties in vaccine approaches, including the inability to generate large numbers of antitumor cells with high affinity for tumor antigen, as well as an immunosuppressive micro environment at the tumor site that can suppress potent effector mechanisms.[16] Many of these difficulties have been overcome by the use of adoptive cell transfer of antitumor immune cells—this treatment approach, referred to as adoptive cell therapy (ACT), provides the best direct evidence that the immune system is capable of curing patients with metastatic cancer.[17–19] Although most studies of adoptive immunotherapy have dealt with the treatment of patients with metastatic melanoma, there are now examples of the successful application of this treatment to patients with other types of malignancies.[20–25]

ACT with tumor-infiltrating lymphocytes

ACT is a treatment approach that involves the identification, *in vitro*, of autologous lymphocytes with anti-tumor activity, the *in vitro* expansion of these cells to large numbers and their infusion into the cancer-bearing host.[1] Lymphocytes used for adoptive transfer can either be derived from the stroma of resected tumors or genetically engineered to express antitumor TCRs (Figure 1). ACT has several theoretical advantages compared with other forms of immunotherapy. Large numbers of cells (often up to 10^{11} cells) with antitumor activity can be grown *in vitro* and cells that exhibit high recognition of tumor antigens can be selected for infusion using *in vitro* assays. The cells can be activated *ex vivo* to exhibit anti-tumor effector functions and thus overcome the suppressive influences that exist *in vivo* that can limit the antitumor activity of T cells. Most importantly, the host can be manipulated before the cell transfer to provide an altered microenvironment for the transferred cells; multiple suppressive mechanisms, such as T-regulatory lymphocytes or myeloid-derived suppressor cells can significantly interfere with the antitumor activity of lymphocytes and the ability to eliminate these suppressor cells before the administration of antitumor effector cells represents a unique advantage of ACT.

Studies in animal models and patients with melanoma demonstrated that lymphocytes infiltrating into growing tumors can often exhibit *in vitro* evidence of antitumor activity when removed from the tumor and grown *in vitro*.[26–28] In patients with melanoma, these tumor-infiltrating lymphocytes (TILs) can directly lyse tumor cells and secrete cytokines such as γ-interferon, IL-2 and tumor necrosis factor when encountering tumor anti-gens.[27,28] In the initial studies of the administration of these TILs to patients with metastatic melanoma, transient tumor reductions were seen; however, the inability of these cells to persist *in vivo* following adoptive transfer severely limited their antitumor activity.[28,29] An important modification of this approach demonstrated that the administration of a non-myeloablative lymphodepleting preparative regimen consisting of cyclophosphamide and fludarabine before the adoptive transfer of anti-tumor effector cells could lead to dramatic increases in the persistence of the transferred cells *in vivo* and a dramatic increase in their antitumor activity.[17,18] This regimen depleted circulating lymphocytes for about 8 days before host hematopoietic cells recovered. TILs with antitumor activity, administered at a time of maximum lymphodepletion, could be found circulating in patients many months after adoptive transfer, and in some patients comprised 75% of all circulating CD8 cells.[17]

The cells expanded almost a thousandfold *in vivo* as they circulated, infiltrated into organs and became activated by tumor deposits throughout the body. Early studies showed that almost 50% of 43 heavily pretreated patients with metastatic melanoma experienced objective tumor regressions following cell transfer[18] and, in updated results,[3] 13% experienced durable, complete regressions ongoing beyond 5 years and are likely cured (Table 1; S. A. Rosenberg, unpublished data).

At the same time the early clinical studies were being conducted, animal experiments demonstrated that there was a direct correlation between the intensity of the lymphodepletion and the antitumor effects of the transferred cells.[30] Thus, two pilot trials were conducted in 25 patients each in which either 2 Gy or 12 Gy total body irradiation was added to the cyclophosphamide–fludarabine lymphodepleting preparative regimen (Figure 2).[30] These treatments resulted in the highest levels of objective and complete responses ever seen in the treatment of patients with metastatic melanoma[3] (Table 1 and Figure 3; Rosenberg, S.A. unpublished data). Objective response rates using RECIST criteria were seen in 49% to 72% of all patients. The complete response rate in the last trial (12 Gy total body irradiation) was 40%. Of the 93 patients that took part in these trials, 20 patients experienced a complete regression of all metastatic cancer and 19 patients have ongoing complete regressions from 3–7 years and might be cured. The 5-year overall survival rate was 29% (Figure 3; S. A. Rosenberg, unpublished data).

Of particular importance was the ability of ACT to mediate durable complete regressions in heavily pretreated patients with extensive tumor burdens (Figure 4). A large proportion (86%) of the 93 patients in these trials had visceral disease (stage M1b or M1c) as did 17 of the 20 complete responders.[3] All but five of the 93 patients and all but two of the complete responders had progressive disease following systemic treatment before receiving ACT. In addition, 83% of the patients were refractory to prior treatment with IL-2 and 40% had received both IL-2 and chemotherapy. The same complete regression rate was seen regardless of whether patients had received IL-2, chemotherapy, γ-interferon or anti-CTLA-4 monoclonal antibody either alone or in combination.[3]

A comparison of ACT with available treatments for patients with metastatic melanoma is shown in Table 2. Only two treatments are approved by the FDA for patients with metastatic melanoma: dacarbazine chemotherapy and IL-2. Several experimental treatments have been reported, including the use of ipilimumab (an anti-CTLA-4 antibody),[11] and the administration of a BRAF inhibitor, the latter suitable for the approximately half of patients that have mutated *BRAF*.[31] Complete response rates for these treatments vary between approximately 1% and 6%, compared with the 21.5% complete response rate seen with ACT. The ability to cure patients with metastatic cancer is dependent on the mediation of durable complete responses, and the capacity of ACT to do so has resulted in impressive long-term survival of patients receiving adoptive immunotherapy.

Studies in murine models and humans have defined the mechanisms of action of the lymphodepleting chemo therapy before cell transfer.[32,33] Lymphodepletion has a variety of positive impacts including the elimination of T-regulatory cells or myeloid-derived suppressor cells and the elimination of endogenous lymphocytes that provide a sink for

growth promoting cytokines such as IL-7 and IL-15. Although IL-15 is not normally detected in the sera of patients, high levels of IL-15 appear in the blood following lymphodepletion and provide a homeostatic growth stimulus to the adoptively transferred lymphocytes.[18] The lymphodepleting regimen can also lead to activation of antigen-presenting cells, in part by increased susceptibility to toll-like receptor stimulation.[34]

Multiple studies have identified the characteristics of cells that are likely to mediate tumor regression. In concert with studies in animal models,[33] the administration of cells with a high proliferative potential—such as cells with longer telomeres,[35] or cells that express markers indicative of less differentiation (such as CD27 and CD28)—is associated with higher levels of clinical response following ACT.[36] The persistence of the cells in the circulation 1 month after transfer[37] and a decrease in the reappearance of $CD4^+Foxp3^+$ T-regulatory cells in the circulation as hematopoietic reconstitution occurs also correlate with response (X. Yao *et al.* unpublished data).

ACT using autologous TILs is not suitable for all patients with metastatic melanoma. Patients must be able to tolerate the lymphodepleting chemotherapy and must remain suitable for treatment during the 4–6 weeks required to grow the cells *in vitro*. A simplified method for generating TILs for therapy using shorter culture times has recently been described,[38] and early studies of the infusion of these ‘younger’ TILs have reported tumor regressions.[39,40] In addition to other requirements, patients must have tumor deposits that can be resected for growth of TILs and although most patients with metastatic melanoma have resectable lesions, for those patients that do not have resectable lesions this requirement can be overcome by genetically engineering circulating lymphocytes to exhibit antitumor activity.

ACT with genetically modified lymphocytes

The success of ACT using autologous TILs in patients with metastatic melanoma suggested that this approach could be effective for the treatment of patients with other cancer types. Melanoma, however, is unique among cancers in that it naturally gives rise to high levels of antitumor T cells infiltrating into tumors as evidenced in part by the objective responses seen to nonspecific immune modulators such as IL-2 and ipilimumab.[9–11] Only rare cells with antitumor activity can be identified from patients with other types of cancer. The ability to transduce genes into lymphocytes with 80–90% efficiency using gamma retroviruses or lentiviruses provides an opportunity to genetically engineer lymphocytes with genes encoding TCRs that recognize tumor antigens or with genes encoding molecules that increase their antitumor activity. A variety of genetic alterations of lymphocytes for possible use in cell transfer are shown in Table 3. Genes encoding cytokines such as IL-2 or IL-15 can enable antitumor T cells to generate their own growth-promoting cytokines,[41,42] lessen the need for the systemic administration of these substances and sustain cell survival following cytokine withdrawal. The survival and function of antitumor T cells used for ACT can be improved by the introduction of co-stimulatory molecules such as CD80, co-receptor molecules such as CD8 or molecules such as BCL2 to inhibit apoptosis, molecules such as CD62L or CCR7 that facilitate the traffic of cells to appropriate *in vivo* locations,[43] and the

introduction of telomerase that prevents telomere shortening and thus enhances the proliferative potential of the transferred cells.[35]

The introduction of genes encoding receptors that recognize cancer antigens can be used to convert normal circulating peripheral lymphocytes into cells with anti-tumor activity. This function provides the reproducible ability to generate cells with antitumor activity against cancers other than melanoma and widens the application of ACT to patients with frequently occurring cancers. Using this gene therapy approach it is only necessary to identify very few cells with antitumor activity that can then serve as the basis for the isolation of the genes encoding these antitumor receptors. Once these genes are incorporated into transducing vectors they can be used to generate cells for the treatment of large numbers of patients.

Conventional TCRs are composed of alpha and beta chains that form a heterodimer that recognizes peptides derived from intracellular cancer-associated antigens and are presented on the surface of MHC molecules on tumor cells. Genes encoding TCRs that recognize a wide variety of cancer antigens have now been identified including the recognition of melanoma–melanocyte antigens and differentiation antigens and a variety of cancer–testes antigens expressed on common epithelial cancers.[44,45] The affinity of these transduced TCRs can be further amplified by modifying individual amino acids in their antigen combining regions.[46] Other genetic modifications of the TCR, such as the introduction of cysteines to form interchain disulfide bonds or the introduction of murine constant regions, can prevent mispairing of introduced alpha and beta chains of the modified TCR with chains from the endogenous TCR.[47,48]

The choice of target antigen is critical to the success of ACT. The first example of the successful treatment of patients with genetically modified lymphocytes involved the introduction of genes encoding TCRs that recognized the MART1 and gp100 melanoma–melanocyte differentiation antigens.[49] Up to 30% of patients receiving cells transduced with these TCRs exhibited objective cancer regressions. When targeting melanoma–melanocyte antigens the transferred T cells also target normal melanocytes in the eye and in the ear that can result in visual or auditory dysfunction.[50] The local application of steroids abrogated these side effects without interfering with the systemic tumor regression mediated by these transferred T cells.

Cancer–testes antigens are expressed during fetal development and represent ideal targets for ACT because they are re-expressed in cells from common epithelial cancers but are not expressed in any adult tissue except the testes (which does not express MHC antigens and is thus protected from immune attack). Dozens of cancer–testes antigens have been described encompassing most tumor types (Figure 5).[51,52] ACT using gene-modified cells to target the NY-ESO-1 cancer–testes antigen resulted in objective cancer regressions in five of seven patients with heavily pretreated synovial cell sarcomas, a tumor type that expresses high levels of the NY-ESO-1 cancer–testes antigen.[20] Objective cancer regressions were observed in five of 12 patients with heavily pretreated metastatic melanomas after treatment with autologous NY-ESO-1 TCR gene-engineered T cells.[20] Examples of responses of patients with synovial cell sarcomas are shown in Figure 6. TCRs against the MAGE-A3 cancer–testes antigen are entering clinical trials.[51] ACT using gene-modified cells that recognize

cancer–testes anti-gens could potentially be suitable for the treatment of 20–30% of patients with common epithelial cancers and these studies are actively being pursued.

The use of ACT for cancer treatment is limited mainly by the ability to generate TCRs that specifically recognize cancer-associated antigens. To broaden the application of this approach, techniques have been developed to generate TCRs reactive with cancer antigens by immunizing HLA transgenic mice with tumor-antigen sequences that are different from sequences found in the mouse. Thus, the problems of tolerance of humans to these antigens can be overcome and high affinity TCRs can be identified. This approach has been successfully used to generate high-affinity TCRs against the gp100 melanoma–melanocyte antigen used to treat patients with metastatic melanoma,[50] and TCRs that recognize carcinoembyronic antigen overexpressed on tumors from patients with colorectal and other cancers.[22]

Chimeric antigen receptors

Conventional TCRs are restricted to the recognition of antigens presented on specific MHC molecules. A technique for the development of antitumor T cells based on the recognition of antibodies (called chimeric antigen receptors [CAR]) was developed by Eshhar and co-workers.[53] In this approach, the antigen-combining regions of the heavy and light chains of antibodies are genetically linked and attached to T-cell intracellular signaling molecules. When these genetic constructs are transduced into lymphocytes, the lymphocyte gains the ability to recognize antigens based on the recognition of the antibody rather than that of a conventional TCR. Cells expressing these CAR have significantly widened the potential for the application of adoptive immunotherapy. T cells expressing CAR targeting the GD2 antigen have been used to mediate tumor regression in patients with neuroblastoma.[23] Carbonic anhydrase-8 is overexpressed on renal cancers and the use of CAR targeting this antigen was reported, although toxicity to the hepatobiliary tree was observed that limited its use.[54] The most successful application of this approach to date has been the use of CARs that target the CD19 B-cell antigen highly expressed in over 80% of patients with non-Hodgkin lymphomas and chronic lymphocytic leukemia. Successful regression of bulky lymphoma deposits in heavily pretreated patients refractory to standard treatment has been achieved in four of six patients receiving ACT using CAR targeting the *CD19* gene (J. Kochenderfer, unpublished observations).[21] Recently, CAR targeting VEGFR2, which is overexpressed in the tumor vasculature, entered clinical testing.[55]

There are potential dangers associated with the use of ACT that are based on the appropriate selection of the target antigen; the potency of genetically modified T cells to kill target cells as well as secrete large amounts of cytokine.[56,57] Although concern has been expressed about the induction of graft-versus-host disease in mouse models when the introduced TCR chains recombine with endogenous TCR chains,[58] no evidence of graft-versus-host disease has been seen in over 100 patients treated with this gene therapy approach.[59]

Conclusions

ACT using autologous TILs represents the most-effective approach for the curative treatment of patients with metastatic melanoma. The need to grow a patient's own cells for therapy represents the ultimate in 'personalized' medicine since a new 'drug' is created for each patient, a treatment paradigm that does not fit into the 'off-the-shelf' requirement of pharmaceutical and bio-technology companies. Currently, only a few academic cancer centers offer ACT for the treatment of patients with metastatic melanoma though recent simplifications of the methods for cell growth could facilitate the production of treatment-quality cells by academic blood banks or individual academic laboratories. The success of ACT using TILs for the treatment of melanoma and gene-modified cells for the treatment of many refractory cancer types is providing a stimulus for the more widespread application of this treatment approach.

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Released: 2 August 2011; Expires: 2 August 2012

Learning objectives

Upon completion of this activity, participants should be able to:

1. Describe the practice of cell transfer immunotherapy
2. Compare cell transfer immunotherapy with other treatments for metastatic melanoma
3. Evaluate the role of immune suppression in cell transfer immunotherapy
4. Assess uses of cell transfer immunotherapy for cancers other than melanoma

Key points

- Adoptive cell transfer immunotherapy can mediate the objective regression of metastatic melanoma in 49–72% of patients
- Complete durable regressions using cell transfer immunotherapy have been seen in up to 40% of patients and it is likely curative in many patients
- The high incidence of durable complete regressions in patients with melanoma receiving cell transfer immunotherapy is similar, independent of the patient's prior treatment
- Cell transfer immunotherapy can be extended to additional cancer types by using autologous lymphocytes that are genetically transduced to express antitumor T-cell receptors (TCRs) or chimeric antigen receptors (CARs)
- Using these TCR or CAR gene transduced cells, objective regressions have been seen in patients with synovial cell sarcoma, lymphoma, and melanoma
- The opportunity to genetically modify autologous lymphocytes with a variety of genes that can improve their antitumor function is opening new possibilities for developing effective cancer treatments

Review criteria

A formal literature search for this Review was not performed. This Review includes a summary of the author's work and knowledge based on reading the oncology and immunology literature. Knowledge gained from regular attendance at conferences, workshops, and other national and international meetings was also included.

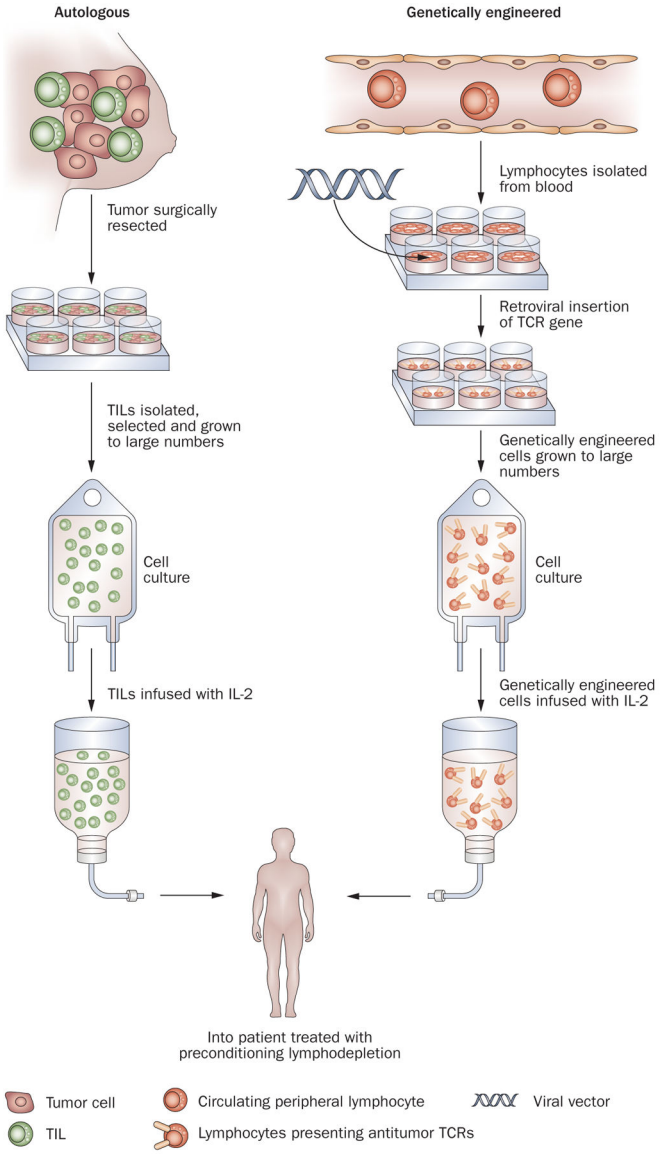

Figure 1 |.

Adoptive cell transfer immunotherapy using either autologous TILs obtained from resected tumors or using peripheral lymphocytes genetically transduced with retroviruses to express antitumor T-cell receptors. Cells are expanded *in vitro* to large numbers (up to 10^{11}) and infused after patients have received a preparative lymphodepleting regimen. Abbreviations: TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte.

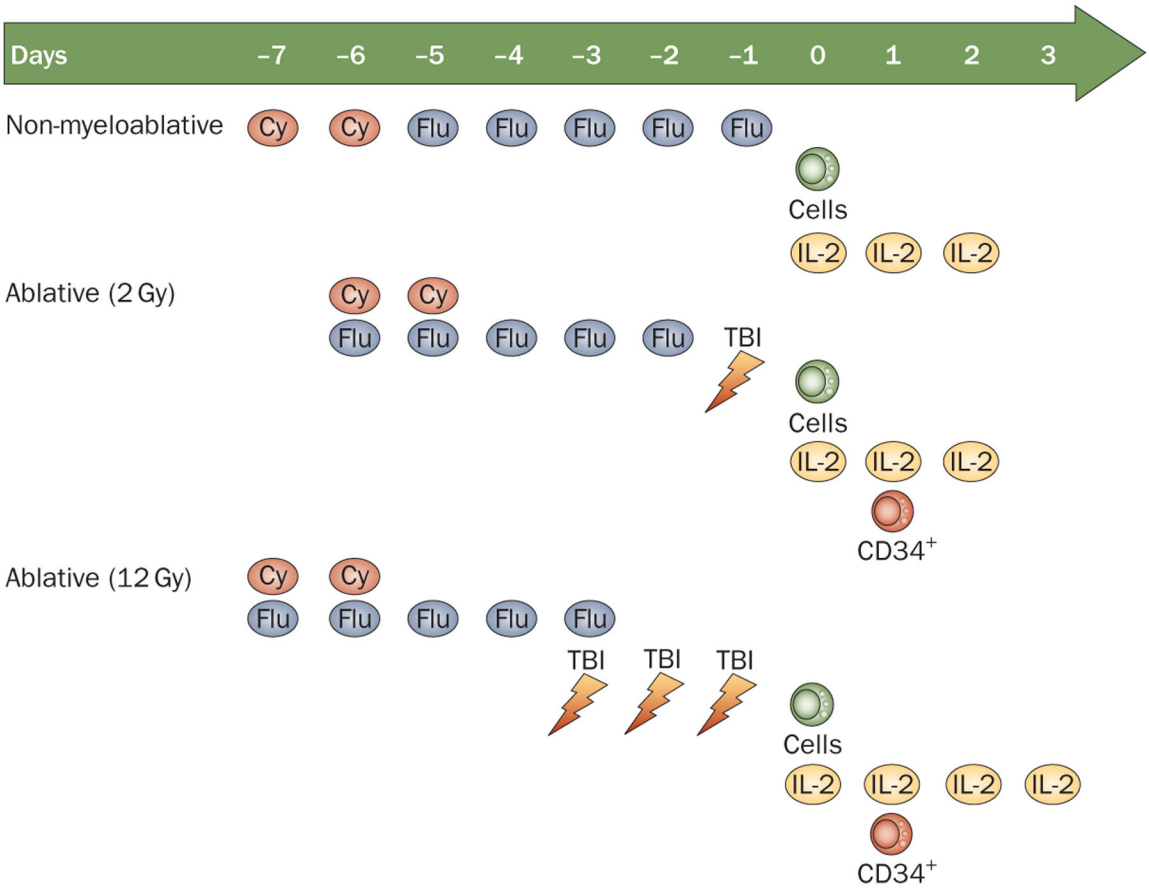

Figure 2 |.

Preparative regimens for cell transfer. A comparison of the lymphodepleting methods used: non-myeloablative and TBI (using 2 Gy and 12 Gy).[3] Abbreviations: Cy, cyclophosphamide; Flu, fludarabine; IL, interleukin; TBI, total body irradiation.

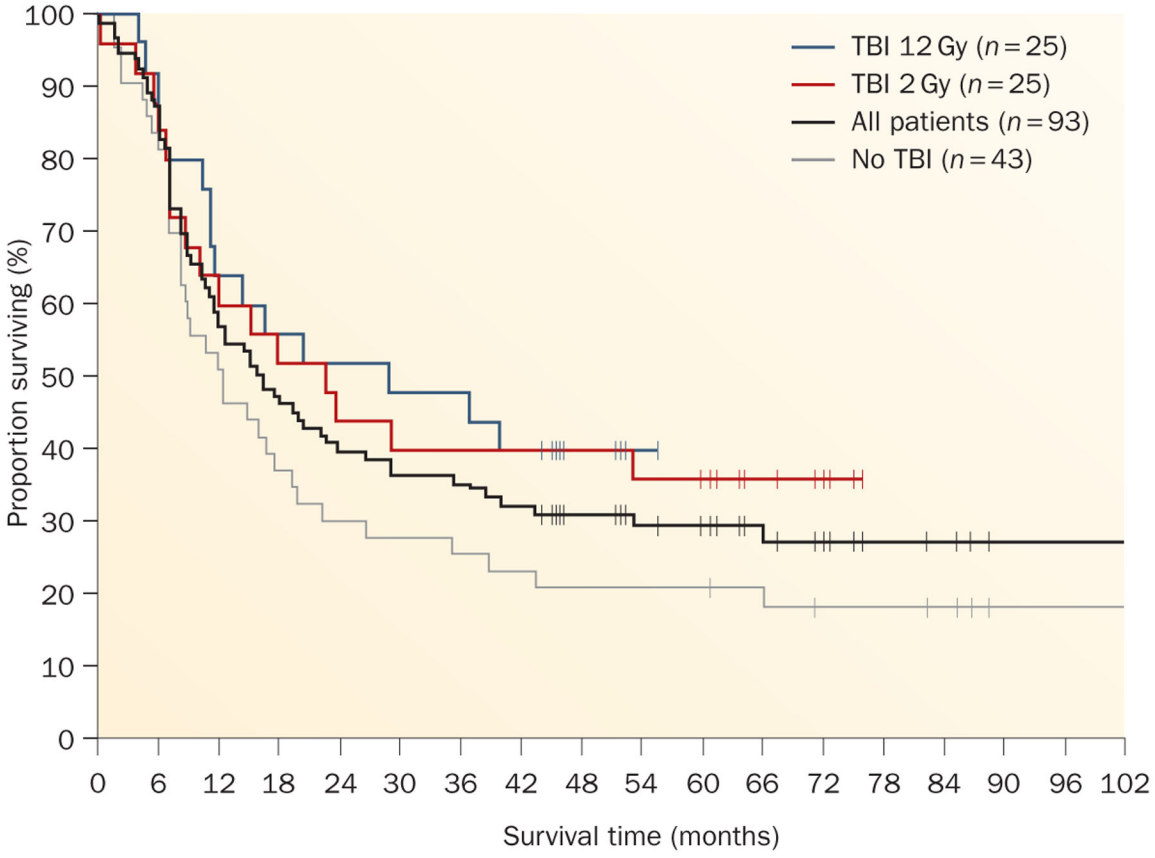

Figure 3 |.

Survival of patients with metastatic melanoma treated with autologous tumor-infiltrating lymphocytes. Patients were treated in three sequential trials using a cyclophosphamide–fludarabine lymphodepleting regimen either alone (no TBI) or plus 2 Gy or 12 Gy TBI (Figure 2). Median follow up of 69 months. Abbreviation: TBI, total body irradiation.

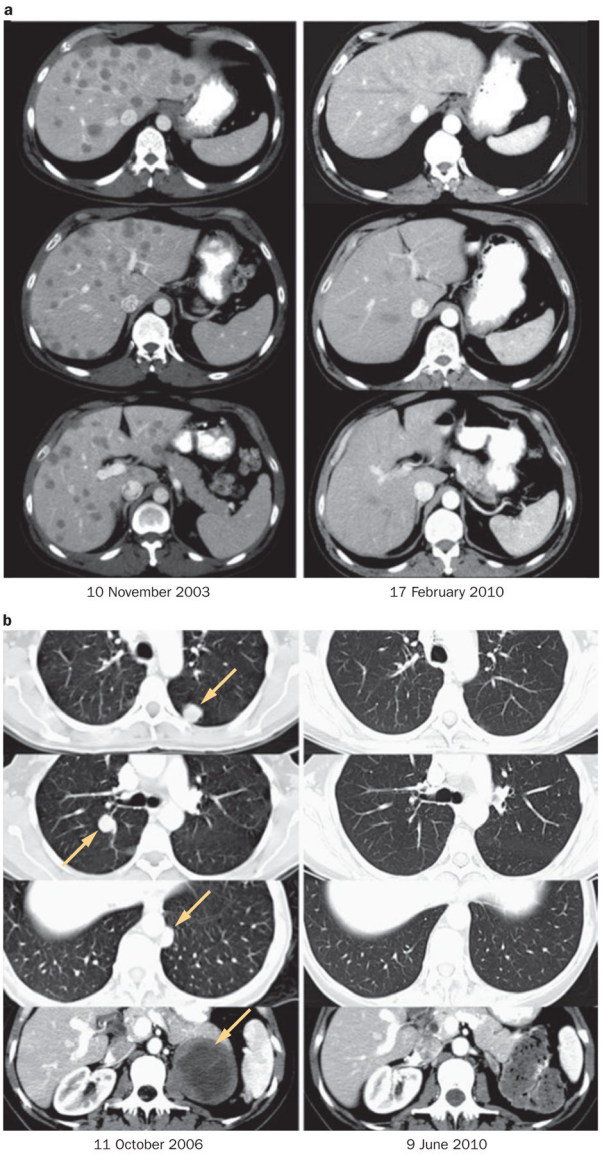

Figure 4 |.

Examples of complete durable responses in patients receiving adoptive cell therapy.[3] **a** | Regression of multiple liver metastases (patient received non-myeloablative lymphodepletion; Figure 2). **b** | Regression of multiple lung metastases and an adrenal metastasis (patient received total body irradiation 12 Gy lymphodepletion; Figure 2). Permission obtained from the American Association for Cancer Research © Rosenberg, S. A. *et al. Clin. Cancer Res.* **17**, 4550–4557 (2011).

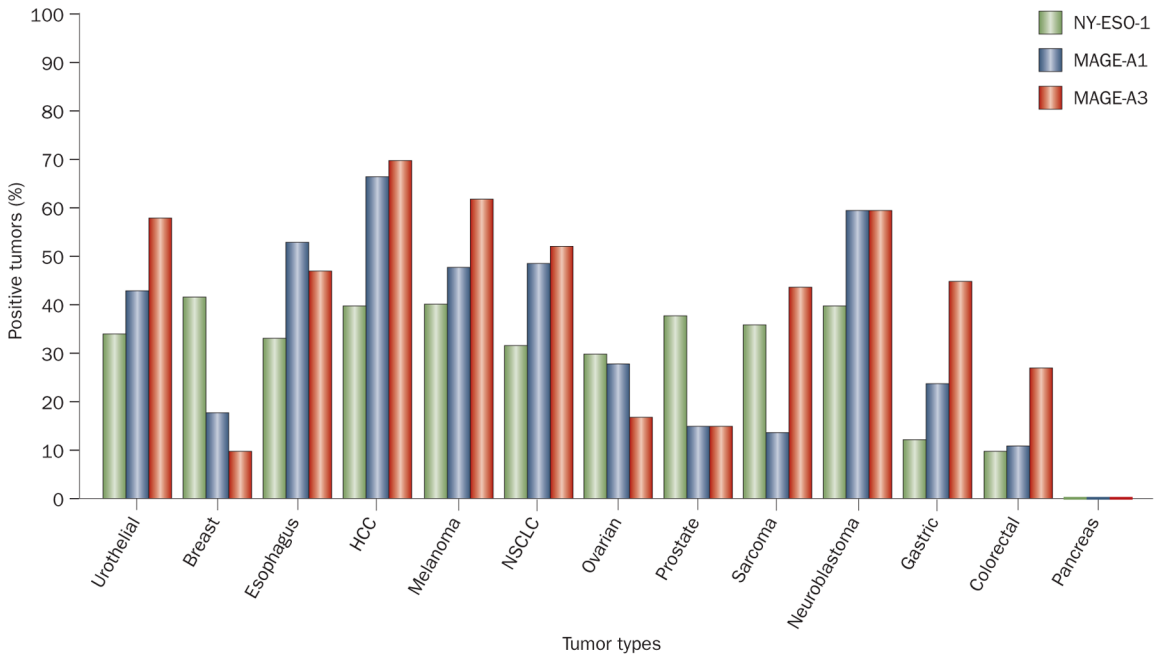

Figure 5 |.

Expression of three cancer–testes antigens (NY-ESO-1, MAGE-A1, MAGE-A3) in a variety of cancer types. Abbreviations: HCC, hepatocellular carcinoma; NSCLC, non-small-cell lung cancer.

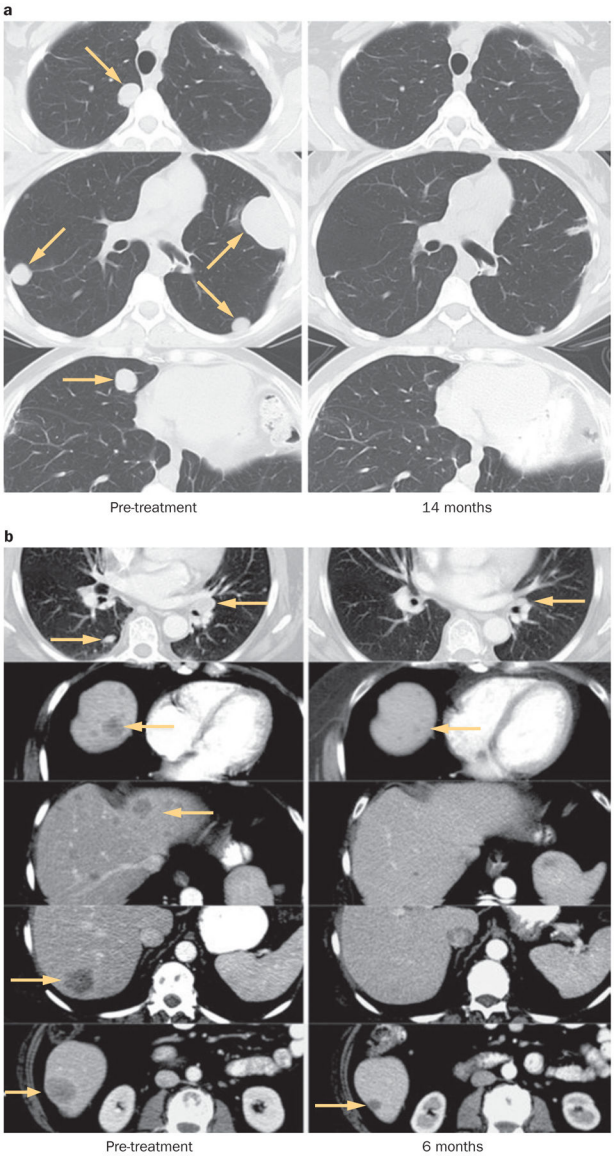

Figure 6 |.

Examples of cancer regression in patients with synovial cell sarcoma treated with autologous T cells transduced with the gene encoding an anti-NYESO-1 T-cell receptor. **a** | Regression of multiple lung metastases. **B** | Regression of multiple lung and liver metastases. Permission for part a obtained from the American Society of Clinical Oncology © Robbins, P. F. *et al. J. Clin. Oncol.* **29**, 917–924 (2011).

Table 1 |

Efficacy of adoptive cell transfer therapy

Treatment	*n*	PR, *n* (duration, months)	CR, *n* (duration, months)*	OR‡
No TBI	43	16 (84, 36, 29, 28, 14, 12, 11, 7, 7, 7, 7, 4, 4, 2, 2, 2)	5 (>86, >84, >83, >82, >69)	49%
2 Gy TBI	25	8 (14, 9, 6, 6, 5, 4, 3, 3)	5 (>73, >70, >65, >62, >59)	52%
12 Gy TBI	25	8 (21, 13,7,6,6,5,3,2)	10 (>53, >50, >49, >49, >44, >43, >43, >43,>42, 19)	72%

*20 CRs: 19 ongoing at 42–86 months.

‡52 responding patients: 42 had prior IL-2 therapy, 22 had prior IL-2 and chemotherapy. Abbreviations: CR, complete response; IL, interleukin; OR, overall response; PR, partial response; TBI, total body irradiation.

Table 2 |

Objective responses in patients with metastatic melanoma

Treatment	*n*	CR	PR	OR
Dacarbazine[60]	149	4 (2.7%)	14 (9.4%)	18 (12.1%)
lnterleukin-2[61]	270	17 (6.3%)	26 (9.6%)	43 (17.9%)
Ipilimumab[11]	540	3 (0.6%)	35 (6.4%)	38 (7.0%)
Vemurafenib[31]	219	2 (0.9%)	104 (47.5%)	106 (48.4%)
Adoptive cell transfer[3]	93	20 (21.5%)	32 (34.4%)	52 (55.9%)

Abbreviations: CR, complete response; OR, overall response; PR, partial response.

Table 3 |

Potential gene alterations to improve the efficacy of cell transfer therapy

Genetic alterations	Target
Expand tumor recognition	T-cell receptors or chimeric T-cell receptors that recognize cancer antigens
Cytokines	*IL-2, IL-12, IL-15, IL-17, IL-21, IL-23*
Co-stimulatory molecules	*CD8, CD27, CD80, 41BBL, OX40L*
Antiapoptotic molecules	*BCL2, BCL2L1, FLIP, TIPE-2*
Reverse inhibitory influences	Knock out: *SHP-1, PD-1, CTLA4, SOCS, CIS*; dominant negative: *TGF-β, CBLB*
Trafficking molecules	*CD62L, CCR7, CXCR2, CXCR4*
Improve cell survival	Telomerase; knock out: *TP53*