Available online at www.sciencedirect.com

ScienceDirect

EJSO 41 (2015) 667–673

EJSO the Journal of Cancer Surgery

www.ejso.com

Avoiding perioperative dexamethasone may improve the outcome of patients with rectal cancer

H.C. Yu [a], Y.X. Luo [a,b], H. Peng [a], L. Kang [a], M.J. Huang [a], J.P. Wang [a,b,*]

[a] Department of Colorectal and Anal Surgery, Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, 510655, China

[b] Gastrointestinal Institute, Sixth Affiliated Hospital, Sun Yat-sen University, Guangzhou, Guangdong, 510655, China

Accepted 29 January 2015

Available online 19 February 2015

Abstract

Background: Perioperative administration of dexamethasone may augment recurrence and mortality after tumor resection possibly by immunosuppression, which, unfortunately, has never been noted. We therefore carried out a retrospective study in rectal cancer to validate the hypothesis.

Methods: Five hundreds and fifteen patients with stage I to III rectal cancers who underwent a curative resection from June 2007 and June 2011 were enrolled in the current study. Patients who had been given intravenous (IV) dexamethasone (4–10 mg) postoperatively and/or intraoperatively were assigned to dexamethasone group. The outcome of dexamethasone group and non-dexamethasone group were compared. The primary outcome was disease-free survival (DFS) and overall survival (OS).

Results: dexamethasone group had significant lower three-year DFS (62.3% vs 71.8%, P = 0.026) and OS (74.1% vs 82.9%, P = 0.031) rate in comparison to non-dexamethasone group, the hazard ratios (HRs) of which were 1.59 (95% CI 1.05–2.39, P = 0.028) and 1.77 (95% CI 1.05–3.01, P = 0.034), respectively. Multivariate analysis revealed that administration of systemic dexamethasone were independently associated with DFS [adjusted HR 1.60 (95% CI 1.03–2.49, p = 0.039)], but for OS, dexamethasone didn't remain significant in this model. In the analyses of a subgroup of 428 patients (55/428 in dexamethasone group) without perioperative blood transfusion, dexamethasone had independently impact on both DFS and OS.

Conclusion: Patients not given dexamethasone had better three-year survival outcomes compared with patients given dexamethasone perioperatively. Our results indicate that rectal cancer patients treated with curative surgery may get survival benefit from avoiding low-dose perioperative dexamethasone.

Keywords: Rectal cancer; Dexamethasone; Survival; Immunosuppression

Introduction

It has been well established that major operations may augment release of cancer cells into circulation[1] and introduce immunosuppression that lasts for several days.[2] This process partially contributes to clinical recurrence and metastasis, but immune defenses are certainly a critical protection.[3] Several studies showed that perioperative immunosuppression increases the risk of recurrence in cancer patients having surgery.[4–6]

Dexamethasone, similar to other corticosteroids, induces generalized immunosuppression.[7] Perioperative administration of dexamethasone may therefore have a deleterious effect on the survival and recurrence after tumor resection, possibly because of immunosuppression. This possibility is supported by studies in animals in which tumor growth was enhanced after dexamethasone given.[8] Unfortunately, the

* Corresponding author. Department of Colorectal and Anal Surgery, Sixth Affiliated Hospital, Sun Yat-sen University, 26 Yuancun Erheng Road, Guangzhou, Guangdong, 510655, China. Tel.: +86 20 38254955; fax: +86 20 38254094.

E-mail addresses: yuhuichuan819@gmail.com (H.C. Yu), luoyx25@mail.sysu.edu.cn (Y.X. Luo), wjp@mail.sysu.edu.cn, jpwanggz@gmail.com (J.P. Wang).

http://dx.doi.org/10.1016/j.ejso.2015.01.034

0748-7983/

prognosis after perioperative administration of systemic dexamethasone has never been noted in patients with cancer.

As numerous patients with rectal cancer receive GCs for antiallergic intervention and prevention of pain, nausea and vomiting during their perioperative treatment,[9–11] the effect of this clinical intervention on cancer outcomes represents an important clinical issue. We therefore conducted a retrospective study to define the association between perioperatively administration of systemic dexamethasone and oncological outcomes in rectal cancer treated with radical surgery.

Methods

The study design and protocol were approved by our institutional review board. Stage I to III rectal cancer patients who underwent a curative resection from June 2007 and June 2011 were identified using a database maintained by Sixth Affiliated Hospital of Sun Yat-Sen University. Rectal cancer was defined as histologically proven adenocarcinoma within 15 cm from the anal verge and was staged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging system. Exclusion criteria were as follows: patients who were on immunosuppressive therapy including recent steroid exposure, or with chronic inflammatory disease including inflammatory bowel disease (IBD); those diagnosed as familial adenomatous polyposis (FAP) and those with multiple primary cancers. Moreover, patients without comprehensive prescription records during perioperative treatment were excluded. Inpatient medical records and anesthesia notes were evaluated, and patients who had been given intravenous (IV) dexamethasone (4–10 mg) postoperatively and/or intraoperatively were assigned to dexamethasone group.

The following data were extracted from patients' medical records: demographic characteristics (age, height, and weight), tumor location, tumor staging, tumor's histological features, presence or absence of blood transfusion, preoperative serum carcinoembryonic antigen (CEA) level, treatment regimen and time to recurrence and survival. Above all, dose, timing and frequency of IV dexamethasone given in the perioperative treatment were recorded. These data were compared between patients who were and were not given perioperative systemic dexamethasone. Dexamethasone was commonly administered to prevent or treat postoperative nausea and vomiting and allergic reaction to drugs and blood transfusion. Since no guidelines exist on how to deal with postoperative nausea and vomiting and there are several alternative approaches, such as promethazine, to treat allergic reaction to blood transfusion, provider preference was the driving force for administration of dexamethasone.

Patients were followed up every three months for the first three years after surgery, every six months for the next two years, and yearly thereafter. Each visit included a medical history, a physical examination, including a rectal examination, and measurement of the serum CEA concentration. Routine radiological examinations consisting of chest radiography, abdominopelvic computed tomography or ultrasonography, whole-body bone scintigraphy, and colonoscopy or double-contrast barium enema were performed six months after surgery and annually thereafter. The follow-up period for the study ended July 2014 with the interval of follow-up varying from three to seven years. The primary outcome was disease-free survival (DFS) and overall survival (OS). Cancer recurrence was detected by CEA $>$ 5 ng/mL and/or a sequential computerized tomography scan with evidence of the disease followed by histopathological confirmation. DFS was defined as the time from the surgery until recurrence or death from any cause, and OS was defined as the time from the surgery to death.

The intergroup comparisons of clinicopathologic variables were performed using the analysis of variance and Kruskal–Wallis tests for continuous variables (depending on the distribution of the continuous variables), and the chi-square and two-tailed Fisher's exact tests for discrete variables. The OS and DFS rate were estimated and compared according to the Kaplan–Meier method and log-rank test, respectively. A univariate screen of potential risk factors of mortality using the Cox proportional hazard model for each variable extracted from medical records was performed. Multivariate analyses using Cox's proportional hazard model were used to identify the independent risk factors that influenced long-term survival. All tests were 2-sided, and p value $<$ 0.05 was considered statistically significant. Data analyses were performed using SPSS version 19.0 for Windows (SPSS, Inc., Chicago, IL).

The study was approved by the Medicine Ethics Committee of the Hospital in Sun Yat-sen University. There was no harm to patients, given that the data were collected retrospectively from database and medical records. All the necessary precautions were taken to secure the privacy of the human subjects in our database, allowing the medical records and databases to be used only by the investigators.

Results

Baseline characteristics

A total of 515 patients matched the inclusion and exclusion criteria and were included in this study (Fig. 1). There were 297 male and 218 female patients, with the median age of 59 years (rang, 21–89 years). The AJCC staging among the patients was distributed as 26%, 32% and 42% for stages I, II and III, respectively. There were 75 patients in dexamethasone group, among which 50 (67%) patients were given intraoperatively, 25 (33%) patients were given postoperatively for once or twice and no patient given dexamethasone preoperatively was identified. Forty-eight patients were given 4–5 mg, and 27 patients were given 8–10 mg. Demographic, morphometric, therapeutic and tumor characteristics were not statistically different in patients given and not given dexamethasone, except for perioperative blood transfusion that had significantly higher