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Trial Watch

Adoptive cell transfer for anticancer immunotherapy

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Abbreviations: ACT, adoptive cell transfer; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CA9, carbonic anhydrase IX; CAR, chimeric antigen receptor; CIK, cytokine-induced killer; DC, dendritic cell; DTH, delayed-type hypersensitivity; EBV, Epstein-Barr virus; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; HCC, hepatocellular carcinoma; HSCT, hematopoietic stem cell transplantation; IL, interleukin; MAGEA3, melanoma antigen family A3; MDSC, myeloid-derived suppressor cell; MLANA, melan A; PBL, peripheral blood lymphocyte; RCC, renal cell carcinoma; TAA, tumor-associated antigen; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; VSC, virus-specific T cell

The expression "adoptive cell transfer" (ACT) is commonly employed to indicate an immunotherapeutic regimen involving the isolation of autologous blood-borne or tumor-infiltrating lymphocytes, their selection/expansion/activation ex vivo, and their reinfusion into the patient, most often in the context of lymphodepleting pre-conditioning and in combination with immunostimulatory treatments. Optionally, the cellular material for ACT is genetically manipulated before expansion to (1) target specific tumor-associated antigens; (2) endogenously express immunostimulatory molecules; and/or (3) persist for long periods upon reinfusion. Consistent efforts have been dedicated at the amelioration of this immunotherapeutic regimen throughout the past decade, resulting in the establishment of ever more efficient and safer ACT protocols. Accordingly, the number of clinical trials testing ACT in oncological indications does not cease to increase. In this Trial Watch, we summarize recent developments in this exciting area of research, covering both high-impact studies that have been published during the last 12 months and clinical trials that have been launched in the same period to evaluate the safety and therapeutic potential of ACT in cancer patients.

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Introduction

The term "adoptive cell transfer" (ACT) is generally employed to identify a peculiar instance of anticancer immunotherapy relying on (1) the isolation of circulating or tumor-infiltrating lymphocytes; (2) their selection/expansion/activation ex vivo; and (3) their (re-)introduction into the patients, near-to-invariably in the context of lymphodepleting pre-conditioning and in combination with immunostimulatory agents.[1-10] Thus, ACT should be conceptually differentiated from 2 other anticancer treatments relying on the (re)infusion of living cells, i.e., dendritic cell (DC)-based therapy and allogeneic hematopoietic stem cell transplantation (HSCT). Indeed, while ACT consists in the (re)infusion of autologous tumor-reactive lymphocytes, DC-based interventions (1) aim at (re)activating an endogenous tumor-specific immune response, de facto constituting anticancer vaccines; and (2) are never implemented upon lymphodepletion.[11-16] Along similar lines, ACT cannot be compared with HSCT, a therapeutic option for patients affected by hematological neoplasms that involves (1) the eradication of a majority of malignant cells by lympho/myeloablating chemo(radio)therapy, and (2) the subsequent re-establishment of a healthy, allogeneic (and hence potentially tumor-reactive) immune system.[17,18] Of note, although the therapeutic activity of ACT is generally ascribed to $CD8^+$ T lymphocytes, the re-infusion of purified $CD4^+$ T cells has been shown to yield durable clinical responses in melanoma patients.[19] Conversely, in spite of encouraging preclinical observations,[20-26] the adoptive transfer of natural killer (NK) cells has been associated with a relatively deceiving clinical activity.[27-29] Although strategies for

endowing NK cells with MHC-independent, tumor-associated antigen (TAA)-specific reactivity may circumvent, at least in part, such a limitation,[30-33] these approaches have not yet been tested in the clinic. Along similar lines, the actual therapeutic potential of B lymphocytes in cancer patients has not yet been investigated,[34] possibly because these cells reportedly exert immunosuppressive effects (at least in some circumstances).[35-37]

In oncological settings including melanoma and renal cell carcinoma (RCC), ACT relies on the reinfusion of tumor-infiltrating lymphocytes (TILs) that have been expanded ex vivo in the presence of growth factors such as interleukin (IL)-2 and (optionally) specific or unspecific activation stimuli.[38,39] In most clinical scenarios, however, this strategy is unfeasible as (1) surgical/bioptic specimens for the isolation of TILs are not available, or (2) neoplastic lesions exhibit limited lymphocytic infiltration. Under these circumstances, ACT relies on peripheral blood lymphocytes (PBLs) that are endowed with tumor reactivity by genetic engineering.[40] Nowadays, this can be accomplished by 2 approaches. PBLs can indeed be manipulated to express a TAA-specific T-cell receptor (TCR),[40-44] or a so-called chimeric antigen receptor (CAR), i.e., a transmembrane receptor consisting in the TAA-binding domain of an immunoglobulin fused to an intracellular tail containing 1 or more immunostimulatory signaling modules.[45-51] As compared with TCRs, CARs are advantageous in that they allow adoptively transferred PBLs to recognize TAAs and exert robust cytotoxic functions in an MHC-independent fashion. In line with this notion, consistent rates of objective responses have been documented in cancer patients receiving CAR-engineered PBLs, especially in the case of hematological neoplasms.[49,52-58] Nonetheless, no protocol for ACT-based immunotherapy is currently approved by the US Food and Drug Administration (FDA) or other international regulatory agencies for use in cancer patients (source http://www.fda.gov).

Genetic engineering can also be employed to improve various aspects of the PBL biology prior to reinfusion, including proliferative capacity and in vivo persistence,[59-62] secretory profile,[60] tumor-infiltrating potential,[63,64] and cytotoxic activity.[65] Moreover, the cellular material for ACT can be derived in conditions that limit terminal differentiation, which is generally associated with at least some degree of proliferative impairment and/or functional exhaustion.[66-68] Such a "rejuvenation" can be achieved with pharmacological modulators that promote the expansion of stem-cell memory T (T_{SCM}) cells,[67,69-71] or via the induced pluripotent stem cell technology.[72-74] Both these approaches allow indeed for the generation of TAA-specific T lymphocytes exhibiting improved persistence and cytotoxic functions in vivo as compared with tumor-reactive T cells obtained by conventional methods.[70-74]

ACT is generally performed in the contest of lymphodepleting regimens and combined with immunostimulatory interventions.[75-77] Lymphodepletion has been consistently associated with an improvement in the clinical efficacy of ACT, presumably as (1) it relieves the potent immunosuppressive networks generally established in cancer patients by myeloid-derived suppressor cells (MDSCs)[78-80] and FOXP3$^+$ regulatory T cells;[81-85] and (2) it reduces the size of the so-called "cytokine sink," the compartment of endogenous immune effectors that may compete with re-infused lymphocytes for crucial cytokines such as IL-7 or IL-15.[86,87] Along similar lines, various immunostimulatory agents have been shown to ameliorate the therapeutic profile of ACT, including (1) several cytokines, boosting the proliferative potential and/or cytotoxic functions of re-infused lymphocytes;[88-91] (2) angiogenesis inhibitors, facilitating the homing of PBLs or TILs to malignant lesions;[92,93] (3) Toll-like receptor ligands, operating as adjuvants;[94-97] and (4) multiple chemotherapeutic agents that have been attributed a direct or indirect immunomodulatory activity.[98,99]

The major side effect of ACT-based immunotherapy stems from the activation of re-infused lymphocytes against a healthy tissue that expresses tumor-associated antigenic determinants, resulting in potentially lethal autoimmune reactions.[6,10,100,101] This is relatively more frequent when ACT relies on PBLs that are genetically instructed to recognize malignant cells, possibly reflecting the capacity of exogenous, high-affinity TCRs or CARs to break immunological tolerance.[102,103] Thus, the specificity of adoptively transferred cells determines not only the efficacy of ACT-based immunotherapeutic regimens but also their safety.[6] We have presented in previous Trial Watches how TAAs can be classified based on expression pattern and what are the advantages/disadvantages associated with the targeting of TAAs belonging to different of such categories.[104,105]

In previous issues of *OncoImmunology*, we detailed the scientific rationale behind the use of ACT for oncological indications and discussed recent clinical trials evaluating the immunotherapeutic profile of this regimen.[75,76] Here, we present the latest advances in the development of ACT-based anticancer immunotherapy.

Literature Update

Since the submission of our previous Trial Watch dealing with topic (March 2013),[75] the results of no less than 14 clinical trials testing ACT-based immunotherapy in cancer patients have been published in the peer-reviewed scientific literature (source http://www.ncbi.nlm.nih.gov/pubmed). These studies involved patients affected by a relatively heterogeneous panel of hematological and solid malignancies, including acute lymphoblastic leukemia (ALL),[58,106] acute myeloid leukemia (AML),[107] B-cell neoplasms,[108,109] lymphoma,[110] synovial sarcoma,[101] melanoma,[101,111,112] as well as breast,[113] esophageal,[101] nasopharyngeal,[114] hepatocellular,[115] and renal carcinoma (**Table 1**).[116,117]

Brentjens and colleagues investigated the safety and efficacy of autologous T cells engineered to express a CD19-targeting CAR in 5 individuals with relapsed B-cell ALL.[58] All these patients achieved minimal residual disease-negative complete remission upon treatment. Moreover, this immunotherapeutic approach was generally well tolerated, although circulating cytokines raised significantly in some patients, a situation that had to be managed with lymphotoxic steroid therapy. Interestingly, the severity of cytokine elevations positively correlated with disease burden prior

Table 1. Recently published clinical trials investigating the safety and efficacy of ACT-based immunotherapy in cancer patients

Indication(s)	Approach	N° of patients	Safety	Efficacy	Ref.
AML	Autologous T cells expressing a Lewis Y antigen-targeting CAR	4	No Grade 3–4 side effects	3 patients achieved objective responses	107
B-cell ALL	Autologous T cells expressing a CD19-targeting CAR	5	Raise in circulating cytokines in some patients, requiring lymphotoxic steroid therapy	All patients achieved minimal residual disease-negative complete remission upon treatment	58
		2	High number of Grade 3–4 side effects and cytokine-release syndrome	All patients achieved complete remission, 1 relapsed 2 mo after treatment owing to the surge of a $CD19^-$ leukemic clone	106
B-cell neoplasms	Allogeneic T cells expressing a CD19-targeting CAR	10	No severe toxicities, the most common side effects being transient hypotension and fever	3 patients achieved objective responses	108
	Allogeneic VSCs expressing a CD19-targeting CAR	8	No infusion-related toxicities	2 patients with relapsing disease achieved objective responses, 2 patients in remission remained so for > 8 we and > 9 mo post-treatment	109
Breast carcinoma	Autologous T cells activated with MCF-7 lysate-pulsed DCs	16	n.a.	7 patients exhibited an immunological response to therapy, correlating with prolonged overall survival	113
HCC	Autologous PBLs plus DCs pulsed with autologous tumor lysates	42	No severe toxicity, the most common side effects being Grade 1 skin reactions	Adjuvant immunotherapy yielded 5-y overall and disease-free survival rates of 64.3% and 35.7%, respectively	115
Lymphoma	Autologous EBV-specific T cells	50	No infusion-related toxicities	28 patients experienced remission and 21 achieved objective responses	110
Melanoma	$CD8^+$ T cell-enriched or young TILs	69	Grade 3 febrile neutropenia and Grade 4 sepsis in several patients	12/34 patients treated with young TILs and 7/35 patients receiving CD8+ T cell-enriched TILs responded to therapy	111
	Young TILs plus high-dose IL-2	80	Pulmonary congestion and hypotension in > 20% of patients	18 patients achieved a partial remission and 5 a complete remission	112
Nasopharyngeal carcinoma	EBV-specific CTLs plus gemcitabine and carboplatin	35	No severe toxicity, the most common side effects being Grade 1–2 fatigue and myalgia	Overall response rate of 71.4%, median OS and DFS of 29.9 and 7.6 mo, respectively	114
RCC	CIK cells plus high-dose IL-2	29	n.a.	Partial responses were documented in 4 individuals, disease stabilization in 18 subjects, and progressive disease in 7 patients; 1-y OS rate of 82.8%	116
	Autologous T cells expressing a CA9-targeting CAR	12	Grade 2–4 elevations of hepatic enzymes in 8 patients	No clinical responses were recorded	117
Esophageal carcinoma Melanoma Synovial sarcoma	Autologous T cells expressing a MAGE-A3-targeting TCR	9	Fatal leukoencephalopathy in 2 patients, Parkinson-like symptoms in 1 patient	5 patients experienced disease regression	101

Abbreviations. ACT, adoptive cell transfer; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CA9, carbonic anhydrase IX; CAR, chimeric antigen receptor; CIK, cytokine-induced cell; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DFS, disease-free survival; EBV, Epstein-Barr virus; HCC, hepatocellular carcinoma; IL-2, interleukin-2; MAGE-A3, melanoma antigen family A3; OS, overall survival; PBL, peripheral blood lymphocyte; RCC, renal cell carcinoma; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; VSC, virus-specific T cells. *Between 2013, March 1st and the date of submission.

to therapy. This suggests that the cytokine-release syndromes that often develop in the course of ACT-based immunotherapy may predict clinical efficacy, at least in some scenarios.[58]

Along similar lines, Grupp and coworkers reported on the clinical activity of autologous T lymphocytes engineered to express a CD19-targeting CAR in 2 children with relapsed and refractory pre-B-cell ALL.[106] In both cases, adoptively transferred T cells underwent a > 1000-fold expansion in vivo and colonized the bone marrow as well as the cerebrospinal fluid. A high number of Grade 3–4 side effects were recorded and both

children developed a cytokine-release syndrome (which required pharmacological management in one case) and B-cell aplasia. This said, both patients underwent complete remission, lasting for more than 11 mo in one of them. The other patient relapsed 2 mo after treatment, owing to the emergence of a $CD19^-$ leukemic clone.[106] These observations lend further support to the notion that immunotherapeutic strategies targeting multiple TAAs may not only improve the safety of this approach but also its efficacy.[118,119]

Ritchie et al. investigated the safety and efficacy of autologous T cells redirected against the Lewis Y antigen (a difucosylated Type 2 blood group-related antigen)[120] in 4 AML patients previously subjected to fludarabine-based pre-conditioning.[107] No Grade 3–4 side effects were recorded and 3 patients experienced objective responses (including a protracted remission). Of note, CAR-expressing T cells were shown to actively traffic to the bone marrow and to other proven sites of disease in the individuals who obtained the greatest benefits from treatment. Moreover, serial PCR-based analyses of the bone marrow and peripheral blood demonstrated that adoptively transferred T cells persisted for up to 10 mo in these patients.[107] This study demonstrates the safety and potential utility of autologous T cells retargeted against the Lewis Y antigen for the treatment of AML.

The group lead by Steven Rosenberg at the National Cancer Institute (Bethesda, MD USA) tested an innovative immunotherapeutic paradigm at the frontier between allogeneic HSCT and ACT in subjects with B-cell neoplasms that failed to respond to conventional allogeneic HSCT and donor lymphocyte infusions.[108] In this setting, 10 patients received a single infusion of allogeneic, rather than autologous, T lymphocytes engineered to express a CD19-specific CAR, in the absence of pre-conditioning. These cells were derived from the PBLs of each patient's allogeneic HSCT donor. None of the individuals enrolled in this study developed severe toxicities including graft-vs.-host reactions, the most common side effects being transient hypotension and fever. However, 3 of them achieved objective responses, including a complete and a partial remission that were ongoing several months after therapy.[108]

Cruz and collaborators investigated a similar approach in 8 patients with B-cell malignancies at high risk for relapse or relapsing upon allogeneic HSCT.[109] In this setting, however, donor T lymphocytes were first stimulated with autologous lymphoblastoid cell lines expressing viral antigens and then redirected against CD19 by the CAR technology. Indeed, virus-specific T cells (VSCs) infused into patients in the context of allogeneic HSCT are known to expand to significant levels, persist for long periods in vivo, and exhibit antiviral activity, but generally are unable to cause inducing graft-vs.-host reactions.[121,122] Thus, Cruz and coworkers aimed at determining whether VSCs could be endowed with antitumor activity while preserving these positive features. No infusion-related toxicities were documented and 2 patients with relapsing disease experienced objective responses to treatment. Moreover, 2 patients who were in remission at infusion remained so 8 wk and 8 mo thereafter.[109] Together with the findings by Kochenderfer et al. discussed above,[108] these observations suggest that not only autologous, but also allogeneic, T cells may be genetically engineered to target specific TAAs. The actual advantages of this approach remain to be determined.

Bollard and colleagues tested the therapeutic potential of autologous Epstein–Barr virus (EBV)-specific T lymphocytes expanded from EBV-related lymphoma patients by means of autologous DCs and EBV-transformed B-lymphoblastoid cell lines engineered to express EBV proteins.[110] Fifty patients were included in this study, none of whom manifested ACT-related side effects. Among 29 individuals affected by high-risk or previously relapsing disease at the time of infusion, 28 were in remission for a median time of 3.1 y, while 13 of the remaining 21 patients exhibited an objective response (including 11 complete responses). Of note, while T lymphocytes specific for EBV-encoded proteins were documented in the peripheral blood of a majority of patients, T cells reacting against non-viral TAAs (an indication of epitope spreading)[123,124] could be detected only in individuals achieving clinical responses.[110] It remains unclear whether epitope spreading actually determines or is simply associated with the clinical activity of ACT-based immunotherapy in this setting.

Dudley and coworkers prospectively assigned 69 subjects with metastatic melanoma to receive adoptively transferred $CD8^+$ T cell-enriched TILs (35 patients) or unselected "young" TILs (34 patients).[111] Young TILs have indeed been suggested to constitute a valuable alternative to their conventional counterparts, mainly because they are maintained in culture for a minimal amount of time and their preparation does not require individualized tumor-reactivity screening steps.[125-127] Importantly, Dudley and colleagues demonstrated that $CD8^+$ T cell-enriched TILs are not therapeutically superior to young TILs, at least for the treatment of advanced melanoma.[5,111] This is relevant as the latter are not only easier to obtain than the former, but also significantly less expensive.[5]

Besser et al. set out to investigate the therapeutic potential of young TILs combined with high-dose IL-2 in 80 Stage IV melanoma patients previously subjected to lymphodepleting pre-conditioning.[112] TIL cultures could be established from 72 out of 80 individuals, yet 15 of these subjects were withdrawn from the study owing to clinical deterioration prior to infusion. Of 57 patients receiving ACT-based immunotherapy, 18 achieved partial and 5 complete remission, the latter persisting in the absence of additional interventions 29 mo after treatment. Several factors were identified as independent predictors of clinical responses, including age, gender, circulating lactate dehydrogenase levels, days of TILs in culture, and number of infused cells.[112] Interestingly, 32 patients received ipilimumab, a FDA-approved monoclonal antibody specific for cytotoxic T lymphocyte assocaited protein 4 (CTLA4),[128-130] prior or after the adoptive transfer of young TILs. Retrospective analyses demonstrated that the failure of these patients to respond to ipilimumab did not alter their propensity to benefit from ACT-based immunotherapy.[112]

The study conducted by Domschke and collaborators enrolled 16 metastatic breast cancer patients bearing tumor-reactive memory T cells in the bone marrow.[113] These subjects received

1 infusion of autologous tumor-reactive T cells exposed ex vivo to DCs pulsed with breast carcinoma MCF-7 cell lysates, and 7 of them manifested an immunological response to therapy. Of note, responsiveness to therapy positively correlated with (1) absence of bone metastases, (2) amount of tumor-reactive T cells in the bone marrow at baseline, and (3) estimated number of adoptively transferred cells. Moreover, the overall survival of immunological responders was significantly higher than that of non-responders.[113] Although this clinical study was not designed for (nor sufficiently powered to) detect the therapeutic activity of ACT-based immunotherapy, the results from Domschke and colleagues confirm the prognostic/predictive value of (at least some) immunological parameters in cancer therapy.

Chia and colleagues tested the adoptive transfer of EBV-specific cytotoxic T lymphocytes in combination with gemcitabine (a potentially immunogenic nucleoside analog)[99,131] and carboplatin (a platinum derivative with limited immunogenic potential)[132,133] as a first-line therapeutic intervention in 35 patients with metastatic and/or locally recurrent EBV^+ nasopharyngeal carcinoma.[114] No patient experienced severe (Grade > 3) toxicities in the course of therapy, and the most common adverse effects were Grade 1–2 fatigue and Grade 1 myalgia. Importantly, such an ACT-based immunotherapeutic regimen yielded an overall response rate of 71.4% (encompassing 3 complete and 22 partial responses), median overall and disease-free survival being 29.9 and 7.6 mo, respectively.[114] The outcome data reported in this study are among the best ever recorded in the setting of advanced EBV^+ nasopharyngeal carcinoma, encouraging the evaluation of ACT-based immunochemotherapy in various other clinical settings.

Shimizu et al. investigated the clinical profile of T lymphocytes activated ex vivo plus DCs pulsed with autologous tumor lysates as an adjuvant intervention in patients with invasive hepatocellular carcinoma (HCC).[115] In this setting, 42 individuals received ACT-based immunotherapy upon surgical tumor resection, whereas 52 subjects underwent surgery only. No Grade 3–4 toxicities were recorded, the most common side effect associated with adjuvant cell-based immunotherapy being Grade 1 skin reactions at the injection site. Moreover, adjuvant immunotherapy yielded 5-y overall and disease-free survival rates of 64.3% and 35.7%, respectively, which compared favorably with those related to surgical resection alone (44.2% and 11.5%, respectively).[115] Interestingly, resected HCC patients developing delayed-type hypersensitivity (DTH) upon cell-based immunotherapy had a better prognosis than those who failed to do so.[115] This finding is in line previous results indicating that DTH reactions may predict the response of cancer patients to various immunotherapeutic regimens.[134-136]

Wang and colleagues evaluated the safety and therapeutic potential of cytokine-induced killer (CIK) cells combined with high-dose IL-2 in 29 patients with metastatic RCC.[116] CIK cells are a heterogeneous mix of effector $CD8^+$ T cells that exerts MHC-unrestricted cytotoxic activity against malignant cells.[137-139] The immunotherapeutic regimen designed by Wang and collaborators failed to induce complete responses, yet yielded a partial response in 4 individuals (13.8%) and disease stabilization in 18 subjects (62.1%). The 1-y overall survival rate was 82.8%. Of note, an inverse correlation was observed between the circulating levels of MDSCs at baseline and the propensity of RCC patients to obtain a survival benefit from therapy.[116] These findings not only suggest that the amounts of circulating MDSCs may predict the response of patients to ACT-based immunotherapy, but also that pharmacological interventions that deplete MDSCs, such as the administration of metronomic gemcitabine,[140,141] may potentiate the clinical activity of adoptively transferred lymphocytes.

Lamers and coworkers enrolled 12 patients bearing carbonic anhydrase IX (CA9)-expressing RCC in a clinical study evaluating the activity of autologous T lymphocytes expressing a CA9-targeting CAR.[117,142] These patients received a maximum of 10 infusions containing 0.2–2.1 x 10^9 T lymphocytes. Grade 2–4 elevations of circulating hepatic enzymes were recorded in 8 patients treated with the lowest T-cell dose. In line with these findings, T cells were found to infiltrate the bile duct epithelium in bioptic specimens, correlating with the local expression of CA9.[117] Of note, the pre-administration of CA9-targeting monoclonal antibodies prevented such toxicities, pointing to a strategy for avoiding (or at least limiting) the on-target side effects of ACT-based immunotherapy.

Morgan et al. evaluated the safety and therapeutic potential of autologous T lymphocytes engineered to express a melanoma antigen family A3 (MAGEA3)-specific TCR in 9 patients affected by $MAGEA3^+$ malignancies, including melanoma, synovial sarcoma, and esophageal carcinoma.[6,101] While 5 patients experienced tumor regression, 3 developed severe mental status changes beginning 1–2 post-infusion. In one of such patients, initial Parkinson-like symptoms resolved over 4 wk. Conversely, in the 2 other cases, the situation rapidly degenerated into coma and death. Autoptic studies revealed a necrotizing leukoencephalopathy with extensive white matter defects associated with the infiltration of $CD3^+/CD8^+$ T cells.[6,101] Prompted by these findings, Morgan and colleagues investigated in detail the expression profile of MAGEA family members in the human brain, identifying in MAGE-A12 the most solid candidate for the unexpected toxicity of their ACT-based immunotherapeutic protocol.[101]

Among recent translational studies investigating ACT-based immunotherapy, we found of particular interest the works of (1) Alizadeh and colleagues, who demonstrated that doxorubicin (an immunogenic anthracycline)[143-145] may improve the therapeutic potential of adoptively transferred lymphocytes as it depletes MDSCs, in thus far resembling gemcitabine; (2) Budde et al., who endowed T cells expressing a CD20-specific CAR with an inducible suicide system based on the pharmacological dimerization of caspase-9, allowing for their rapid elimination in vitro and in vivo;[146] (3) Labarriere and collaborators, who developed and validated a full good manufacturing practice (GMP) process to select and amplify melan A (MLANA)- and MELOE-1-specific T cells for the treatment of metastatic melanoma patients from 100 mL of peripheral blood;[147] (4) Ma and coworkers, who studied the functional activity and dynamics of T lymphocytes expressing a MLANA-specific TCR upon reinfusion in melanoma patients;[148] (5) Karlsson et al.,

who demonstrated that the cytotoxic activity of T lymphocytes bearing a CD19-specific CAR can be boosted by the co- or pre-administration of ABT-737, a small molecule inhibitor of anti-apoptotic BCL-2 family members,[149-152] at least in vitro;[153] (6) Mardiros and colleagues, who developed and demonstrated the specificity as well as therapeutic potential of 2 distinct CARs specific for IL-3 receptor, α (IL3RA, best known as CD123);[154] and (7) Robbins and coworkers, who designed and validated a whole exome sequencing-based screening procedure to identify neo-antigens potentially recognized by TILs.[155] This approach may be of particular translational value as it may allow for the relatively straightforward selection and expansion of TILs that recognize patient-specific TAAs.

Taken together, these observations indicate that several groups worldwide firmly believe in the clinical potential of ACT-based immunotherapy and are investing consistent efforts in the development of safe, efficient and cost-effective ACT protocols.

Update on Ongoing Clinical Trials

When this Trial Watch was being redacted (February 2014), official sources listed no less than 33 clinical trials launched after March 1st, 2013 that would evaluate the efficacy and safety of ACT-based immunotherapy in cancer patients (source http://www.clinicaltrials.gov).

In line with an increasing amount of encouraging clinical findings,[48,49,56,58,106] a significant fraction of the trials launched in the last 12 mo involves the administration of CAR-expressing T cells to individuals with hematological neoplasms, notably ALL, chronic lymphocytic leukemia, and non-Hodgkin lymphoma (**Table 2**). With a few exceptions (NCT01815749; NCT01840566), these studies rely on ACT-based immunotherapy as a standalone intervention in the context of lymphodepleting pre-conditioning (NCT01853631; NCT01860937; NCT01864889; NCT01864902; NCT01865617; NCT02028455; NCT02030847; NCT02050347; NCT02051257). Conversely, in NCT01815749 and NCT01840566, genetically modified autologous T cells are administered to patients upon myeloablative pre-conditioning and allogeneic or autologous HSCT. In addition, ACT-based immunotherapy is being tested in various cohorts of multiple myeloma patients. These clinical trials involve (1) autologous HSCT followed by the infusion of activated marrow-infiltrating lymphocytes and lenalidomide-based maintenance therapy[156-159] (NCT01858558); (2) the administration of autologous T cells manipulated to express a TCR specific for the cancer/testis antigens NY-ESO-1 and cancer/testis antigen 2 (CTA2, best known as LAGE-1)[160-162] (NCT01892293); and (3) the infusion of autologous or donor-derived T cells stably transduced to express a CAR targeting syndecan 1 (SDC1, best known as CD138)[163,164] (NCT01886976).

Reflecting the particular sensitivity of melanoma to immunotherapeutic interventions,[16,165-167] no less than 9 clinical trials have been initiated during the last 12 mo to investigate the safety and therapeutic potential of ACT-based regimens in this oncological setting (**Table 2**). Most of these studies involve the administration to pre-conditioned patients of TILs expanded ex vivo following conventional procedures, in combination with high- or low-dose IL-2 (NCT01807182; NCT01814046; NCT01883323; NCT01946373; NCT01995344). Alternatively, (1) TILs are infused together with low-dose IL-2 in the absence of pre-conditioning (NCT01883297); (2) TILs are administered to pre-conditioned patients in combination with DCs pulsed ex vivo with autologous tumor lysates and a NY-ESO-1-derived peptide (NCT01946373); (3) young TILs are co-administered with IL-2 in a trial comparing 2 distinct pre-conditioning regimens (NCT01993719); or (4) PBLs engineered to express a dominant negative variant of the transforming growth factor β1 (TGFβ1) receptor are administered to pre-conditioned patients, followed by high-dose IL-2 (NCT01955460). Finally, 1 study aims at assessing the clinical profile of autologous $CD8^+$ PBLs given in combination with ipilimumab (NCT02027935).

Hematological cancers and melanoma are not the sole oncological indications in which ACT-based immunotherapy is being actively investigated (**Table 2**). Indeed, during the last 12 mo several clinical trials have been initiated to test: (1) T lymphocytes expressing a ganglioside D2-specific CAR and endowed with an inducible suicide system, in neuroblastoma patients (NCT01822652); (2) activated T lymphocytes combined with the multi-kinase inhibitor sorafenib,[168-171] in HCC patients; (3) CIK cells as standalone therapeutic intervention, in subjects affected by cholangiocarcinoma (NCT01868490) or colorectal carcinoma (NCT01839539); (4) autologous T cells manipulated to express a CAR specific for *v-erb-b2* avian erythroblastic leukemia viral oncogene homolog 2 (ERBB2, best known as HER2),[172,173] in patients bearing $HER2^+$ solid neoplasms (NCT01935843); (5) autologous T lymphocytes expressing a CAR specific for epidermal growth factor receptor (EGFR),[174,175] in subjects with advanced $EGFR^+$ malignancies (NCT01869166); and (6) autologous PBLs genetically modified to express a NY-ESO-1-targeting TCR, in subjects affected by metastatic NY-ESO-1^+ tumors (NCT01967823).

As for the clinical trials listed in our previous Trial Watches dealing with this topic,[75,76] the following studies have changed status during the past 12 mo: NCT01236573, now listed as "Suspended"; NCT00871481, now listed as "Completed"; as well as NCT01555892, NCT01567891, NCT01653717, NCT01729091, and NCT01758458, now listed as "Recruiting." Nor the reasons underlying the suspension of NCT01236573, testing IL-12-expressing TILs combined with ipilimumab in metastatic melanoma patients, nor the results of NCT00871481, investigating the therapeutic profile of NY-ESO-1-redirected TILs combined with IL-2 and ipilimumab in a similar setting, appear to be available (source http://www.clinicaltrials.gov).

In summary, the enthusiasm that has gathered around ACT-based immunotherapy throughout the past 2 decades remains high. The use of autologous CAR-expressing T lymphocytes for the treatment of B-cell neoplasms or genetically unmodified TILs for the therapy of melanoma stand out as the protocols of this type most intensively evaluated in the clinic today.

Table 2. Clinical trials recently launched to evaluate the safety and efficacy of ACT-based immunotherapy in cancer patients*

Indication(s)	Approach	Phase	Status	Notes	Ref.
Acute myeloid leukemia	Autologous T cells expressing a CD33-specific CAR	I/II	Recruiting	As a standalone intervention	NCT01864902
ALL	Autologous T cells expressing a CD19-specific CAR	I	Recruiting	Combined with cyclophosphamide	NCT01860937
		II	Recruiting	As a standalone intervention	NCT02030847
ALL CLL NHL	Autologous T cells expressing a CD19-specific CAR	I/II	Recruiting	As a standalone intervention	NCT01865617
		I	Not yet recruiting	As a standalone intervention	NCT02050347
Cholangiocarcinoma	Autologous CIK cells	I/II	Recruiting	As a standalone intervention	NCT01868490
CLL NHL	Autologous T cells expressing a CD19-specific CAR	I	Not yet recruiting	As a standalone intervention	NCT01853631
Colorectal carcinoma	Autologous CIK cells	II	Recruiting	After adjuvant or neoadjuvant therapy	NCT01839539
Hepatocellular carcinoma	Activated T lymphocytes	II	Active, not recruiting	As a standalone intervention	NCT01897610
Leukemia Lymphoma	Autologous T cells expressing a CD19-specific CAR	I/II	Recruiting	As a standalone intervention	NCT02028455
		n.a.	Recruiting	As a standalone intervention	NCT01864889
Melanoma	Autologous TGFβ1 DNR-expressing PBLs	I	Not yet recruiting	As a standalone intervention	NCT01955460
	Autologous $CD8^+$ PBLs	II	Not yet recruiting	Combined with ipilimumab	NCT02027935
	Conventional TILs	I	Not yet recruiting	As a standalone intervention	NCT01883297
			Recruiting	Combined with a DC-based vaccine	NCT01946373
		II	Not yet recruiting	As a standalone intervention	NCT01995344
					NCT01883323
			Recruiting	As a standalone intervention	NCT01807182
					NCT01814046
	Young TILs	II	Recruiting	As a standalone intervention	NCT01993719
Multiple myeloma	Activated MILs	II	Recruiting	Combined with a lenalidomide-based regimen	NCT01858558
	Autologous T cells expressing a CD138-specific CAR	I/II	Recruiting	As a standalone intervention	NCT01886976
	Autologous T cells expressing a NY-ESO-1-specific TCR	I/II	Recruiting	As a standalone intervention	NCT01892293
Neuroblastoma	Autologous T cells expressing a GD2-specific TCR	I	Recruiting	Inducible caspase-9-based suicide system	NCT01822652
NHL	Autologous T cells expressing a CD19-specific CAR	I	Recruiting	As a standalone intervention upon autologous HSCT	NCT01815749
					NCT01840566
			Not yet recruiting	As a standalone intervention upon autologous HSCT	NCT02051257

Abbreviations. ACT, adoptive cell transfer; ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; CIK, cytokine-induced killer; CLL, chronic lymphocytic leukemia; DC, dendritic cell; DNR, dominant negative receptor; EGFR, epidermal growth factor receptor; HSCT, hematopoietic stem cell transplantation; MIL, marrow-infiltrating lymphocyte; NHL, non-Hodgkin lymphoma; PBL, peripheral blood lymphocyte; TCR, T-cell receptor; TGFβ1, transforming growth factor β1; TIL, tumor-infiltrating lymphocyte. *Between 2013, March 1st and the date of submission.

Table 2. Clinical trials recently launched to evaluate the safety and efficacy of ACT-based immunotherapy in cancer patients* (continued)

Indication(s)	Approach	Phase	Status	Notes	Ref.
Solid tumors	Autologous T cells expressing a EGFR-specific CAR	I/II	Recruiting	As a standalone intervention	NCT01869166
	Autologous T cells expressing a HER2-specific CAR	I/II	Recruiting	As a standalone intervention	NCT01935843
	Autologous T cells expressing a NY-ESO-1-specific TCR	II	Recruiting	As a standalone intervention	NCT01967823

Abbreviations. ACT, adoptive cell transfer; ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; CIK, cytokine-induced killer; CLL, chronic lymphocytic leukemia; DC, dendritic cell; DNR, dominant negative receptor; EGFR, epidermal growth factor receptor; HSCT, hematopoietic stem cell transplantation; MIL, marrow-infiltrating lymphocyte; NHL, non-Hodgkin lymphoma; PBL, peripheral blood lymphocyte; TCR, T-cell receptor; TGFβ1, transforming growth factor β1; TIL, tumor-infiltrating lymphocyte. *Between 2013, March 1st and the date of submission.

Concluding Remarks

Accumulating evidence suggests that ACT-based anticancer immunotherapy may soon cease to be a promising experimental regimen and become an established clinical reality. This said, the 2 treatment-related deaths recorded by Morgan and colleagues upon the infusion of autologous T cells expressing a MAGE-A3-targeting CAR[6,101] should warn the scientific and medical community about the potential downsides of this approach.

As for many other TAA-specific immunotherapeutic regimens, including DNA-based as well as peptide-based vaccines,[176,177] the efficacy as well as the safety of ACT-based interventions relying on genetically engineered T cells depends on the TAA of choice.[178] Strategies based on the simultaneous targeting of 2 distinct TAAs are being actively investigated, not only as they would be associated with limited on-target toxicity for normal tissues that express one single TAA, but also as they may limit the surge of antigen-loss tumor variants.[119,179,180] Moreover, the safety and efficacy of ACT-based immunotherapeutic regimens relying on genetically manipulated T lymphocytes appear to depend on the affinity and avidity of exogenously introduced TAA receptors, be them TCRs or CARs.[102,103,181] Significant efforts have been dedicated at the development of 2nd and 3rd generation CARs that deliver potent immunostimulatory cues to T cells, de facto bypassing the need for co-stimulatory signaling.[182,183] The recent unfortunate death of 2 patients treated with CD123-redirected T cells suggests that the successful clinical application of some of these CARs requires adequate brakes.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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