Lung Cancer (2007) **55**, 343—348

available at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/lungcan

Being overweight influences the development of hepatic dysfunction in Japanese patients with non-small-cell lung cancer undergoing cytotoxic chemotherapy

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Received 5 April 2006; received in revised form 23 August 2006; accepted 23 October 2006

KEYWORDS
Lung cancer;
Chemotherapy;
Hepatic dysfunction;
Risk factor;
Overweight

Summary
Purpose: The aim of this study was to identify risk factors for hepatic dysfunction during cytotoxic chemotherapy in Japanese patients with non-small-cell lung cancer (NSCLC).
Patients and methods: We retrospectively reviewed the medical records of patients with NSCLC who received cytotoxic chemotherapy at Okayama University Hospital between January 2003 and March 2006. ''Overweight'' was defined as a body mass index (BMI) of 25 or more, according to the World Health Organization (WHO) criteria. We investigated the incidence and pattern of hepatic dysfunction during chemotherapy and evaluated the possible associations between hepatic dysfunction and several clinical factors, including BMI.
Results: Of the 155 Japanese patients enrolled in this study, 19 (12%) were overweight. Grade 2 or worse hepatic dysfunction was observed in 5 of the 19 overweight patients (26%) but in only 13 of the 136 non-overweight patients (10%). A multivariate analysis demonstrated that a higher BMI significantly increased the risk of grade 2 or worse hepatic dysfunction after the initiation of cytotoxic chemotherapy (odds ratio = 4.04, 95% confidence intervals: 1.13—14.5, $p = 0.032$).
Conclusion: Our data suggest that being overweight can influence the development of hepatic dysfunction in Japanese patients receiving cytotoxic chemotherapy for the treatment of NSCLC, although further investigation is required.

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doi:10.1016/j.lungcan.2006.10.014

1. Introduction

Chemotherapy is the mainstay of treatment strategies for advanced non-small-cell lung cancer (NSCLC) [1]. However, many chemotherapeutic agents have narrow therapeutic windows, providing modest efficacy [2] while possibly inducing various toxicities [3]. One of the causes of individual differences in toxicity profiles is thought to be the large interpatient pharmacokinetic variability of chemotherapeutic agents [4]. Additionally, several studies have reported that elevated body mass index (BMI) can influence drug pharmacokinetics [5—8]. Thus, patients who are overweight may have an altered toxicity profile when treated with cytotoxic chemotherapy.

Hepatic dysfunction is a well-known adverse effect of cancer chemotherapy. Chemotherapeutic agents can induce various degrees of hepatic dysfunction, although the majority of effects are usually mild to moderate. However, some cases experience severe hepatic dysfunction, possibly leading to treatment interruption [9—11]. Thus, the prediction of unfavorable adverse event prior to drug administration would be extremely useful. To the best of our knowledge, the risk factors for hepatic dysfunction after the administration of chemotherapeutic agents have not been fully evaluated. In this study, we investigated the frequency and severity of hepatic dysfunction during chemotherapy and evaluated whether being overweight influenced the incidence of this event in patients receiving cytotoxic chemotherapy for the treatment of NSCLC.

2. Patients and methods

2.1. Patients

We retrospectively reviewed the medical records of Japanese patients with NSCLC who were admitted to Okayama University Hospital between January 2003 and March 2006. All patients with pathologically confirmed NSCLC who received systemic cytotoxic chemotherapy as a first-line treatment with or without thoracic radiation therapy were enrolled. Chemotherapeutic agents were dosed based on body surface area. Potential factors linked to hepatic dysfunction during chemotherapy, such as pretreatment liver function tests, chronic alcohol consumption, the presence of hepatitis B surface antigen and hepatitis C antibody, and body height and weight were reviewed for each patient.

2.2. Definition of ''overweight''

Overweight (BMI $\geq$ 25.0) was defined according to the criteria of the World Health Organization (WHO) [12]. BMI was calculated as body weight in kilograms divided by the square of body height in meters.

2.3. Assessment of hepatic dysfunction after administration of chemotherapeutic agents

The following biochemical parameters were evaluated in liver function tests: aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total bilirubin (T-Bil). These parameters were assessed before and at least biweekly after the initiation of chemotherapy. If an abnormality was detected, the parameter was usually monitored at least once a week until the abnormality disappeared. Hepatic dysfunction was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.

2.4. Statistical analysis

Statistical analyses were performed using the StatView® 5.0 program (BrainPower Inc., Calabasas, CA, USA). The associ-

Table 1 Demographics of the 155 patients with NSCLC

Age (median [range])	65 (32—85)
Gender (male/female)	109 (70%)/46 (30%)
Performance status (0—1/2—4)	141 (91%)/14 (9%)
Histology (Ad/Sq/others)	94 (61%)/46 (30%)/15 (9%)
Stage (IIB/IIIA/IIIB/IV/rec)	6 (4%)/20 (13%)/55 (35%)/51 (33%)/23 (15%)
Smoking history (yes/no)	116 (75%)/39 (25%)
Positive HBs antigen or HCV antibody (yes/no)	16 (10%)/139 (90%)
Liver metastasis (yes/no)	12 (8%)/143 (92%)
Body mass index (median [range])	22.0 (12.7—28.5)
Body mass index ($\geq$25/<25)	19 (12%)/136 (88%)
Hepatic dysfunction before chemotherapy (yes/no)	28 (18%)/127 (82%)
Chemotherapy regimen used	
Cisplatin + docetaxel	51 (33%)
Carboplatin + paclitaxel	35 (23%)
Carboplatin + gemcitabine	13 (8%)
Cisplatin + docetaxel + irinotecan	13 (8%)
Cisplatin + mitomycin + vindesine	11 (7%)
Irinotecan + amrubicin	6 (4%)
Vinorelbine	5 (3%)
Others	21 (14%)

Abbreviations: Ad = adenocarcinoma, Sq = squamous cell carcinoma, rec = postoperative recurrence, HBs = hepatitis B virus surface, HCV = hepatitis C virus.