Cytotherapy, 2015; 17: 979–988

International Society for Cellular Therapy
ISCT®

Combined cellular immunotherapy and chemotherapy improves clinical outcome in patients with gastric carcinoma

JIUWEI CUI*, LINGYU LI*, CHANG WANG*, HAOFAN JIN, CHENG YAO, YIZHUO WANG, DAN LI, HUIMIN TIAN, CHAO NIU, GUANJUN WANG, WEI HAN, JIANTING XU, JINGTAO CHEN & WEI LI

Cancer Center, The First Hospital of Jilin University, Changchun, China

Abstract

Background aims. Despite the availability of multiple treatment strategies, patients with gastric carcinoma (GC) have a dismal prognosis. The aim of this study was to evaluate the efficacy and safety of cellular immunotherapy (CIT) with the use of autologous natural killer cells, γδT cells and cytokine-induced killer cells in combination with chemotherapy in patients with GC. *Methods.* In this open-label pilot cohort study, patients were treated with the combination therapy (chemo/CIT group) or chemotherapy alone (control group). Progression-free survival (PFS), overall survival (OS), quality of life (QOL) and adverse events were investigated. *Results.* Fifty-eight patients were analyzed, 30 in the chemo/CIT group and 28 in the control group. The median PFS of the chemo/CIT group was significantly longer compared with the control group ($P = 0.021$). In subgroup analysis, in patients with stage III GC, node-positive metastasis or poorly differentiated carcinoma, the 2-year PFS rate in chemo/CIT versus control groups was 62.5% versus 26.7% ($P = 0.022$), 50% versus 27.3% ($P = 0.016$) and 56.3% versus 28.6% ($P = 0.005$), respectively. The median OS in either group has not yet been reached, and there was no significant difference in OS between the groups. The QOL was improved in the patients treated with chemo/CIT compared with the control group. CIT was well tolerated and not related to any significant adverse events. *Conclusions.* A combination of CIT and chemotherapy for patients with GC was safe, improved QOL, and might prevent recurrence, especially in GC patients with advanced stage, poorly differentiated carcinoma or lymph node metastasis.

Key Words: *cellular immunotherapy, chemotherapy, combination therapy, gastric cancer*

Introduction

Gastric carcinoma (GC) is the second most common cause of cancer mortality worldwide and is especially prevalent in China [1]. Despite the availability of multiple treatment strategies, the prognosis of patients with GC is dismal, with a 5-year overall survival (OS) rate of ≤25% as a result of high rates of recurrence and metastasis [2]. In patients with GC, the host immune response is compromised [3]. Functional deficiencies in a variety of immunocytes produce a tumor microenvironment that encourages disease progression [4], which suggests that cellular immunotherapy (CIT) with *ex vivo*–activated and expanded immunocytes could improve patient immune status to enhance the therapeutic outcome in patients with GC.

Currently, the focus of CIT in GC is on cytotoxic T lymphocyte (CTL)-based and dendritic cell–based vaccines that showed promise in preclinical studies [5]. Nevertheless, the clinical outcomes of these immunotherapies have been disappointing, partly because of the complexity of immune escape mechanisms of tumor cells such as the downregulation of major histocompatibility complex (MHC) molecules and target antigens on tumor cells [6]. Therefore, non-MHC–restricted immunotherapy could be a novel strategy to treat patients with GC.

Non-MHC–restricted cytotoxic lymphocyte natural killer (NK) and γδT cells are innate immunity effector cells. Both recognize and attack cells that express specific ligands on activation such as NK group 2 member D (NKG2D) [7–9]. Cytokine-induced killer (CIK) cells are a heterogeneous population of immunocytes [10] that include CD3+CD56+ cells, which partly share the same killing mechanism as NK cells. CIK cells can regulate the immune status *in vivo* and directly kill tumor cells both *in vitro* and *in vivo* [11]. Tumor cells exhibiting downregulation of MHC class I, as an escape mechanism for CTLs, are

*These authors contributed equally to this work.
Correspondence: **Wei Li**, PhD, Cancer Center, The First Hospital of Jilin University, No. 71. Xinmin Street, Changchun, 130021, China. E-mail: drweili@yeah.net

(Received 21 January 2015; accepted 4 March 2015)

ISSN 1465-3249
http://dx.doi.org/10.1016/j.jcyt.2015.03.605

susceptible to these non-MHC–restricted NK and CIK cells. Furthermore, NKG2D ligand is highly expressed on many tumor cells including GC cells, facilitating targeting by NK and CIK cells [12].

CIT, based on one of the cells, has proven to be efficacious in clinical studies in patients with GC [13]. NK, γδT and CIK cells functioned in a similar manner and demonstrated synergistic cell-killing effects when used in combination [9]. We postulated that a combination of the three cell types might elicit an improved therapeutic response compared with CIT, which uses one cell type alone.

Chemotherapy can enhance the efficacy of CIT by inhibiting immune suppression and reducing tumor burden to improve tumor cell susceptibility [14]. For example, cisplatin or oxaliplatin therapy could upregulate the expression of NKG2D on tumor cells, increasing the susceptibility of GC tumor cells to NK, γδT or CIK cell–mediated cell-killing [15]. In addition, CIT could improve the efficacy of chemotherapy [16], which suggests a potential synergetic efficacy for a combination of chemotherapy and CIT.

In the present prospective cohort study, we investigated the safety and efficacy of CIT in combination with chemotherapy as a novel therapeutic strategy for the treatment of patients with GC.

Methods

Patients and study design

The study protocol was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Ethics Committee of the First Hospital of Jilin University. For this prospective, observational, pilot cohort study, all patients with GC who met the following criteria between May 2009 and November 2012 were included: (i) ≥18 years old with primary GC; (ii) an Eastern Cooperative Oncology Group (ECOG) performance status ≤2; and (iii) normal hepatic, renal and hematological functions. Exclusion criteria included (i) other immunotherapies; (ii) clinically serious infections; (iii) a history of organ transplantation; (iv) pregnancy or breast-feeding. After an informed discussion, patients made the decision to receive chemotherapy alone or in combination with CIT, and they were classified as the control and chemo/CIT groups, respectively. In the chemo/CIT group, patients either received sequential CIT therapy after the last chemotherapy (sequential therapy group, STG) or CIT simultaneous with chemotherapy (combined therapy group, CTG). The decision whether to undergo STG or CTG was made by the patient. The study flow chart is summarized in Figure 1. Eligible patients received chemotherapy on the basis of 5-fluorouracil and platinum according to National Comprehensive Cancer Network (NCCN) Guidelines. Written informed consent was obtained from all patients before enrollment.

Patients were followed-up every 3 months with a complete physical examination, basic serum chemistry analyses and computed tomography (CT) of the chest and abdomen. During the follow-up period, patients completed questionnaires of quality of life (QOL) according to the questionnaire survey schedule

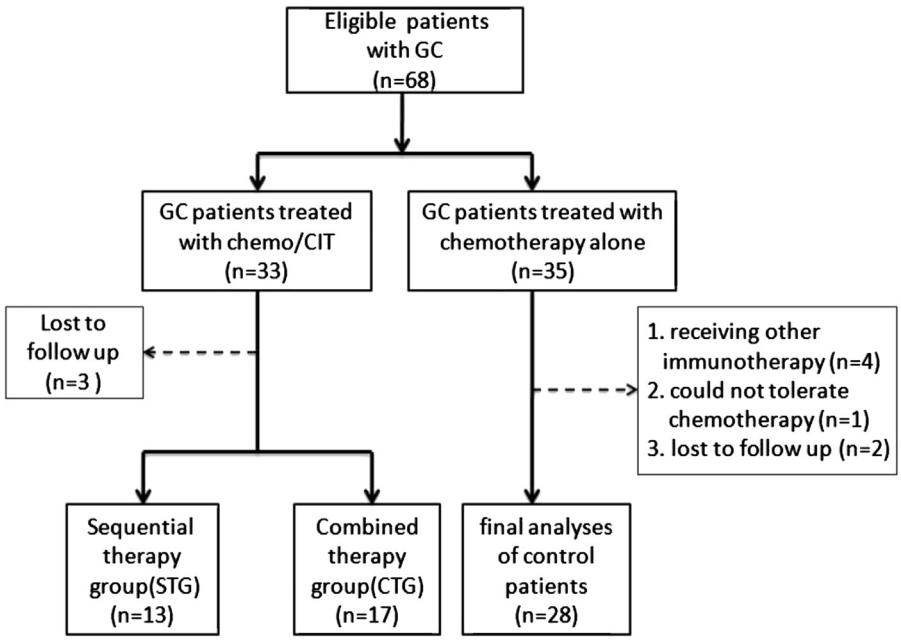

Figure 1. Flow chart of the study. Follow-up consisted of a physical examination, blood count measurements, liver function tests, computed tomography and chest radiography. Gastroscopy was performed when regional recurrence was suspected.