RESEARCH ARTICLE

Weight Loss Correlates with Macrophage Inhibitory Cytokine-1 Expression and Might Influence Outcome in Patients with Advanced Esophageal Squamous Cell Carcinoma

Zhi-Hao Lu[1&], Li Yang[2&], Jing-Wei Yu[1], Ming Lu[1], Jian Li[1], Jun Zhou[1], Xi-Cheng Wang[1], Ji-Fang Gong[1], Jing Gao[1], Xiao-Tian Zhang[1], Jie Li[1], Yan Li[1], Lin Shen[1*]

Abstract

Background: Weight loss during chemotherapy has not been exclusively investigated. Macrophage inhibitory cytokine-1 (MIC-1) might play a role in its etiology. Here, we investigated the prognostic value of weight loss before chemotherapy and its relationship with MIC-1 concentration and its occurrence during chemotherapy in patients with advanced esophageal squamous cell carcinoma (ESCC). Materials and Methods: We analyzed 157 inoperable locally advanced or metastatic ESCC patients receiving first-line chemotherapy. Serum MIC-1 concentrations were assessed before chemotherapy. Patients were assigned into two groups according to their weight loss before or during chemotherapy:>5% weight loss group and≤5% weight loss group. Results: Patients with weight loss>5% before chemotherapy had shorter progression-free survival period (5.8 months *vs*. 8.7 months; *p*=0.027) and overall survival (10.8 months *vs*. 20.0 months; *p*=0.010). Patients with weight loss >5% during chemotherapy tended to have shorter progression-free survival (6.0 months *vs*. 8.1 months; *p*=0.062) and overall survival (8.6 months *vs*. 18.0 months; *p*=0.022), and if weight loss was reversed during chemotherapy, survival rates improved. Furthermore, serum MIC-1 concentration was closely related to weight loss before chemotherapy (*p*=0.001) Conclusions: Weight loss both before and during chemotherapy predicted poor outcome in advanced ESCC patients, and MIC-1 might be involved in the development of weight loss in such patients.

Keywords: Weight loss - esophageal SCC - macrophage inhibitory cytokine-1 - chemotherapy - overall survival

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Introduction

Esophageal cancer is the eighth most common cancer worldwide (Kamangar et al., 2006). Because of its special anatomic structure and biological characteristics, the rate of malnutrition of esophageal cancer is among the highest reported malnutrition rates (Riccardi and Allen, 1999). Weight loss, which is a major feature of malnutrition, could be attributed to diminished dietary intake as well as to increased energy expenditure mediated by metabolic alterations caused by the tumor (Bosaeus et al., 2002).

Effects of weight loss before chemotherapy on survival in esophageal cancer patients were controversial. A study concluded that esophageal cancer patients with>10% weight loss before chemotherapy had significantly shorter overall survival (OS) than those with≤10% weight loss (Pedersen et al., 1982). However, another study showed that OS in esophageal cancer patients with weight loss before chemotherapy was not statistically different from that of patients without weight loss (Andreyev et al., 1998).

Weight loss during chemotherapy is also very common, which may be a consequence of a combination of tumor-related factors and chemotherapy-related toxicities. Hence, the mechanism of weight loss during chemotherapy might differ from that of weight loss before chemotherapy. It has been proved that weight change during primary chemotherapy is a potential prognostic factor for OS in epithelial ovarian carcinoma (Hess et al., 2007) and advanced gastric cancer (Lu et al., 2014). However, it is unclear if weight loss during chemotherapy could potentially impact survival or just be a transient phenomenon in esophageal cancer patients, especially in esophageal squamous cell carcinoma (ESCC) patients.

In late-stage cancer, it is believed that tumor- or stromal cell-derived molecules disturb the control of appetite and weight control, often leading to wasting (Tisdale, 2002). Macrophage inhibitory cytokine-1

*[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of GI Oncology, Peking University School of Oncology, Beijing Cancer Hospital& Institute, [2]Department of Oncology, Zhangzhou Municipal Hospital, Fujian Province, China. [&]Equal contributors *For correspondence: linshenpku@163.com*

(MIC-1) is a transforming growth factor-β (TGF-β) superfamily protein (Bootcov et al., 1997). It is involved in the physiological regulation of appetite and energy storage (Tsai et al., 2013) with a normal range of 150-1,150 pg/ml in the circulation of individuals (Brown et al., 2002a; Brown et al., 2002b). Its expression level may be induced by inflammation, injury and malignancy (Breit et al., 2011) and high concentration of MIC-1 has been observed in many types of cancers (Welsh et al., 2003; Bauskin et al., 2006; Lu ZH et al., 2014). In a study involving both cachectic prostate cancer patients and mice bearing human prostate cancer xenografts, elevated MIC-1 concentrations were associated with weight loss (Johnen et al., 2007). However, the relationship between serum MIC-1 concentrations and weight loss in advanced or metastatic ESCC patients remains to be understood.

Therefore we carried out this study to find out whether weight loss before or during chemotherapy influences outcome and the relationship between serum MIC-1 concentrations and weight loss in inoperable locally advanced or metastatic ESCC patients.

Materials and Methods

Ethics statement

This study was approved by the Medical Ethics Committee of Peking University Cancer Hospital (Beijing, China) and was performed according to the Declaration of Helsinki Principles. Written informed consents were obtained from all study participants for their information to be stored in the hospital database and used for future research.

Patients and Data Collection

Detailed clinical data for patients treated at Peking University Cancer Hospital Gastrointestinal Medical Oncology Department were recorded in a regularly updated electronic database. Eligibility criteria included: (1)Chemotherapy-naïve patients with pathologically confirmed, inoperable locally advanced or metastatic ESCC, (2)Patients who received first-line chemotherapy, and (3)Life expectancy≥3 months. Patients who could not eat soft food were excluded. All patients provided written informed consent before receiving chemotherapy.

Parameters measured included age, gender, Karnofsky performance score (KPS), histological differentiation, stage, radiotherapy or esophagectomy or second-line chemotherapy after first-line chemotherapy, weight loss before and during chemotherapy, chemotherapy regimen, treatment-related toxicity, overall response rate (ORR), progression free survival (PFS) and over survival (OS). Whole blood samples were obtained before chemotherapy for analysis of serum MIC-1 concentrations. A healthy control cohort consisting of laboratory and hospital staff was recruited for comparative MIC-1 analysis (n=129; 54 males, 75 females; median age, 44 years; range, 20-80 years). Exclusion criteria for the controls included recent weight change, any illness, or pregnancy.

At the first visit, patients were asked about their stable weight before the illness (W0) by the doctor and were weighed by nurses as pre-treatment body weight (W1). Patients were weighed on each chemotherapy visit in the morning on an empty stomach and a record was made by an experienced nurse team. All patients were admitted to our ward and were weighed on the same spring balance scales without shoes and wearing the same type of patient gowns. The body weight at the last chemotherapy visit was designated as W2. The extent of weight change before chemotherapy was calculated as a percentage according to the following formula: (W1-W0)/W0×100%. The extent of weight change during chemotherapy was calculated as: (W2-W1)/W1×100%.

Toxicity was recorded according to the National Cancer Institution (NCI) Common Toxicity Criteria Version 3.0 (CTC 3.0) by direct questioning, physical examination, and laboratory tests. When grade 3 or 4 non-hematological toxicity or prolonged grade 4 hematological toxicity occurred, the dose of cytotoxic drugs was reduced to 75%. Objective response to treatment was classified using the Response Evaluation Criteria in Solid Tumors (RECIST 1.0) every 6 weeks. PFS and OS were calculated from the date of the first visit to the date of disease progression and death, respectively.

Serum MIC-1 concentrations

The serum MIC-1 concentrations (pg/ml) were determined using a sensitive in house sandwich enzyme-linked immunosorbent assay (ELISA), as previously described (Moore et al., 2000; Brown et al., 2002a). All samples were assayed at least two times, and the coefficient of variation between the samples was <10%.

Statistical methods

SPSS (version 13.0) statistical software was used for the statistical analyses. Chi-square tests were used for comparison of categorical data. Independent variables were analyzed using the Mann-Whitney U test. Receiver operating characteristic (ROC) curve was constructed to determine the optimal sensitivity and specificity followed by the determination of cutoff value for serum MIC-1 concentrations. Serum MIC-1 data were presented as box plots. Mild outliers (MIC-1 concentration more than 1.5 times the interquartile range (IQR) above the third quartile) were represented as circles and extreme outliers (MIC-1 concentration more than 3 times the IQR above the third quartile) were presented as stars. For visual clarity, the Y-axes were limited to a maximum MIC-1 concentration of 5000 pg/ml. Survival curves were generated by the method of Kaplan and Meier and compared using the Log-rank test. Multivariate survival analysis was performed using a Cox regression model including those variables with p <0.05 on univariate analysis. p -values were two-sided and a p value of <0.05 was considered significant.

Results

Patient characteristics

From March 2005 to January 2012, 271 advanced or metastatic ESCC patients were treated at our Department. A total of 157 patients were eligible to this study. Seventy-five patients (47.8%) were inoperable locally advanced

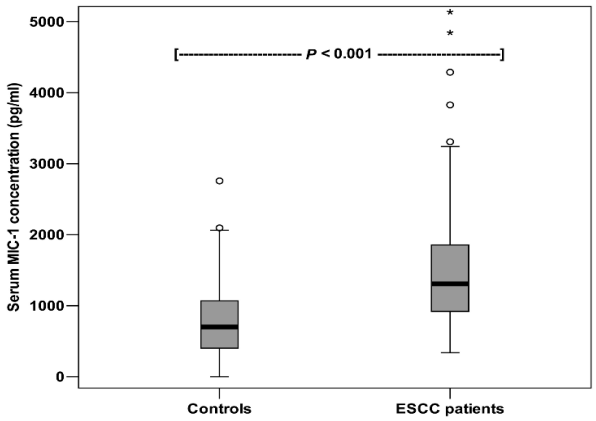

Figure 1. Serum MIC-1 Concentration in ESCC Patients and Healthy Controls Box plot showing increased serum MIC-1 concentration in ESCC patients (n=114; median=1309 pg/ml; interquartile range, 915-1860 pg/ml) when compared with the healthy controls (n=129; median=351 pg/ ml; interquartile range, 199-537 pg/ml; $p<0.001$).

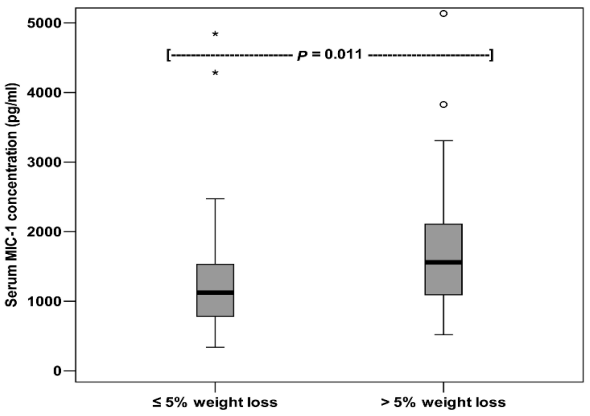

Figure 2. Serum MIC-1 Concentration and Weight Loss Before Chemotherapy Box plot showing increased serum MIC-1 concentration in patients with>5% weight loss before chemotherapy (n=45; median=1560 pg/ml; interquartile range, 1090-2141 pg/ml) when compared with those with≤5% weight loss before chemotherapy (n=65; median=1124 pg/ml; interquartile range, 776-1560 pg/ml; $p=0.011$).

disease and 19 of them (25.3%) received esophagectomy after first-line chemotherapy. The last date of follow-up was December 1, 2012, and 11 patients (7.0%) were lost to follow-up. At this time, 97 patients (61.8%) died and the median OS was 16.5 months. The detailed patient characteristics are listed in Table 1.

Weight loss and MIC-1

Weight loss: Of the 148 patients with data for weight change before chemotherapy, 86 (58.1%) patients had lost a median of 8.5% (interquartile range, 4.5-13.2%) of their body weight. Of the 157 patients with data for weight change during chemotherapy, 90 (57.3%) patients had lost a median of 3.6% (interquartile range, 1.8-5.2%) of their body weight.

MIC-1: A total of 114 patients had blood samples for analysis of MIC-1 concentration before chemotherapy. The serum MIC-1 concentrations were elevated in patients with advanced ESCC when compared with the healthy controls ($p<0.001$; Figure 1). Based on the results of the ROC analysis, the cut-off value was defined as 994pg/ml, and the sensitivity and specificity of the analysis was 84.4% and 62.4%, respectively. All the 114 patients were assigned to two groups: high MIC-1 concentration group (>994 pg/ml, 67.5%) and low MIC-1concentration group (≤994 pg/ml, 32.5%).

Weight loss and MIC-1: The serum MIC-1 concentrations were higher in patients with>5% weight loss before chemotherapy than those with≤5% weight loss ($p=0.011$; Figure 2). Nevertheless, serum MIC-1 concentrations before chemotherapy were not associated with weight loss during chemotherapy ($p=0.465$) (Table 1).

There was no relationship in terms of gender, age, KPS, histological differentiation, distant metastases and ORR with weight loss before or during chemotherapy (Table 1), respectively.

Univariate and multivariate analyses of risk factors for OS

Univariate and multivariate analyses of risk factors for OS were shown in Table 2. In Cox's proportional

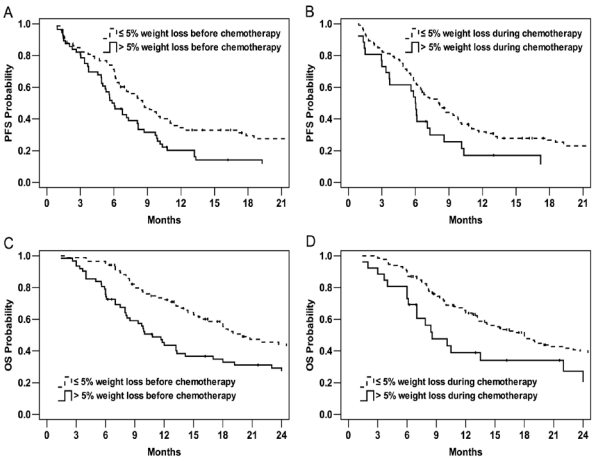

Figure 3. Kaplan-Meier Curves of Survival of Patients According to Weight Loss Before or During Chemotherapy A. Patients with>5% weight loss (median 5.8 months, n=56) had shorter PFS than patients with≤5% weight loss (median 8.7 months, n=73; $p=0.027$) before chemotherapy. B. Patients with>5% weight loss (median 6.0 months, n=26) tended to show shorter PFS than patients with≤5% weight loss (median 8.1 months, n=112; $p=0.062$) during chemotherapy. C. Patients with>5% weight loss (median 10.8 months, n=62) had shorter OS when compared with patients with≤5% weight loss (median 20.0 months, n=86; $p=0.010$) before chemotherapy. D. Patients with>5% weight loss (median 8.6 months, n=26) had shorter OS when compared with patients with≤5% weight loss (median 18.0 months, n=131; $p=0.022$) during chemotherapy.

hazards model, weight loss before chemotherapy, weight loss during chemotherapy, gender, resection after chemotherapy, objective response, and KPS were significant independent determinants of OS.

Effect of weight loss and MIC-1 on progression-free survival

Disease progression was documented in 108 (78.3%) of the 138 patients without esophagectomy following chemotherapy at last follow-up. Patients with>5% weight loss before chemotherapy had shorter PFS than those with≤5% weight loss (5.8 months *vs*. 8.7 months, $p=0.027$; Figure3.A). PFS tended to be shorter in patients

with>5% weight loss during chemotherapy compared to those with≤5% weight loss, although the difference did not reach statistical significance (6.0 months *vs*. 8.1 months, *p*=0.062; Figure3.B). Patients in high MIC-1 concentration (>994 pg/ml) group tended to have worsened PFS than those in low MIC-1 concentration (≤994 pg/ml) group (6.5 months *vs*. 8.6 months, *p*=0.06).

Effect of weight loss and MIC-1 on overall survival

Patients with>5% weight loss before chemotherapy had shorter OS than those with≤5% weight loss (10.8 months *vs*. 20.0 months; *p*=0.010; Figure3.C). However, OS was not statistically different in patients with or without weight loss before chemotherapy (*p*=0.094). Patients with>5% weight loss during chemotherapy had a significant reduction in OS compared to those with≤5% weight loss (8.6 months *vs*. 18.0 months; *p*=0.022; Figure3.D).

Furthermore, we conducted a subgroup analysis of the effect of the weight change during chemotherapy on OS. In the≤5% weight loss before chemotherapy group, patients with≤5% weight loss during chemotherapy had longer OS compared to those with>5% weight loss (22.0 months *vs*. 10.1 months; *p*=0.005). This trend could also be found in>5% weight loss before chemotherapy group, although the difference did not reach statistical significance (11.7 months *vs*. 7.0 months; *p*= 0.522).

Patients in high MIC-1 concentration (>994 pg/ml) group before chemotherapy had shorter OS when compared with those in low MIC-1 concentration (≤994 pg/ml) group (12.0 months *vs*. 18.5 months, *p*= 0.047).

Discussion

Weight loss before chemotherapy has been acknowledged to be a predictor for poor survival in cancer patients (Pedersen et al., 1982; Andreyev et al., 1998; Ross et al., 2004; Van Cutsem and Arends, 2005). However, its effects on survival in ESCC patients were controversial, which may be due to different cutoff values of weight loss (Pedersen et al., 1982; Andreyev et al., 1998).

It was reported that a weight loss of 5% alters measurable physiological parameters, such as immune response, results of lung and cardiac function tests, and autonomic regulation (Jones, 1992). Fox et al. had demonstrated that the ≥5% weight loss definition could identify the most patients with cachexia (Fox et al., 2009). A pilot study conducted in patients with advanced cancer during treatment with palliative chemotherapy showed that weight loss of 5% or more predicted shorter survival (Buskermolen et al., 2012). So we addressed the prognostic effects of>5% weight loss before chemotherapy and our results indicated that>5% weight loss before chemotherapy predicted poor survival in locally advanced or metastatic ESCC patients.

Then, would weight loss during chemotherapy do the same effect in those patients? To our knowledge, there has been no definite evidence about it. We exclusively focused on weight loss during chemotherapy. The effects on OS of different degrees of weight loss during chemotherapy (0%, 3%, 5%) were analyzed and only 5% of weight loss predicted shorter OS. There was no relationship between weight loss during chemotherapy and gastrointestinal toxicity, which indicated that gastrointestinal toxicities may not play a major role in the occurrence of weight loss during chemotherapy. However, patients with weight loss>5% during chemotherapy experienced more frequency of severe (grade 3 or 4) toxicities of all kinds (*p*=0.004) and dose reductions due to toxicities (*p*=0.001). But, neither severe (grade 3 or 4) toxicities (*p*=0.820) nor dose reductions (*p*=0.466) had any impact on OS. Hence, it's hard to distinguish the pure relationship between severe toxicities and weight loss during chemotherapy in this study.

In the present study, patients exhibiting weight loss during chemotherapy had poor PFS and OS. If the weight loss was reversed during chemotherapy, the survival rates improved. This indicates that any method to prevent weight loss or prompt weight restoration could potentially improve the prognosis in these patients. Interventions to address weight loss in cancer patients, such as nutritional support (Koretz, 2007; Baldwin et al., 2012), appetite stimulants (Cuvelier et al., 2014), inhibitors of inflammatory cytokines (Gordon et al., 2005; Schmitz and Ecker, 2008; Mocellin et al., 2013), anti-inflammatory agents (Lundholm et al., 2004), anabolic agents (Dalton et al., 2013), and exercise training (Oldervoll et al., 2011; Argiles et al., 2012), have been investigated widely. Although some results have been encouraging, there is still lack of an adequate evidence base for its therapy. Hence, understanding the underlying causes of weight loss is essential to investigate interventions to manage weight loss in cancer patients (Fearon et al., 2013).

Appetite loss, which is acknowledged to be one of the causes of weight loss, occurs in more than 50% of the incurable cancer patients (Teunissen et al., 2007) and it was reported that loss of appetite was one of the most important factors for weight loss in patients with esophageal carcinoma during radiotherapy (Jiang et al., 2014). However, there have been no studies on advanced ESCC patients that examined the mechanisms underlying appetite loss. MIC-1 (Johnen et al., 2007; Macia et al., 2012; Tsai et al., 2013) could act on TGF-β RII receptors in hypothalamic neurons, and then reduce neuropeptide Y expression and increase pro-opiomelanocortin expression, which may decrease appetite. MIC-1 is overproduced in many types of cancers (Welsh et al., 2003; Bauskin et al., 2006). Both experiments in animals and studies in human beings demonstrated a direct correlation between the degree of serum MIC-1 elevation and the amount of weight loss (Johnen et al., 2007; Macia et al., 2012). Furthermore, such weight loss can be reversed by neutralization of tumor-produced MIC-1 with a specific monoclonal antibody (Johnen et al., 2007). So, we hypothesized that MIC-1 was associated with weight loss in patients with locally advanced or metastatic ESCC. Our study did demonstrate that MIC-1 concentration was closely related to weight loss before chemotherapy, which indicated that MIC-1 may cause weight loss by decreasing appetite in ESCC patients. Some studies had also indicated that serum MIC-1 was closely associated with energy intake and expenditure and systemic inflammation (Skipworth RJ

et al., 2010; Tsai VW et al., 2013). Our study concerning those fields is ongoing.

It has been reported that elevated MIC-1 in circulation predicted poor prognosis in some cancer patients (Brown et al., 2003; Wiklund et al., 2010; Lu ZH et al., 2014). In our study, elevated serum MIC-1 concentration was associated with shorter survival on univariate but not on multivariate analysis, which was consistent with the results of the study by Skipworth et al (Skipworth et al., 2010). Such difference may be explained by the different definitions of MIC-1 elevation. Furthermore, as weight loss before chemotherapy was an independent prognostic factor and MIC-1 was closely related with it, MIC-1 might impact survival by the ways of weight loss, which made MIC-1 a potential therapeutic target to ameliorate weight loss and furthermore to improve prognosis.

There are some limitations of this study. Firstly, this was a retrospective analysis of data that were not collected prospectively for the purpose of this analysis. Secondly, the stable body weight before illness was obtained by directly questioning, which might be somewhat biased. Thirdly, as we did not reserve serum samples during chemotherapy, we could not study the clinical significance of serum MIC-1 during chemotherapy. We are focusing on this in an ongoing study.

Nevertheless, this exploratory study showed that both weight loss>5% before and during chemotherapy predicted a worse outcome in inoperable locally advanced or metastatic ESCC patients, and if weight loss was reversed during chemotherapy, survival rates tended to get improved. Serum MIC-1 concentrations were closely related to weight loss before chemotherapy and might impact survival by ways of weight loss. Hence, MIC-1 might be a potential therapeutic target to ameliorate weight loss and furthermore to improve the prognosis in these patients. These findings provide a rationale for developing strategies to minimize weight loss in inoperable advanced or metastatic ESCC patients, which should to be examined in prospective trials to assess the ability to improve the prognosis.

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