OncoImmunology 4:11, e1046673; November 2015; © 2015 Taylor & Francis Group, LLC

Trial Watch: Adoptive cell transfer for oncological indications

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Keywords: checkpoint blockers, chimeric antigen receptor, GM-CSF, TCR, TLR agonists, tumor-associated antigens

Abbreviations: ACT, adoptive cell transfer; CAR, chimeric antigen receptor; CIK, cytokine-induced killer; CMV, cytomegalovirus; CTL, cytotoxic $CD8^+$ T lymphocyte; DC, dendritic cell; EBV, Epstein–Barr virus; HPV, human papillomavirus; HSCT, haematopoietic stem cell transplantation; IL, interleukin; mAb, monoclonal antibody; MAGEA3, melanoma antigen family A3; MDSC, myeloid-derived suppressor cell; MLANA, melan-A; NK, natural killer; PBL, peripheral blood lymphocyte; PBMC, peripheral blood mononuclear cell; PMEL, premelanosome protein; TAA, tumor-associated antigen; TCR, T-cell receptor; TIL, tumor-infiltrating lymphocyte; TLR, Toll-like receptor

One particular paradigm of anticancer immunotherapy relies on the administration of (potentially) tumor-reactive immune effector cells. Generally, these cells are obtained from autologous peripheral blood lymphocytes (PBLs) *ex vivo* (in the context of appropriate expansion, activation and targeting protocols), and re-infused into lymphodepleted patients along with immunostimulatory agents. In spite of the consistent progress achieved throughout the past two decades in this field, no adoptive cell transfer (ACT)-based immunotherapeutic regimen is currently approved by regulatory agencies for use in cancer patients. Nonetheless, the interest of oncologists in ACT-based immunotherapy continues to increase. Accumulating clinical evidence indicates indeed that specific paradigms of ACT, such as the infusion of chimeric antigen receptor (CAR)-expressing autologous T cells, are associated with elevated rates of durable responses in patients affected by various neoplasms. In line with this notion, clinical trials investigating the safety and therapeutic activity of ACT in cancer patients are being initiated at an ever increasing pace. Here, we review recent preclinical and clinical advances in the development of ACT-based immunotherapy for oncological indications.

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Submitted: 04/24/2015; Accepted: 04/25/2015
http://dx.doi.org/10.1080/2162402X.2015.1046673

Introduction

One strategy to eradicate established malignant lesions involves the intravenous administration of autologous or allogeneic immune effector cells that are naturally or artificially endowed with tumoricidal activity and expanded/activated *ex vivo*.[1-3] This approach, which is known as "adoptive cell transfer" (ACT) or "adoptive cell therapy", relies on immune cell populations that mediate direct tumoricidal effects, including conventional cytotoxic $CD8^+$ T lymphocytes (CTLs), given alone or together with helper $CD4^+$ T cells, natural killer (NK) cells, and so-called "cytokine-induced killer" (CIK) cells (i.e., $CD3^+CD56^+$ NK cell-like non-MHC restricted CTLs).[4-9] Therefore, ACT-based anticancer immunotherapy should be conceptually differentiated from both haematopoietic stem cell transplantation (HSCT) and dendritic cell (DC)-based vaccination. In the former scenario, neoplastic bone marrow progenitors are ablated by high dose chemoradiotherapy, and histocompatible haematopoietic stem cells are subsequently provided to reconstitute normal lympho-, myelo- and erythropoiesis.[10-12] In the latter setting, autologous DCs are loaded *ex vivo* with a source of tumor-associated antigens (TAAs) and re-administered to patients along with immunostimulatory interventions, a protocol that aims at the elicitation of an endogenous, TAA-specific immune response.[13-16] Thus, whereas the efficacy of DC-based anticancer interventions fully relies on the host immune system (implying that DC-based vaccination constitutes a *bona fide* example of active immunotherapy), this is not completely the case of ACT-based regimens. Nonetheless, the full-blown efficacy of ACT-based immunotherapy depends on the persistence, expansion and activation of

re-infused cells *in vivo*, which are supported by cellular and humoral components of the host immune system. Thus, ACT-based immunotherapeutic regimens cannot be considered as pure instances of passive immunotherapy.[3,17]

Elevated amounts of natural tumor-infiltrating lymphocytes (TILs) have been correlated with improved disease outcome in cohorts of patients affected by various neoplasms.[18-23] Thus, TILs would represent a convenient source of potentially tumor-reactive cells for ACT-based immunotherapy.[24-26] However, TILs are not always available since (1) not all neoplastic lesions can be surgically resected/biopsied, and (2) some tumors contain limited amounts of TILs. When TILs are not available, ACT-based immunotherapy relies upon PBLs that are artificially endowed (by genetic engineering) with tumoridical functions.[5] This can be accomplished by stably transfecting PBLs with a construct coding for a TAA-specific T-cell receptor (TCR),[5,27-30] or a so-called chimeric antigen receptor (CAR).[31-37] The latter consists in the antigen-binding domain of a TAA-specific immunoglobulin fused in-frame with an intracellular signaling tail composed of one or more immunostimulatory modules.[31-37] This technology is advantageous since it endows PBLs with the ability to recognize and kill (malignant) cells that express the CAR target in an MHC-independent manner.[35,38-44] Additional advantageous features can be provided to PBLs via genetic engineering,[45] including (but not limited to) (1) superior proliferative potential and *in vivo* persistence;[46-49] (2) improved effector functions (i.e., cytotoxicity and cytokine secretion);[47,50,51] and (3) enhanced tumor-homing capacities.[52,53] Moreover, PBLs can be genetically modified and expanded/activated in the presence of pharmacological agents that prevent (at least to some extent) terminal differentiation.[54-57] This is particularly relevant because terminally differentiated CTLs are generally characterized by reduced proliferative capacity and functional exhaustion.[55,58,59]

Cancer patients allocated to ACT-based immunotherapy are generally subjected to lymphodepleting chemo(radio)therapeutic regimens.[60] A large body of clinical data indicates that this approach is indeed associated with improved disease outcome, presumably since (1) it efficiently relieves the immunosuppressive network established within malignant lesions and systemically by myeloid-derived suppressor cells (MDSCs) and $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs);[61-69] and (2) it consistently blunts the so-called "cytokine sink", i.e., the ability of endogenous lymphocytes to compete with re-infused T, NK or CIK cells for critical cytokines like interleukin (IL)-7 and IL-15.[70,71] Similarly, accruing preclinical and clinical evidence demonstrates that various chemo- and immunotherapeutic interventions can improve the efficacy of ACT.[72-74] These interventions include (though presumably are not limited to) (1) various cytokines that support the expansion, survival or effector functions of re-infused lymphocytes (e.g., granulocyte-macrophage colony stimulating factor, GM-CSF; IL-2; IL-7);[75-78] (2) Toll-like receptor (TLR) agonists (which normally function as immunological adjuvant);[79-82] (3) conventional chemotherapeutics with off-target immunostimulatory effects,[83,84] such as cyclophosphamide (an alkylating agent employed for the treatment of several neoplasms),[85-88] gemcitabine (a nucleoside analog commonly used against pancreatic carcinoma patients),[89-91] and oxaliplatin (a platinum salt approved for use in advanced colorectal carcinoma patients);[92-94] (4) monoclonal antibodies (mAbs) that block immunological checkpoints, such as the cytotoxic T lymphocyte associated protein 4 (CTLA4)-targeting agent ipilimumab as well as the programmed cell death 1 (PDCD1)-targeting agents pembrolizumab and nivolumab;[95-97] (5) angiogenesis inhibitors (because they favor the normalization of the tumor vasculature, hence restoring/promoting the access of re-infused lymphocytes to the tumor bed);[98,99] and (6) colony stimulating factor 1 receptor (CSF1R) inhibitors, which inhibit MDSCs and other immunosuppressive cell population, like tumor-associated macrophages.[100-102]

According to the results of various clinical trials, the re-infusion of autologous PBLs genetically modified to express TAA-specific TCRs or CARs is well tolerated by cancer patients, and can induce considerable rates of objective, long-lasting clinical responses, in particular among young individuals affected by hematological neoplasms.[1-3,103,104] ACT-based immunotherapy is associated with a sizeable (though limited) risk of potentially lethal autoimmune reactions. These generally originate from the activation of adoptively transferred cells against healthy tissues that express TAA-related antigenic determinants.[6,8,105,106] As a standalone example of such risk, 2 y ago Morgan and colleagues reported the unexpected death of two among nine subjects with melanoma antigen family A3 $(MAGEA3)^+$ tumors treated with autologous PBLs expressing a MAGEA3-specific TCR.[8,106] Such an unfortunate occurrence was subsequently attributed to the ability of adoptively transferred PBLs to cross-recognize MAGEA12-expressing cells in the brain.[106] Besides these potentially fatal (but fortunately rare) toxicities, ACT is associated with relatively mild side effects, including the so-called "cytokine release syndrome", which reflects the massive activation of adoptively transferred cells against their targets.[107] Such events, however, are generally manageable by the administration of corticosteroids or more specific immunosuppressive agents, such as the IL-6-targeting mAb tocilizumab.[5,72,73,108-111] Of note, despite encouraging preclinical results,[112-118] the adoptive transfer of NK cells to cancer patients appears to mediate limited therapeutic effects, for hitherto unclear reasons.[119-121] Efforts are currently being devoted to the development of novel approaches to fully harness the cytotoxic potential of NK cells for ACT-based immunotherapy.[122-126]

In spite of an accruing body of compelling clinical data, no ACT-based immunotherapeutic regimen is currently approved by the US Food and Drug Administration or equivalent regulatory agency for use in cancer patients. Along the lines of our monthly Trial Watch series,[127,128] here we summarize recent preclinical, translational and clinical progress in the development of ACT-based immunotherapeutic regimens for cancer therapy.

Update on the development of ACT-based anticancer immunotherapy

Completed clinical studies

Since the submission of our most recent Trial Watch discussing this topic (April 2014),[129] data from no less than 20 clinical trials investigating the therapeutic profile of ACT-based

immunotherapy have been published in the peer-reviewed scientific literature (source http://www.ncbi.nlm.nih.gov/pubmed), and preliminary results from five additional studies have been presented at the American Society of Clinical Oncology (ASCO) annual meeting (source http://meetinglibrary.asco.org/). Reflecting previous, very encouraging clinical findings, a significant fraction of these studies involved CAR-expressing autologous T cells.[130-137] These were redirected against CD19, which is expressed by various forms of leukemia,[130,136,137] CD20, a lymphoma-associated antigen,[131] melan-A (MLANA), which is selectively expressed by melanocytes,[132] NY-ESO-1, a cancer/testis antigen expressed by multiple malignancies,[133] mutant epidermal growth factor receptor (EGFR), which is found at the surface of cancer cells of various origin,[134] or mesothelin, another relatively widespread TAA.[135] In this context, CAR-expressing T cells were administered as standalone immunotherapeutic interventions,[133-136] combined with standard chemotherapy,[131] in conjunction with tumor-targeting mAbs,[137] or in the context of DC-based vaccination.[132]

In addition, various studies relied on the administration of autologous TILs or peripheral blood mononuclear cells (PBMCs) expanded *ex vivo* generally (but not always) upon selection for antigen specificity, or exposure to a source of TAAs in the presence of activating stimuli.[138-149] In particular, three of these trials involved CTLs specific for so-called viral TAAs, i.e., TAAs encoded by oncogenic viruses (uniquely expressed by malignant cells),[144,145,149] namely cytomegalovirus (CMV), which is implicated in the pathogenesis of several tumors including glioblastoma and nasopharyngeal carcinoma,[144] Epstein–Barr virus (EBV), which is etiologically linked to lymphomagenesis,[145] and human papillomavirus type 16 and 18 (HPV-16 and HPV-18), which are associated with a considerable proportion of cervical carcinoma cases.[149] Two studies relied on the administration of CTLs selected for their ability to react against shared TAAs, including *erb-b2* receptor tyrosine kinase 2 (ERBB2), which is overexpressed by an elevated fraction of breast carcinomas,[147] MLANA and premelanosome protein (PMEL), both of which are expressed by melanoma cells.[140] One study utilized a preparation of TILs highly enriched in polyfunctional $CD4^+$ T_H1 cells specific for a patient-specific mutation in erbb2 interacting protein (ERBB2IP).[142] The remaining studies investigated the therapeutic profile of unselected TILs or PBMCs, expanded *ex vivo* according to conventional procedures.[138,141,143,146,148] In these clinical settings, ACT was employed as a standalone immunotherapeutic intervention,[146-149] performed in the context of DC- or peptide-based anticancer vaccination,[138] or combined with total body irradiation.[143]

Three studies investigated the clinical profile of autologous CIK cells,[150,151] administered with either standard chemotherapy,[151] or DC-based interventions.[150,152] Finally, two studies assessed the safety and efficacy of adoptively transferred NK cells,[153,154] given either upon HSCT,[153] or in combination with autologous DCs.[154]

Taken together, the results of these studies corroborate the notion that ACT-based immunotherapy is well tolerated and can induce durable clinical responses in a consistent proportion of patients affected by various neoplasms. As a single exception, Chandran and colleagues (National Cancer Institute, NIH, Bethesda, MD, USA) reported that the administration of highly avid PMEL- and MLANA-specific CTLs together with IL-2 was unable to provide objective therapeutic benefits in a cohort of 15 patients with refractory metastatic melanoma, despite normal clonal engraftment and documentable cytotoxic activity against melanocytes.[140]

Preclinical and translational advances

Among the preclinical and translational studies dealing with ACT-based immunotherapy published during the last 13 months in peer-reviewed scientific journals, we found of particular interest the works of (1) Crompton and colleagues (from the National Cancer Institute, NIH, Bethesda, MD, USA), who demonstrated that chemical inhibitors of *v-akt* murine thymoma viral oncogene homolog 1 (AKT1) can be employed to expand tumor-specific CTLs with memory T-cell features;[155] (2) Geng and collaborators (from the University of Maryland, Baltimore, MD, USA), who genetically engineered TAA-specific CTLs to secrete bacterial flagellin (a TLR5 agonist), resulting in superior antitumor activity;[156] (3) Soto-Pantoja and co-workers (from the National Cancer Institute, NIH, Bethesda, MD, USA), who found that the expression of CD47 (an anti-phagocytic signal)[157-159] considerably blunt the ability of radiation therapy to promote the activation of adoptively transferred CTLs;[160-162] (4) Huang et al. (from the Harvard Medical School, Boston, MA, USA), who demonstrated that carcinoembryonic antigen-related cell adhesion molecule 1 (CEACAM1) heterodimerizes with hepatitis A virus cellular receptor 2 (HAVCR2, best known as TIM-3) on the surface of activated CTLs, and that this interaction is required for the immunosuppressive activity of TIM-3;[163] (5) Lin and colleagues (from the Duke University Medical Center, Durham, NC, USA), who identified miR-23a as a strong repressor of the transcription factor PR domain containing 1, with ZNF domain (PRDM1, also known as BLIMP1), which is involved in CTL effector functions;[164] (6) Caruana and collaborators (from the Baylor College of Medicine and Houston Methodist Hospital, Houston, TX, USA), who engineered CAR-expressing CTLs to recover the ability to secrete heparanase (an enzyme involved in the degradation of the extracellular matrix), resulting in improved tumor infiltration and accrued antineoplastic activity;[165] and (7) Motz and coworkers (from the University of Pennsylvania School of Medicine, Philadelphia, PA, USA), who found that the neoplastic endothelium actively counteracts tumor infiltration by adoptively transferred CTLs by expressing pro-apoptotic FAS ligand (FASLG).[166-168]

Recently initiated clinical trials

Since the submission of our latest Trial Watch dealing with this topic (April 2014),[129] no less than 67 different clinical trials have been launched to test the safety and efficacy of ACT-based immunotherapy in cancer patients (source http://clinicaltrials.gov/). A considerable proportion of these studies investigate the therapeutic profile of autologous PBMCs expanded *ex vivo* and

genetically modified to express a TAA-specific CAR (NCT02081937; NCT02107963; NCT02111850; NCT02132624; NCT02134262; NCT02135406; NCT02146924; NCT02153580; NCT02159495; NCT02186860; NCT02194374; NCT02203825; NCT02208362; NCT02215967; NCT02228096; NCT02247609; NCT02259556; NCT02277522; NCT02311621; NCT02315612; NCT02349724; NCT02395250). With a few exceptions, namely NCT02208362 (a Phase I study enrolling brain cancer patients), NCT02395250 (a Phase I trial recruiting individuals with hepatocellular carcinoma), NCT02311621 (a Phase I study enrolling subjects with neuroblastoma), as well as NCT02107963 and NCT02349724 (two Phase I studies recruiting patients with solid neoplasms), all these trials involve patients with hematological malignancies (mainly, acute lymphoblastic leukemia, B-cell lymphoma and multiple myeloma). In virtually all these studies, ACT is performed as a standalone immunotherapeutic intervention upon lymphodepleting cyclophosphamide- and fludarabine-based chemotherapy. Interestingly, NCT02315118 (a Phase I/II trial) also investigates the therapeutic profile of autologous CTLs genetically engineered to express a CAR, but such receptor is not specific for a TAA. Rather, it recognizes the constant fragment (Fc) of human immunoglobulins, *de facto* endowing CTLs with the ability to perform antibody-dependent cellular cytotoxicity (ADCC).[169] Accordingly, in the context of NCT02315118, patients with B-cell chronic lymphocytic leukemia or non-Hodgkin's lymphoma receive ACT in combination with rituximab,[170,171] a CD20-specific mAb commonly employed for the treatment of CD20-expressing hematological malignancies (**Table 1**).

Another considerable fraction of the clinical trials initiated during the last 13 months to assess the safety and efficacy of ACT-based immunotherapy in cancer patients involves autologous PBMCs expanded *ex vivo* and genetically engineered to express a TAA-specific TCR (NCT02059850; NCT02062359; NCT02070406; NCT02096614; NCT02153905; NCT02210104; NCT02280811; NCT02319824; NCT02366546; NCT02390739). The vast majority of these studies specifically target NY-ESO-1 (NCT02059850; NCT02062359; NCT02070406; NCT02210104; NCT02319824; NCT02366546) or members of the melanoma antigen protein family such as MAGEA3 and MAGEA4 (NCT02096614; NCT02153905). In addition, NCT02390739 (a Phase I/II study) tests the therapeutic profile of autologous PBLs transduced with a construct coding for a murine TCR specific for thyroglobulin (TG), which is selectively expressed by thyrocytes,[172,173] in thyroid cancer patients; NCT02173093 (a Phase I/II trial) investigates the safety and efficacy of CTLs coated with a bispecific antibody targeting ganglioside GD2 (a neuroblastoma-associated antigen)[174-177] in neuroblastoma and osteosarcoma patients; and NCT02274506 initially intended to assess the clinical profile of allogenic CTLs genetically redirected against CD19 in subjects with leukemia or lymphoma. NCT02274506, however, has been withdrawn prior to enrollment for undisclosed reasons (**Table 1**).

Some recently initiated clinical trials investigate the safety and efficacy of CTLs selected for pre-determined features, including TAA specificity (NCT02203903; NCT02239861; NCT02291848); activation state, based on the surface expression of tumor necrosis factor receptor superfamily, member 9 (TNFRSF9, also known as CD137 or 4-1BB),[178] (NCT02111863); and differentiation, based on the reduced expression of CD45RA (NCT02337595). Moreover, a few recent study assess the therapeutic profile of CTLs specific for viral antigens, including E6 and E7 from HPV-16/-18 (in cervical carcinoma patients) (NCT02280811; NCT02379520), EBV-encoded proteins (in subjects with EBV-associated hematological malignancies) (NCT02057445; NCT02065362) and CMV-derived antigens (in nasopharyngeal carcinoma patients) (NCT02210065). All these studies rely on ACT as a standalone immunotherapeutic intervention following lymphodepleting chemotherapy. We found of particular interest the approach adopted by NCT02065362, in which EBV-specific CTLs are genetically modified to express a dominant negative variant of transforming growth factor, β receptor 1 (TGFβR1), rendering these cells resistant to transforming growth factor, β 1 (TGFβ1)-driven immunosuppression (**Table 1**).

A relatively heterogeneous group of recent clinical trials assesses the safety and efficacy of autologous PBLs or TILs (NCT02133196; NCT02277392; NCT02278887; NCT02327390; NCT02342613; NCT02360579; NCT02375984) or allogeneic CTLs (NCT02065869) expanded *ex vivo* according to conventional protocols (optionally in the presence of activating stimuli, such as in NCT02277392; NCT02342613) or upon exposure to pharmacological agents that promote T-cell rejuvenation[58] (NCT02133196). These studies mainly enroll melanoma patients (NCT02278887; NCT02327390; NCT02360579; NCT02375984) or subjects with hematological malignancies (NCT02065869; NCT02342613). Three clinical trials investigate the therapeutic efficacy of CIK cells, either administered as standalone immunotherapeutic interventions (NCT02280278) or combined with DC-based vaccination (NCT02202928; NCT02215837), in patients with solid tumors. Finally, seven studies test the clinical profile of autologous (NCT02118415; NCT02185781; NCT02229266) or allogenic (NCT02100891; NCT02123836; NCT02316964) NK cells, in subjects affected by hematological malignancies (NCT02123836; NCT02185781; NCT02229266; NCT02316964) or solid neoplasms (NCT02100891; NCT02118415) (**Table 1**).

As for the studies discussed in our previous Trial Watches dealing with ACT-based anticancer immunotherapy,[72,73,129] the following trials have changed status during the last 13 months: NCT01722149, NCT01735604, NCT01740557, NCT01853631, NCT01883297, NCT01897610, NCT01955460, NCT02027935, NCT02050347, and NCT02051257, which are now listed as "Recruiting"; NCT01585415, NCT01653717, NCT01683279, NCT01723306, NCT01815749, and NCT02030847, which are now listed as "Active, not recruiting"; NCT01716364, whose status is now "Unknown"; and NCT01747486, which now appears as "Completed" (source http://clinicaltrials.gov/). To the best of our knowledge, however, the results of NCT01747486 (a Phase II studies testing the

Table 1. Clinical trials recently started to evaluate the therapeutic profile of adoptive cell transfer in cancer patients*

Type	Indication(s)	Phase	Status	TAA(s)	Co-encoded molecule(s)	Notes	Ref.
Allogenic CTLs	Hematological malignancies	I	Withdrawn	CD19	None	Genetically modified, as standalone intervention	NCT02274506
			Recruiting	EBV antigens	None	Genetically modified, as standalone intervention	NCT02057445
		I/II	Recruiting	n.a.	n.a.	Genetically modified, as standalone intervention	NCT02065869
Allogenic NK cells	ALL MDS	I	Recruiting	n.a.	n.a.	As standalone intervention	NCT02123836
	Hematological malignancies	n.a.	Not yet recruiting	n.a.	n.a.	Combined with decitabine-based chemotherapy	NCT02316964
	Solid tumors	II	Recruiting	n.a.	n.a.	As standalone intervention upon HSCT	NCT02100891
Autologous CTLs	Hematological malignancies	I	Recruiting	Various	None	Enriched, in TAA-specific cells, as standalone intervention	NCT02203903
	MM	I	Not yet recruiting	Various	None	Enriched, in TAA-specific cells, as standalone intervention	NCT02291848
	Nasopharyngeal carcinoma	I	Recruiting	None	DN TGFβR1	EBV-specific cells, as standalone intervention	NCT02065362
	Reproductive tract neoplasms	I	Not yet recruiting	E6 E7	None	As standalone intervention	NCT02379520
	Solid tumors	I	Not yet recruiting	Various	None	Enriched, in TAA-specific cells, as standalone intervention	NCT02239861
		I/II	Recruiting	GD2	None	Armed with GD2-specific bispecific antibody, as standalone intervention	NCT02173093
Autologous NILs	Melanoma	I	Not yet recruiting	n.a.	n.a.	As standalone intervention	NCT02327390
Autologous NK cells	ALL	I	Recruiting	n.a.	n.a.	As standalone intervention	NCT02185781
	AML	II	Not yet recruiting	n.a.	n.a.	Combined with cytarabine-based chemotherapy	NCT02229266
	NSCLC	II	Recruiting	n.a.	n.a.	As standalone intervention	NCT02118415
Autologous PBMCs	Gynecological tumors	I	Recruiting	n.a.	n.a.	As standalone intervention	NCT02277392
	Hematological malignancies	I/II	Recruiting	n.a.	n.a.	Depleted in $CD45RA^+$ cells, standalone intervention	NCT02337595
		II	Recruiting	n.a.	n.a.	Enriched in CMV-specific cells, as standalone intervention	NCT02210065
Autologous TILs	Hematological malignancies	I	Not yet recruiting	n.a.	n.a.	As standalone intervention	NCT02342613
	Lung carcinoma	II	Recruiting	n.a.	n.a.	Young TILs, as standalone intervention	NCT02133196
	Melanoma	II	Not yet recruiting	n.a.	n.a.	As standalone intervention	NCT02360579
			Recruiting	n.a.	n.a.	Enriched in $CD137^+$ cells, as standalone intervention	NCT02111863
						As standalone intervention	NCT02375984
		III	Recruiting	n.a.	n.a.	As standalone intervention	NCT02278887
CAR-expressing CTLs	ALL	I	Active, not recruiting	CD19	tEGFR	As standalone intervention	NCT02146924
			Not yet recruiting	CD19	None	As standalone intervention	NCT02186860
		II	Recruiting	CD19	None	As standalone intervention	NCT02228096
	B-cell neoplasms	I	Recruiting	CD22	None	As standalone intervention	NCT02315612
	Brain neoplasms	I	Not yet recruiting	IL13RA2	tCD19	As standalone intervention	NCT02208362
	CLL NHL	I/II	Recruiting	CD16	None	Combined with rituximab- based immunotherapy	NCT02315118

(*Continued on next page*)

Table 1. Clinical trials recently started to evaluate the therapeutic profile of adoptive cell transfer in cancer patients* *(Continued)*

Type	Indication(s)	Phase	Status	TAA(s)	Co-encoded molecule(s)	Notes	Ref.
CAR-expressing CTLs	HCC	I	Recruiting	GPC3	None	As standalone intervention	NCT02395250
	Hematological malignancies	I	Recruiting	CD19	tEGFR	As standalone intervention	NCT02153580
				KLRK1 ligands	None	As standalone intervention	NCT02203825
		I/II	Recruiting	CD19	None	As standalone intervention	NCT02081937
							NCT02132624
	Hodgkin's lymphoma	0	Not yet recruiting	CD19	None	As standalone intervention	NCT02277522
	Leukemia	I	Not yet recruiting	CD123	tEGFR	As standalone intervention	NCT02159495
			Recruiting	ROR1	None	Combined with rituximab- based chemoimmunotherapy	NCT02194374
	Lymphoma	I/II	Recruiting	CD19	None	As standalone intervention	NCT02247609
				CD30	None	As standalone intervention	NCT02259556
	MM	I	Recruiting	CD19	None	As standalone intervention	NCT02135406
				TNFRSF17	None	As standalone intervention	NCT02215967
	Neuroblastoma	I	Recruiting	CD171	tEGFR	As standalone intervention	NCT02311621
	NHL	I/II	Recruiting	CD19	None	Combined with chemotherapy	NCT02134262
	Solid tumors	I	Active, not recruiting	CEA	None	As standalone intervention	NCT02349724
			Recruiting	GD2	None	As standalone intervention	NCT02107963
		I/II	Recruiting	MAGEA3	None	As standalone intervention	NCT02111850
CIK cells	CRC	III	Recruiting	n.a.	n.a.	Combined with surgery and adjuvant chemotherapy	NCT02280278
	Gastrointestinal neoplasms	II	Recruiting	n.a.	n.a.	Combined with DC-based immunotherapy and chemoradiotherapy	NCT02202928 NCT02215837
TCR-expressing CTLs	Melanoma	I/II	Recruiting	MAGEA3	None	As standalone intervention	NCT02153905
		II	Recruiting	NY-ESO-1	None	Enriched in $CD62L^+$ cells, as standalone intervention	NCT02062359
	Melanoma Sarcoma	I	Not yet recruiting	NY-ESO-1	None	Enriched in $CD4^+$ cells, as standalone intervention	NCT02210104
	Reproductive tract and oropharyngeal tumors	I/II	Recruiting	E6	None	As standalone intervention	NCT02280811
	Sarcoma	I	Recruiting	NY-ESO-1	None	Enriched in $CD8^+$ cells, combined with palliative RT	NCT02319824
						As standalone intervention	NCT02059850
	Solid tumors	I	Not yet recruiting	NY-ESO-1	None	Combined with DC-based immunotherapy	NCT02070406
			Recruiting	MAGEA4	None	As standalone intervention	NCT02096614
				NY-ESO-1	None	As standalone intervention	NCT02366546
	Thyroid carcinoma	I/II	Not yet recruiting	TG	None	As standalone intervention	NCT02390739

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CAR, chimeric antigen receptor; CEA, carcinoembryonic antigen; CIK, cytokine-induced killer; CLL, chronic lymphocytic leukemia; CMV, cytomegalovirus; CRC, colorectal carcinoma; CTL, cytotoxic T lymphocyte; DC, dendritic cell; DN, dominant negative; EBV, Epstein–Barr virus; GPC3, glypican 3; HCC, hepatocellular carcinoma; HSCT, haematopoietic stem cell transplantation; IL13RA2, interleukin 13 receptor, α 2; KLRK1, killer cell lectin-like receptor subfamily K, member 1; MAGEA3, melanoma antigen family A3; MAGEA4, melanoma antigen family A4; MDS, myelodysplastic syndrome; MM, multiple myeloma; n.a., not available or not applicable; NHL, non-Hodgkin's lymphoma; NIL, node-infiltrating lymphocyte; NK, natural killer; NSCLC, non-small cell lung carcinoma; PBL, peripheral blood lymphocyte; PBMC, peripheral blood mononuclear cell; ROR1, receptor tyrosine kinase-like orphan receptor 1; RT, radiation therapy; TAA, tumor-associated antigen; tCD19, truncated CD19; TCR, T-cell receptor; tEGFR, truncated epidermal growth factor receptor; TG, thyroglobulin; TGFβR1, transforming growth factor, β receptor 1; TIL, tumor-infiltrating lymphocyte; TNFRSF17, tumor necrosis factor receptor superfamily, member 17. *initiated after April 01 2014.

therapeutic profile of CTLs redirected against CD19 through the CAR technology in relapsing or refractory chronic lymphocytic leukemia patients) have not been released yet.

Concluding Remarks

The number of studies recently initiated to test the safety and efficacy of ACT-based immunotherapy in cancer patients does not cease to increase.[72,73,129] Moreover, several startup companies focusing of the development of novel paradigms of ACT-based anticancer immunotherapy have recently been created.[103] This reflects accumulating clinical data demonstrating that the adoptive transfer of CTLs is relatively safe and can induce durable responses in a large proportion of patients, especially when CTLs are genetically redirected against a specific TAA. Among all the ACT protocols currently being tested in the clinic, the infusion of autologous CTLs genetically engineered to express a TAA-specific CAR undoubtedly stands out as the most promising approach. Although security measures must be envisioned to avoid potentially lethal autoimmune reactions,[179] CAR-expressing CTLs have the potential to become the first paradigm of ACT-based cancer immunotherapy approved for use in humans. The future will tell whether the expectations on the CAR technology will be met or whether another ACT regimen will obtain regulatory approval beforehand.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Funding

Authors are supported by the Ligue contre le Cancer (équipe labelisée); Agence National de la Recherche (ANR); Association pour la recherche sur le cancer (ARC); Cancéropôle Ile-de-France; AXA Chair for Longevity Research; Institut National du Cancer (INCa); Fondation Bettencourt-Schueller; Fondation de France; Fondation pour la Recherche Médicale (FRM); the European Commission (ArtForce); the European Research Council (ERC); the LabEx Immuno-Oncology; the SIRIC Stratified Oncology Cell DNA Repair and Tumor Immune Elimination (SOCRATE); the SIRIC Cancer Research and Personalized Medicine (CARPEM); and the Paris Alliance of Cancer Research Institutes (PACRI).

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