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ORIGINAL ARTICLE - CANCER RESEARCH

Cytokine-induced killer (CIK) cells in cancer immunotherapy: report of the international registry on CIK cells (IRCC)

Leonard Christopher Schmeel · Frederic Carsten Schmeel · Christoph Coch · Ingo G. H. Schmidt-Wolf

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Abstract
Purpose Cytokine-induced killer (CIK) cells represent an exceptional T cell population uniting a T cell and natural killer cell like phenotype in their terminally differentiated $CD3^+CD56^+$ subset, which features non-MHC-restricted tumor-killing activity. CIK cells are expandable from peripheral blood mononuclear cells and mature following the addition of certain cytokines. CIK cells have provided encouraging results in initial clinical studies and revealed synergistic antitumor effects when combined with standard therapeutic procedures.
Methods Therefore, we established the international registry on CIK cells in order to collect and evaluate data about clinical trials using CIK cells for the treatment of cancer patients. Moreover, our registry is expected to set new standards on the reporting of results from clinical trials using CIK cells. Clinical responses, overall survival (OS), adverse reactions and immunologic effects were analyzed in 45 studies present in our database. These studies investigated 22 different tumor entities altogether enrolling 2,729 patients.
Results A mean response rate of 39 % and significantly increased OS, accompanied by an improved quality of life, were reported. Interestingly, side effects of CIK cell treatment were minor. Mild fevers, chills, headache and fatigue were, however, seen regularly after CIK cell infusion. Moreover, CIK cells revealed numerous immunologic effects such as changes in T cell subsets, tumor markers, cytokine secretion and HBV viral load.
Conclusion Due to their easy availability and potent antitumor activity, CIK cells emerged as a promising immunotherapy approach in oncology and may gain major importance on the prognosis of cancer.

Keywords Cytokine-induced killer cells · CIK · Clinical trials · Immunotherapy · International registry · Cancer treatment

Introduction

Over the last decades, numerous innovations were achieved in the development of anticarcinogenic drugs, particularly with regard to targeted therapies and considerable progress of surgical techniques, chemotherapeutic regimens and radiation remarkably improved overall cancer therapy. But despite these major advances, most patients might relapse and are burdened with severe side effects caused by chemotherapy and radiation and even targeted therapies. Indeed, treatment failure to conventional therapy and recurrence are frequently observed in present cancer treatment, underlining that more effective therapeutic strategies are still indispensable.

Leonard Christopher Schmeel and Frederic Carsten Schmeel have contributed equally to this work.

L. C. Schmeel · F. C. Schmeel · I. G. H. Schmidt-Wolf (✉)
Department of Internal Medicine III, Center for Integrated Oncology (CIO), University Hospital Bonn, Rheinische Friedrich-Wilhelms-Universität Bonn, Sigmund-Freud-Straße 25, 53105 Bonn, Germany
e-mail: Ingo.Schmidt-Wolf@ukb.uni-bonn.de

F. C. Schmeel
Department of Radiology, University Hospital Bonn, Rheinische Friedrich-Wilhelms-Universität Bonn, Sigmund-Freud-Straße 25, 53105 Bonn, Germany

C. Coch
Institute of Clinical Chemistry and Clinical Pharmacology, Clinical Study Support Core (CSSC), University Hospital Bonn, Rheinische Friedrich-Wilhelms-Universität Bonn, Sigmund-Freud-Straße 25, 53105 Bonn, Germany

Much effort has been made in the innovative field of immunotherapy. In recent years, it has become an essential component of cancer treatment besides current standard therapies. The basic principle behind this is as simple as persuasive: It aims at using body's natural abilities to elicit an immune response in order to reject tumor tissue, thereby avoiding significant adverse effects typically accompanying treatment with current chemotherapeutics. In addition, treatment strategies activating the immune system against the tumor should not be as susceptible for evolved resistance of the cancer cells as treatments directly acting on the cancer cell. Adoptive cell-based immunotherapy, in this context, uses procedures stimulating immune effector cells to better recognize and, finally, eliminate cancer cells. In such an immunotherapeutic approach, Cytokine-induced killer (CIK) cells are currently emerging as a promising and effective treatment option, especially when combined with standard therapy in an adjuvant treatment setting (Hontscha et al. 2011). The first reports in the literature and the very first phase I trial performed by Schmidt-Wolf et al. already corroborated the high cytotoxic activity of this new type of antitumor effector cells and underlined their favorable safety and tolerability profile (Schmidt-Wolf et al. 1991, 1999). Meanwhile, 25 years after their first description, a large amount of clinical trials, which we have assessed in our international database, demonstrated encouraging results and showed that CIK cells may prevent recurrence, improve the progression as well as the overall survival while enhancing quality of life in cancer patients.

CIK cells are also known as natural killer like T cells and express both the T cell marker CD3 and the NK-cell marker CD56. As compared with standard lymphokine-activated killer (LAK) cells, CIK cells demonstrate an enhanced cytotoxic activity (Lu and Negrin 1994). The reason for this is mainly based on their higher proliferation rate finally leading to an increase in total lytic units (Schmidt-Wolf et al. 1994). In comparison with LAK cells that are induced by incubation with interleukin (IL), CIK cells can be generated easily from peripheral blood lymphocytes (PBLs) by sequential ex vivo incubation with a monoclonal antibody against CD3 (anti-CD3), interferon-γ (IFN-γ) and IL-2 in a time-sensitive schedule. Induction procedures may vary dependent on the either protocol used. However, the time-controlled administration of IFN-γ before the addition of IL-2 and anti-CD3 is decisive for the creation of a high cytotoxic potential (Schmidt-Wolf et al. 1991). In particular, IFN-γ activates monocytes providing crucial signals important for the expansion to CD56-positive T cells (Lopez et al. 2000). The complementary addition of IL-2 and anti-CD3 afterward principally promotes mitogenic stimulants (Ochoa et al. 1987).

Among the heterogeneous T cell population mainly the $CD3^+CD56^+$ subset accounts for the antitumor efficacy as it represents the cell type with the highest killing abilities within the CIK cell culture. These terminally differentiated CD3 and CD56 double-positive CIK cells developed from former CD56-negative T cells and exhibit a non-MHC restricted cytolytic activity against several tumor targets, as NK cells do (Lu and Negrin 1994; Schmidt-Wolf et al. 1993; Franceschetti et al. 2009). Although the exact mechanisms of tumor tracing have not been completely clarified so far, the natural killer group 2 member D (NKG2D) cell-surface receptor in association with the adaptor molecule DAP10 is supposed to be the most responsible in CIK-induced cytolysis. An interaction between the NKG2D receptor and its ligands, typically MIC A/B and ULBP 1–4, leads to perforin-mediated tumor cell lysis (Verneris et al. 2001, 2004). Various hematologic and solid tumor cells overexpress NKG2D ligands, making them attractive to CIK cell-induced cytolysis (Groh et al. 1999; Salih et al. 2003; Pende et al. 2002).

By now, CIK cell culture conditions were extensively improved and modified with the main objective of generating a faster expansion to $CD3^+CD56^+$ cells. Therefore, current studies applied, among others, IL-15 instead of or along with IL-2, showing that CD56-positive CIK cells can be generated within a shorter period of time and, additionally, exhibit a stronger cytotoxic activity than compared with solely IL-2 expanded cells. Moreover, the number of regulatory T cells known to inhibit antitumor immunity was also depressed by IL-15 but not or to a lesser extent by IL-2 (Rettinger et al. 2012; Tao et al. 2013; Wei et al. 2014).

Recently, several clinical trials were conducted combining strategies of passive adoptive CIK cell transfusions with active immunization approaches. Active immunotherapy is meant to boost the targeted immune response through presentation of tumor-specific vaccines, and there is growing evidence that CIK cells conditioned that way exhibit an increased antitumor efficacy. Along with other application schemes, for example, the combined application of CIK cells with dendritic cells (DCs) or rather the coculture containing DCs pulsed with tumor antigen joint with CIK cells might further improve antitumor toxicity (Thanendrarajan et al. 2011).

As things stand at present, CIK cells might usefully complement current adjuvant cancer treatment. Their transfer into clinical application is strongly facilitated by several key issues including their significant MHC-unrestricted antitumor activity against a broad range of cancers and their simple cultivation conditions. However, up to now, even after 25 years of promising experimental as well as clinical experiences, standard integration in clinical practice is still rendered difficult due to persisting disparities in study design and reporting on clinical results. This is the reason why we have established the international registry on CIK

cells (IRCC) in cooperation with the Stanford University School of Medicine in 2010. The IRCC aim to collect and assess clinical data about CIK cell therapy in clinical trials and to set up new standards on the global reporting about results from CIK cell application. This standardized evaluation of clinical trials allows assessing the clinical benefits of CIK cell therapy in its entirety and will systematically advance this new anticancer treatment approach in the nearer future. Moreover, it will help to build up a standard process in CIK cell treatment and thereby sooner benefit the patients. To achieve the goal of an appropriate assessment and in order to get an effective overview of the current state of CIK cell treatment, we designed a list of indices and created a registry form available on our homepage. New and outstanding trials can also be registered on www.cik-info.org.

Our most recently published report of the IRCC comprised data from 11 clinical trials using adjuvant CIK cell-based immunotherapy in cancer patients (Hontscha et al. 2011). In the below sections, we provide an update on our former report and outline the most prominent clinical results obtained from 45 clinical trials with a total of 2,729 patients newly added to our registry database to date.

Materials and methods

Search strategy and selection criteria

We searched for studies in the PubMed database, Online Proceedings of the American Society of Clinical Oncology (ASCO) Annual Meetings and the European Cancer Conference (ECCO). In order to identify human clinical trials on CIK cells, a combination of keywords including "cytokine-induced killer cells," "clinical trials," "cancer" and "tumor" was applied. Papers published in English were reviewed, whereby only data from English abstracts were assessed in Chinese papers, if this was considered appropriate and sufficiently reliable. In addition to the computerized search, a manual search in the reference sections of included papers was performed. We collected and evaluated data of 45 clinical studies presenting results of either neo-adjuvant/adjuvant CIK cell therapy or combined conventional and immunotherapy. Studies were considered as eligible when investigating the feasibility and efficacy of CIK cells on patients suffering from different cancer entities and in all disease stages.

Data collection

For all included trials, we gathered the author's names and addresses including e-mail, title, journal, phase, cell entity (autologous or allogeneic), tumor entity, number of patients (males and females), median- and age range, stage of disease, inclusion as well as exclusion criteria, total number of CIK cells (including number of cells per infusion and total number of infusions), storage conditions (fresh or frozen), clinical and immunologic responses, hematologic and non-hematologic toxicity, and follow-up (time period of follow-up and duration of responses).

Evaluation of studies

The above-mentioned indices were entered in our registry's database (IRCC) and compared. Many studies had interesting points in common. So the absolute numbers of patients, male–female ratio, etc. could be determined, and we were able to work out means and standard deviations. Particular attention was given to the overall response rate (ORR), overall survival (OS), progression-free survival (PFS), immunologic responses and improved of quality of life. ORR was defined by the sum of complete remissions (CRs) plus partial remissions (PRs) as reported by the authors. Furthermore, stable disease (SD), minimal response (MR) (<50 % regression) and progressive disease (PD) were possible terms for outcome, but the latter 3 were not included as remissions.

Results

Here, we summarize the substantial data listed in our database and present the most prominent clinical results obtained from 24 phase I and 21 phase II clinical trials in accordance with the registry evaluation form.

Patient characteristics

In 45 evaluated trials, a total of 2,729 patients were enrolled, whereof 61 % were male and 39 % were female. 1,520 patients thereof, representing 55.7 % of the total patient collective, were treated either with CIK cells as an adjuvant mono therapy or combined along with standard therapy regimen.

The patients' age ranged between 18 and 93 years with a median age of 56 ± 15.9 years.

Commonly used inclusion criteria are listed in Table 1. Karnofsky score, metastases, age, adequate renal and hepatic function as well as a normal leukocyte and platelet count were important criteria. In contrast, evidence of another malignant neoplasm, immunosuppressive therapy, additional severe diseases and pregnancy were considered as exclusion criteria. The assessed clinical trials covered a broad spectrum of varying tumor entities and disease stages (Table 2). Most studies provided concrete information on the stage of disease. Seventeen studies enrolled patients with an advanced stage only; all remaining trials either

Table 1 Inclusion and exclusion criteria of CIK cell immunotherapy

Common inclusion criteria	Common exclusion criteria
Pathologically confirmed relapse or progression of disease	Immunosuppressive therapy
No active GVHD	Decompensated heart insufficiency
Karnofsky performance score of >40	Ventricular rhythm disorders
Child-pugh stage A or B	Severe coronary artery diseases
No metastases/metastatic stage (depending on study conditions)	Active uncontrolled acute GVHD
Solitary tumor	Evidence of another active malignant neoplasm
No preoperative CIK cell transfusion	Life expectancy <3 months
Maximal cytoreductive surgery as the initial treatment	Chronic infection disease
Serum creatinine of <2 mg/dL	Alcohol abuse
Direct bilirubin of <3 mg/dL	Drug addiction
Transaminases <3 times the upper limit or normal	Severe psychiatric disease
Leukocyte count >3,000/μL	Pregnant or lactating females
Platelet count >100,000/μL	Refused to participate
18–80 years old	

included both patients in advanced and early settings or did not specify the stage of disease any further.

Cells, cycles and infusions

In 41 of 45 studies, autologous CIK cells were used for infusion; whereas five studies, which included 52 patients, operated with allogeneic cells.

The vast majority of studies used fresh CIK cells except for three trials, which utilized frozen CIK cells that were thawed prior to infusion or rather flow cytometric analysis.

We obtained concrete information on the number of CIK cells used for a single infusion in 33 studies. Among these, the number of CIK cells varied in a wide range from 1.5×10^6 up to 5×10^{10} with a median and mean count of 5×10^9 and 7.7×10^9 cells, respectively. In some designs, dose escalation was performed and the amount of CIK cells was increased when no adverse reactions were observed at or post-transfusion. The median and mean number of infusions were four and 5.4 ± 3.6, respectively.

Clinical response, quality of life and patient outcome

Disclosures regarding the PFS and OS were provided in 19 of 45 clinical trials. Here, 1,135 patients were enrolled in immunotherapy, and 1,108 patients were included in the respective control groups. Remarkably, 15 of the 19 paired trials that included 874 patients, representing approximately 77 % of patients in the immunotherapy group, reported on significantly prolonged PFS and OS rates in patients treated with CIK cells as compared to the respective control groups that received none or standard therapy alone. In this context, Table 2 summarizes the appropriate clinical data. More specifically, it was reported that in a collective of 352 hepatocellular carcinoma (HCC) patients the 1-, 3- and 5-year OS was significantly prolonged after immunotherapy in 352, 300 and 204 patients, respectively. In a total of 153 patients with gastric cancer (GC), a significantly prolonged 1-, 2-, 3- and 5-year OS was reported in 54, 83, 51 and 67 patients, respectively, and in 120 patients with renal cell carcinoma (RCC), a prolonged 3- and 5-year OS after CIK cell administration was shown in 120 and 46 patients, respectively. In the setting of early and advanced non-small cell lung cancer (NSCLC) with a total of 156 patients in immunotherapy group, it was reported that the 1-, 2- and 3-year OS rates were significantly prolonged in 69, 61 and 87 patients, respectively. The effects on breast cancer (BC) were investigated in two trials of which one reported on significantly prolonged 1- to 4-year OS rates in 45 triple-negative BC patients. Besides that, 13 of 15 colorectal carcinoma (CRC) patients had a significantly prolonged 5-year OS, whereas two patients had at least an increase in 1-year OS. Furthermore, 30 patients suffering from multiple myeloma (MM) demonstrated an increased OS compared to the respective control group. However, the four remaining studies also showed a beneficial effect from CIK cell immunotherapy due to an enhanced PFS or disease-free survival (DFS). Most interestingly in this regard, Liu et al. reported on a significantly prolonged PFS in 46 patients suffering from ovarian cancer (OC) with a median PFS of 37.7 in immunotherapy versus 22.2 months in the control group. Here, the OS was also

Table 2 Therapeutic effects of CIK cell immunotherapy in phase I/II clinical trials sorted by tumor entity

Study reference	Cancer disease	Patients (*n*) total	Patients (*n*) treated with CIK cells	Clinical outcome			Therapeutic success
				CR (*n*)	PR (*n*)	OS (*n*)	
Jiang et al. (2005)	Acute leukemias (not specified)	41	19	–	–	–	–
Linn et al. (2012a, b), Laport et al. (2011), Introna et al. (2007, 2010)	Acute lymphocytic leukemia	7	7	1	1	–	High
Linn et al. (2012a, b), Laport et al. (2011), Introna et al. (2007, 2010), Yang et al. (2012, 2014b), Wang et al. (2013)	Acute myelogenous leukemia	49	40	3	1	–	–
Laport et al. (2011), Yang et al. (2012), Cai et al. (2012)	Chronic lymphocytic leukemia	10	10	5	1	–	Very high
Linn et al. (2012a, b), Introna et al. (2007)	Chronic myelogenous leukemia	13	13	1		–	–
Schmidt-Wolf et al. (1999), Linn et al. (2012a, b), Laport et al. (2011), Yang et al. (2010, 2012), Leemhuis et al. (2005), Huang et al. (2006), Lu et al. (2012), Zhang et al. (2012), Olioso et al. (2009)	Non-Hodgkin lymphoma	60	60	28	4	–	Very high
Linn et al. (2012a, b), Laport et al. (2011), Introna et al. (2007), Yang et al. (2012), Leemhuis et al. (2005), Huang et al. (2006), Olioso et al. (2009)	Hodgkin lymphoma	20	20	3	2	–	High
Laport et al. (2011), Yang et al. (2012, 2014a, b), Zhong et al. (2012), Zhou et al. (2013)	Myeloma	68	38	3	2	30	Very high
Laport et al. (2011), Introna et al. (2007), Yang et al. (2012), Liu et al. (2011)	Myelodysplastic syndrome	15	15	3	2	–	High
Zhang et al. (2012), Olioso et al. (2009), Hao et al. (2010), Niu et al. (2011), Shi et al. (2004), Zhou et al. (2006), Hui et al. (2009), Qiu et al. (2011), Pan et al. (2013), Yu et al. (2014)	Hepaotocellular carcinoma	936	497	1	16	352	Very high
Zhang et al. (2012), Niu et al. (2011)	Gallbladder carcinoma	3	2	–	–	1	Very high
Olioso et al. (2009)	Pancreatic cancer	3	3	–	–	–	–
Zhang et al. (2012), Niu et al. (2011), Gao et al. (2014), Shi et al. (2012a), Jiang et al. (2006), Zhao et al. (2013), Liu et al. (2013)	Gastric cancer	511	233	–	–	153	Very high
Schmidt-Wolf et al. (1999), Niu et al. (2011), Gao et al. (2014), Zhu et al. (2013)	Colorectal carcinoma	58	43	–	–	15	High
Schmidt-Wolf et al. (1999), Zhang et al. (2012), Olioso et al. (2009), Zhan et al. (2012), Liu et al. (2012), Su et al. (2010), Wang et al. (2014), Zhu et al. (2013)	Renal cell carcinoma	328	209	21	38	120	Very high
Zhang et al. (2012)	Ureter carcinoma	1	1	–	–	–	–
Zhang et al. (2012), Niu et al. (2011), Shi et al. (2012b), Zhong et al. (2011), Li et al. (2012), Yang et al. (2013)	Non-small cell lung cancer	403	203	–	–	156	Very high
Zhang et al. (2012), Niu et al. (2011), Pan et al. (2014)	Breast cancer	93	47	–	–	46	Very high

Table 2 continued

Study reference	Cancer disease	Patients (*n*) total	Patients (*n*) treated with CIK cells	Clinical outcome			Therapeutic success
				CR (*n*)	PR (*n*)	OS (*n*)	
Niu et al. (2011), Liu et al. (2014)	Ovarian cancer	94	47	–	–	–	–
Niu et al. (2011)	Cervical cancer	2	1	–	–	–	–
Huang et al. (2006)	Rhabdomyosarcoma	2	2	–	–	–	–
Zhang et al. (2012)	Sarcoma	2	2	–	–	–	–
Zhang et al. (2012), Niu et al. (2011)	Melanoma	10	8	–	–	1	–
	Total	2,729	1,520	69	67	874	

Therapeutic effects of CIK cell immunotherapy in phase I/II clinical trials sorted by tumor entity

Therapeutic success was defined as "High" if it was observed (i) complete remission (CR) in more than 10 % and/or (ii) significantly prolonged overall survival in more than 20 % of patients who underwent CIK cell treatment as compared with control group. The therapeutic success was defined as "Very high" in tumor entities in which we obtained data about (i) CR in more than 20 % of patients and/or (ii) significantly prolonged overall survival in more than 40 % of patients as compared with control group. All other clinical responses as partial remission, minor remission, stable disease and progressive disease were not defined as therapeutic success

CR: complete remissions in patients treated with CIK cells

PR: partial remissions in patients treated with CIK cells

OS: significantly prolonged overall survival in patients treated with CIK cells as compared with control group

prolonged with a median of 61.5 versus 55.9 months, but there was no significant difference ($p = 0.289$) (Liu et al. 2014). In another trial concerning GC after surgical gastrectomy, Shi et al. showed in a retrospective subgroup analysis that only such patients with an intestinal-type tumor had a significantly higher OS after immunotherapy than patients with a more aggressive histopathology. This finding was, however, merely of analytic value since the study failed to demonstrate a significantly different 5-year OS rate in 74 patients whereof 47 had an intestinal-type GC ($p = 0.071$). In contrast, the 5-year DFS rates were also significantly prolonged in 28.3 versus 10.4 % ($p = 0.044$) of patients in the immunotherapy and control group, respectively (Shi et al. 2012a, b). In a setting of NSCLC, two studies with each 30 and 14 patients in immunotherapy group, demonstrated a significantly enhanced PFS of 3.2 and 6.9 versus 2.56 and 5.2 months, respectively, as compared to the respective control groups. Another trial conducted by Zhu et al. did not compare OS rates but provided data about significantly prolonged DFS rates in CRC patients after surgical resection. The 2-year DFS rates of patients in the CIK group and the control group were 59.65 ± 24.80 and 29.35 ± 6.39 %, respectively (Zhu et al. 2013).

We obtained specific information on the ORR after CIK cell treatment in 19 of 45 studies that included 353 patients in immunotherapy groups. Of a total of 353 patients, a clinical response was determined in 136 patients accounting for an ORR of approximately 39 %. However, comparability of clinical outcome data may be limited due to heterogeneous clinical settings and varying combination therapies. Nevertheless, 69 patients had at least a temporary CR after the administration of CIK cells. In addition, 67 patients achieved PR and SD, respectively. Apart from this, Jiang et al. did not provide concrete statements on the clinical response but enrolled 41 patients in a setting of acute leukemia whereof 19 received immunotherapy prior to chemotherapy. Here, 27.3 % in the control group and, in contrast, 73.4 % of patients in the CIK group achieved continuous CR after 4 years of follow-up ($p < 0.005$) (Jiang et al. 2005).

Furthermore, three studies investigated if the efficacy of CIK cells is depending on the administered infusion count. Therefore, Jiang et al., Liu et al. and Pan et al. divided their immunotherapy group in several subgroups, which received different numbers of CIK cell infusions (Tao et al. 2013; Pan et al. 2013; Liu et al. 2012). They demonstrated that an increased infusion count was significantly associated with better prognosis.

In addition to clinical outcome data, many trials provided other relevant clinical information such as quality of life (QOL) and patients' general condition. Five studies gathered information on changes in QOL by using objective criteria. Mainly the patients' Karnofsky score before

and after CIK cell treatment was determined (Yang et al. 2010, 2012, 2014a, b; Zhong et al. 2012; Qiu et al. 2011). The Karnofsky Performance Scale Index is a commonly used tool, which allows patients to be classified as to their functional impairment. Four of the five mentioned studies demonstrated an improved QOL after CIK cell treatment by a significantly higher Karnofsky score. Even if the remaining 40 clinical trials did not evaluate their patients according to objective and consistent criteria, patients were found to have a markedly improved general presentation, attenuated fatigue, improved mental status and appetite. A reduced infection incidence and independence from blood transfusions were also observed.

Immunologic response

An immunologic response was regularly observed after CIK cell application among the 23 studies that provided detailed data about changes in tumor marker levels and/or phenotypic characteristics.

A significant increase of the patients' absolute numbers of $CD3^+$, $CD3^+CD56^+$, $CD3^+CD8^+$ and $CD8^+$ T cells in peripheral blood was observed in 16, 15, 7 and 5 of these 23 studies, respectively. In 7 studies, the $CD4^+/CD8^+$ ratio significantly increased as well. However, three trials reported significantly decreased $CD4^+CD25^+CD127^+$ regulatory T cells and two studies described declined numbers of $CD8^+$ T cells. Apart from that, the concentrations of the immunomodulatory cytokines interferon gamma (IFN-γ) and interleukin 2 (IL-2) were significantly up-regulated in three studies and in one single study, respectively.

Tumor markers such as β2-mikroglobulin (β2M), CEA, AFP, LDH, CA 19-9, CA 72-4, MG-7Ag significantly decreased in the majority of cases along with CIK cell therapy.

In one study, patients suffering from chronic HBV infection experienced a large reduction in the viral load from 1.9×10^6 to 1.4×10^5 copies/mL after 3 months of consistent CIK cell therapy (Shi et al. 2004).

Treatment toxicity and adverse effects

It is indeed noteworthy that actually no severe side effects were reported for all of the 1,520 patients treated with CIK cells. Authors stated without explaining more precisely that there was no obvious treatment toxicity in 933 patient cases. All of these patients did not require any specific treatment besides symptomatic therapy. However, the remaining 587 patient cases were described in detail. We figured out that fever (37.5–40 °C) occurred in 40.9 % of cases and hence accounts for the most common side effect accompanying CIK cell immunotherapy. The second most common adverse effects were headache and fatigue, both developed by 32 % of patients. Fever-related chills rank third with an occurrence in 26.7 % of patients. Instances of rashes or nausea and vomiting were more rarely noticed in the patient collective, viz. in 11 and 8.6 %, respectively. A significant but rare side effect, developed by three out of 1,529 patients, was chest distress or ventricular arrhythmia for about 10 min after CIK cell infusion that terminated without intervention. However, the etiology of the arrhythmias and a possible association to CIK cell therapy was never elucidated. Table 3 briefly summarizes the obtained results.

Table 3 Side effects associated with CIK cell immunotherapy

Adverse reaction	Relative frequency (%)
Fever 37.5–40 °C	40.9
Fatigue	32
Headache	32
Fever-related chills	26.7
Rash	11
Nausea and vomiting	8.6
Ventricular arrhythmia and chest distress	0.2

Mild graft-versus-host disease (GVHD) occurred in seven of 52 patients treated with allogeneic CIK cells (Linn et al. 2012a, b; Laport et al. 2011; Introna et al. 2007; Zhou et al. 2013). Three patients developed acute GVHD of the skin (grade 2–3); GVHD (grade 2) of the liver was seen in two other patients, and intestinal GVHD (grade 3) was observed in one patient. The seventh patient developed limited chronic GVHD manifested as joint stiffness and aches. All cases of GVHD responded to corticosteroids, which were eventually discontinued.

It is important to underline that all adverse reactions (except GVHD in allogeneic settings) were not lasting beyond 24 h. Most side effects recovered spontaneously or were easy to control with symptomatic measures like non-steroidal compounds.

Discussion

Cancer treatment can potentially be improved by cellular immunotherapies, which drive the host's immune system toward cancer recognition and enhance an immunologic reaction (Thanendrarajan et al. 2012).

Among them, CIK cells represent a valuable immunotherapeutic approach since they have previously shown significant antitumor activity in preclinical experiments and animal tumor models (Schmidt-Wolf et al. 1991; Kim et al. 2007).

Based on the findings of our previous report, we stated that the application of CIK cells in cancer therapy may

prevent recurrence, improve quality of life and progression-free survival (Hontscha et al. 2011). Since this report, much effort has been made to assess clinical benefits achieved by CIK cell therapy along or even after conventional therapeutic regimens.

Currently, the number of trials investigating cancer treatment with CIK cells is rapidly increasing. Research and thus cancer patients will benefit from improved information exchange and worldwide availability of data gathered in respective clinical trials. Heterogeneity among studies in terms of study design, clinical setting and response assessment make it difficult to draw objective conclusions. Particularly, combination therapies further complicate an interpretation of data. But taken together, a beneficial effect from CIK cells could be assumed. In 2010, we therefore established the IRCC as the very first worldwide platform intended to register clinical trials on CIK cells; particularly, in order to collect knowledge about the clinical application of CIK cells and to improve the comparability of clinical trials by reducing disparities among them. Our primary aim for the future is to provide standard instruments for study designs, which will allow drawing reliable conclusions.

After the evaluation of 45 clinical trials by applying the registry indices, our data suggest that an adoptive CIK cell therapy is superior to standard therapy alone in a broad variety of both hematopoietic and solid neoplasms.

The reviewed clinical studies indicate that CIK cell immunotherapy is a pretty safe and valuable approach in the treatment of cancer patients, even if the disease reached an advanced stage or patients did not respond to any kind of pretreatment. The administration of CIK cells, either alone or combination with chemotherapy, led to CR in patients suffering from different types of neoplasms. Notable examples of CR are predominantly detectable in hematologic malignancies (Schmeel et al. 2014). Approximately 50 % of patients suffering from either Non-Hodgkin lymphoma or chronic lymphocytic leukemia achieved CRs after CIK cell therapy. Considerable numbers of CRs are also to be found in patients bearing renal cell carcinoma; when combined with standard therapy, around 10 % achieved CR, even in advanced stages. Also in cases, when no CR was observed, CIK cell treatment was mostly superior to standard therapies alone: Across almost all neoplasms of which we have concrete statements, CIK cell treatment significantly prolonged the OS and PFS rates accompanied by an improved quality of life; this applies in particular to advanced NSCLC, HCC, GC, BC, RCC and MM. Although one trial investigating OC failed to demonstrate a significant prolonged OS, however, a remarkable and significantly prolonged progression-free survival was reported (Liu et al. 2014).

It remains to be seen if an elevated infusion count results in a more favorable prognosis. In this context, it is tempting to speculate that the higher the infusion count, the better the benefit of patients; especially since three clinical trials clearly demonstrated a more favorable prognosis in patients administered a higher CIK cell infusion count (Jiang et al. 2005; Pan et al. 2013; Liu et al. 2012).

CIK cell application revealed considerable antitumor effects against various malignancies and, most interestingly, major side effects are missing. Severe adverse reactions occurred only in a tiny minority of patients and more common side effects were mostly mild, easily controllable and well tolerated. However, mild fevers, chills, headache and fatigue were seen regularly after CIK cell infusion, but resolved without intervention within 24 h or were treated successfully by simple symptomatic therapy such as anti-inflammatory treatment and anti-emetic treatment.

Another important aspect of our evaluation was the observation that CIK cell therapy was able to induce significant immunologic effects. In general, immune response is regularly observed to be impaired in patients with advanced stages of cancer (Von Roenn et al. 1987). Therefore, functional or numerical changes of T lymphocyte subsets are often used parameters to assess the patient's immune function (Robinson et al. 1999). For this reason, many studies performed phenotype analysis before and after CIK cell therapy, which revealed, inter alia, changes within T cell subpopulations. Especially, rises in $CD3^+$, $CD3^+CD8^+$ and $CD3^+CD56^+$ T cells were frequently observed in the assessed clinical trials. These findings might indicate the relevance of these T cell subsets for the antitumor effect and thus seem to play an important role in clinical outcome. In this respect, the registered increase in IFN-γ is of major interest as well. IFN-γ represents a key immunostimulatory and immunomodulatory cytokine that was shown to primarily improve cell-based immune responses such as promoted NK cell activity. The importance stems from numerous antitumor effects as IFN-γ inhibit tumor growth, blocks angiogenesis or stimulates macrophages. Enhanced expression of the major histocompatibility complex (MHC) I molecule and improved cytotoxicity reflect two more IFN-γ properties (Schroder et al. 2004). We could therefore deduce that raised IFN-γ levels are not only essential for the cultivation of CIK cells, but may also synergistically complement CIK cells' efficacy due to an enhanced cytotoxic immunologic response. This assumption is backed up by increased numbers of $CD8^+$ cytotoxic T cells and $CD3^+CD8^+$suppressor/cytotoxic T cells, an increased $CD4^+/CD8^+$ ratio and decreased $CD4^+CD25^+CD127^+$ regulatory T cells (Oleinika et al. 2013; Kilinc et al. 2009).

Moreover, Shi et al. (2004) made a pretty interesting observation on the effect of CIK cell treatment on the HBV viral load in patients with HCC. Already 1 month after CIK treatment decreased viral loads were measured. It is a pity

since up to now chronic infection diseases are considered as exclusion criteria.

As a matter of fact, quite heterogeneous data assessment still remains a weighty problem in finding definite conclusions on immunologic effects induced by CIK cells. In order to homogenize future trials, we would suggest evaluating at least the following T cell subsets and cytokines: $CD3^+$, $CD8^+$, $CD3^+CD8^+$, $CD3^+CD56^+$, $CD3^-CD56^+$, $CD4^+CD25^+$, $CD4^+/CD8^+$ ratio, IFN-γ, TNF-α and TGF-α.

Based on the available data, CIK cells provided entirely convincing results about their non-MHC-restricted antitumor activity, even in advanced settings. Best feasibility and a high safety profile additionally round CIK cell therapy's benefit-risk profile. But as yet drawing definitive conclusions on the efficacy is still difficult due to heterogeneous study designs, different patient inclusion criteria, varying disease stages, divergent outcome measures and widely spread pretreatments before CIK cell application. Besides, control groups are missing in some studies applying combined chemo-immunotherapy, making definite conclusions imprecise. Studies based on a rather small scope of patients also hamper certain conclusions. In the future, larger randomized studies plus longer follow-up durations should address these open questions to elucidate the best possible treatment strategy. After the promising results of current phase I and II studies, confirmatory phase III studies should be conducted and will probably push the establishment of CIK cells and their clinical efficacy forward. To achieve best therapeutic advances, it will be of major interest to further enhance the progression in fields such as improving CIK cells' antitumor toxicity, exploring additional combination therapies, standardizing CIK cultivation and therapy schedule. Conventional therapies should eventually be excluded to precisely evaluate the efficacy of CIK cell therapy. However, in routine clinical application and in the light of the latest state of research, it currently seems rather unfeasible to solely treat patients with CIK cells.

Another issue that should be faced by future trials is the efficacy of CIK cells in early disease stages as predominantly patients in advanced stadiums are enrolled so far. But our findings indicate that it is likely that also patients in early stages might benefit from the safe and effective combination of CIK cells with both standard chemotherapies and/or other immunotherapies (Shi et al. 2004; Yu et al. 2014; Li et al. 2012).

Existing data indicate that the application of CIK cells in cancer therapy may prevent recurrence, improve quality of life and prolong the overall as well as the progression-free survival.

Not only due to their potent ex vivo expansibility within only a short period of time and, most important, their methodological simplicity, CIK cell application emerged as a new fascinating tool in cancer therapy and will definitely have the potential to gain pivotal importance on the prognosis of cancer.

Building on our findings, we would suggest the following points to future trials. Since some studies reported on better outcome after an increased infusion count and an elevated number of CIK cells per infusion without increased rates of adverse reactions, we would recommend utilizing a minimum of 1×10^{10} CIK cells with at least 30 % of $CD3^+CD56^+$ cells per infusion. Infusions should be administered every 2–4 weeks and at least six times. Our recommendations concerning the evaluation of immunologic effects should also be taken into consideration. Whenever possible, follow-up durations of at least 60 months are to be strived to draw reliable conclusions on the long-term efficiency. Finally, building upon the great response in recent years, we would once more like to encourage all interested readers to contact us in case of further studies with CIK cells in order to collect future clinical trials. The following parameters should be reported: Publication details, title, journal, phase of clinical trial, use of autologous or allogeneic cells, tumor entity, number of patients, sex of patients, median age, age range, stage of disease, inclusion criteria, exclusion criteria, number of CIK cells per infusion, total number of infusions, number of cycles, HLA type of patients' CIK cells, storage of CIK cells, toxicity, clinical and immunologic response, time period of follow-up, results of follow-up and survival status of patients.

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