RESEARCH ARTICLE

Evidence Based Analysis of Cisplatin for Treating Patients with Cutaneous Squamous Cell Carcinoma

Xiao-Hong Shao[1], Yun-Sheng Xu[1], Xue-Qi Zhang[1], Wen-Feng Li[2]*

Abstract

Background: This analysis was conducted to evaluate the efficacy and safety of cisplatin based chemotherapy for treating patients with cutaneous squamous cell carcinoma. Methods: Clinical studies evaluating the efficacy and safety of cisplatin based regimens on response and safety for patients with cutaneous squamous cell carcinoma were identified using a predefined search strategy. Pooled response rates (RR) of treatment were calculated. Results: In cisplatin based regimens, 4 clinical studies which including 50 patients with advanced cutaneous squamous cell carcinoma were considered eligible for inclusion. Regimens included cisplatin, doxorubicin, or vindesine. Pooled analysis suggested that, in all patients, the pooled RR was 60% (30/50) in cisplatin based regimens. Nausea and vomiting were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred with the cisplatin based treatments. Conclusion: Evidence based analysis suggests that cisplatin based regimens are associated with a good response rate and acceptable toxicity for treating patients with cutaneous squamous cell carcinoma.

Keywords: Cutaneous SCC - cisplatin-based therapy - toxicity - response rate

Asian Pac J Cancer Prev, **15 (22)**, 9813-9815

Introduction

Skin cancer contains melanoma, basal cell cancer and cutaneous squamous cell carcinoma (CSCC) (Veness et al., 2005). Lifetime risk for SCC is estimated to be 7%-11%, and demonstrates an increasing trend in these 30 years (Miller et al., 1994). CSCC is generally more aggressive, and potentially life threatening, than BCC. Most patients with CSCC who are not cured by local therapies require systematic treatment.

Investigation on systemic therapy is relatively limited. A number of systemic therapies are used to treat patients with advanced CSCC, including cytotoxic chemotherapeutic (cisplatin, 5-fluorouracil [5-FU], bleomycin, and doxorubicin), 13-cis-retinoic acid (13cRA), immunotherapy (interferon _2a [IFN-_], etc), and molecularly targeted agents (gefitinib, cetuximab, and erlotinib). Sadek et al. (1990) reported on 14 patients (13 evaluable) from a prospective observational study for patients with advanced CSCC treated with cisplatin, 5-FU, and bleomycin for 1-4 months. Two case series reported patients achieving a CR with the combination of cisplatin and 5-FU (Khansur et al., 1991; Fujisawa et al., 2006). Khansur et al. (1991) reported on seven patients with primary CSCC and locoregional progression treated with cisplatin and 5-FU. A CR was achieved in three of seven patients and a PR was achieved in three of seven patients. The median duration of CR was 1 year. Two of the three patients with a CR were disease free at a 13-month and 24-month follow up. Fujisawa et al. (2006) reported on two patients achieving a CR after one or two cycles of cisplatin and 5-FU. In one of the patients, therapy was discontinued after achieving a surgically confirmed CR. d in four of 13 patients with a complete response (CR) and seven of 13 with a partial response (PR) (Miller et al., 1981). Guthrie et al. (1985) treated three SCC patients with cisplatin and doxorubicin. One patient had a CR for 17 months, one had a PR for 3 months, and one had stable disease (SD). The authors suggested that the combination of cisplatin and doxorubicin had activity in cutaneous SCC. However, no large clinical trial was published to demonstrate the efficacy of cisplatin in CSCC. On this background, we report a pooled analysis on cisplatin in treating patients with refractory or relapsed CSCC.

Materials and Methods

Search strategy

We searched PUBMED, by using the following search term: (cisplatin) and (cutaneous squamous cell carcinoma). All clinical studies evaluating the impact of cisplatin on the response or survival and side effects for cutaneous squamous cell carcinoma published in English prior to November 1st, of 2014 were identified. If samples

*[1]Department of Dermatology, [2]Department of Radiotherapy, The First Affiliated Hospital of Wenzhou Medical University, Zhejiang Wenzhou, China *For correspondence: ltby_qgqs@sina.com*

of two studies overlap, only the latest one was included. Additional articles were obtained from references within the articles identified by the electronic search. We did not consider meeting abstracts or unpublished reports.

Inclusion and exclusion criteria

We reviewed abstracts of all citations and retrieved studies. The following criteria were used to include published studies: (1) clinical studies, combined with paclitaxel or pirarubicin; (2) The study was performed in accordance with the Helsinki Declaration (1964, amended in 1975 and 1983) of the World Medical Association. Eligibility criteria included histologically or cytologically verified metastatic and/or locally advanced cutaneous squamous cell carcinoma, the presence of at least one bidimensionally measurable lesion, a performance status (WHO) 2, age< 18 years. Studies were excluded if one of the following existed: (1) duplicate data; (2) no sufficient data were reported.

Data collection and analysis

Selection of trials and data extraction: The titles and abstracts of publications identified according to the above search strategy were assessed independently for inclusion by two authors; the full text was selected for further assessment if the abstract suggests relevance. Disagreement was resolved by discussion. Data was extracted by independent authors. The following recorded data were extracted: author, publication data, and country of the first or corresponding author, the number of patients.

Results

There were 65 papers relevant to the search words by the end of November 1st, of 2014. Via steps of screening the title and reading the abstract, 4 studies were identified (Ikegawa et al., 1989; Guthrie et al., 1990; Goldberg et al., 1994; Nakamura et al., 2013) when cisplatin was used in combination of chemotherapy. These studies had been carried out in Japan, Israel, and the United States. The following outcomes were presented in at least all studies and extracted for combined analysis: response rate, including the rate of complete or partial response (CR or PR) and toxicities. When cisplatin was used in combined chemotherapy with cyclophosphamide, and/or doxorubicin, 4 studies included in this study are presented and the short-term outcomes suggested that the response rate of Nakamura et al. was 25%, of Ikegawa et al. was 50%, of Guthrie et al. was 67.9%, and of Goldberg et al. was 75%. Totally, 50 patients were enrolled and 30 patients achieved CR or PR, the pooled response rate thus was 30/50 (60%). Observation on toxicities: Nausea and vomiting were the main side effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in these cisplatin based treatment.

Discussion

Skin cancer is an important research topic in China (Deng et al., 2013; Hao et al., 2013; Wang et al., 2013; Wu et al., 2013). CSCC with distant metastasis, while rare, is more common than metastatic basal cell cancer. A 10-year cohort study involving 985 patients with SCC found a 3.7% risk of metastasis and 2.1% risk of disease-specific death. Patients with metastatic CSCC should receive appropriate therapy although participation in a clinical trial is encouraged. Possible agents for patients in this setting include cisplatin monotherapy, cisplatin plus 5-FU, or epidermal growth factor receptor (EGFR) inhibitors, eg., cetuximab. At present, few evidence is available regarding systemic therapy for this condition, and no prospective phase III studies were available (Cranmer et al., 2010).

Cisplatin as a single agent or combined with 5-FU is a widely used regimen in clinical. A phase II study with biochemotherapy and interferon alfa, cis-retinoic acid, as well as cisplatin, were assessed for response in 35 patients, and among them, 11 patients had distant metastases (Shin 2002). One of these 11 patients experienced complete response, and among 12 patients with only regional lymph node metastases, 2 had partial and 1 had complete response (Shin, 2002). Nakamura et al retrospectively examined the response rate of combination platinum and anthracycline chemotherapy for metastatic CSCC. They recruited 8 patients, and all these 8 patients received combination chemotherapy: cisplatin (60-90 mg/m^2/day, day 1) and adriamycin (20-40 mg/m^2/day, day 1 or 2) was administered in 5 patients; cisplatin (10-15 mg/m^2/day, days 1-5) and epirubicin (10-15 mg/m^2/day, days 1-5) was administered in 2 patients; and carboplatin (200-400 mg/m^2/day, day 1) and adriamycin (20-40 mg/m^2/day, day 1 or 2) was administered in one patient. They found complete response in 2 patients (cisplatin + adriamycin for lung metastasis, cisplatin + epirubicin for lymph node metastasis), partial response in 1 (cisplatin + adriamycin for lymph node metastasis), stable disease in 2, and progressive disease in 3. A durable response was observed in 2 patients showing complete responses (Nakamura et al., 2013). Goldberg et al. also treated 8 patients (4 men and 4 women; mean age 70, range 49-86) with advanced CSCC with cisplatin-based chemotherapy. The disease was local in 4, local with regional lymph node involvement in 2, involved regional lymph nodes in 1 and was local with distant metastases in 1 patient. All were treated with a combination of cisplatin and 5-Fu, 2 patients were treated in addition with a combination of cyclophosphamide, doxorubicin, and cisplatin. Complete pathological response was seen in 2/8 and partial response in 4/8 with an overall response rate of 75%. Tumor progression was observed in 2 patients. Survival of patients who responded was from 3-47 months (mean 12). Two patients who did not respond to chemotherapy died within 1 and 3 months after treatment. Significant side-effects in 6 included myelotoxicity and transient renal toxicity (Goldberg et al., 1994). They concluded that cisplatin based chemotherapy is effective in treating patients with advanced CSCC and may have curative potential when combined with local therapy (Goldberg et al., 1994).

Our results suggested that when cisplatin was used in combination with chemotherapy. Totally, 50 patients could be enrolled and 30 patients achieved CR or PR, the pooled response rate thus was 30/50 (60%). Observation on toxicities: Nausea and vomitting were the main side

effects. No grade III or IV renal or liver toxicity were observed. No treatment related death occurred in these cisplatin based treatment.

Thus, in conclusion, we suggested that cisplatin based regimens are associated with good response rate and accepted toxicities for treating patients with CSCC.

References

Alam M, Ratner D (2001). Cutaneous squamous-cell carcinoma. *N Engl J Med*, **344**, 975-83.

Bleomycin in advanced squamous cell carcinoma: A random controlled trial, et al (1976). Report of Medical Research Council Working Party on Bleomycin. *Br Med J*, **1**, 188-90.

Clayman GL, Lee JJ, Holsinger FC, et al (2005). Mortality risk from squamous cell skin cancer. *J Clin Oncol*, **23**, 759-65.

Cranmer LD, Engelhardt C, Morgan SS, et al (2010). Treatment of unresectable and metastatic cutaneous squamous cell carcinoma. *Oncologist*, **15** 1320-8.

Deng QQ, Huang XE, Ye LH, et al (2013). Phase II trial of Loubo® (Lobaplatin) and pemetrexed for patients with metastatic breast cancer not responding to anthracycline or taxanes. *Asian Pac J Cancer Prev*, **14**, 413-7.

Fujisawa Y, Umebayashi Y, Ichikawa E, et al (2006). Chemoradiation using lowdose cisplatin and 5-fluorouracil in locally advanced squamous cell carcinoma of the skin: A report of two cases. *J Am Acad Dermatol,* **55**, S81-5.

Goldberg H, Tsalik M, Bernstein Z, et al (1994). Cisplatin-based chemotherapy for advanced basal and squamous cell carcinomas. *Harefuah*, **127**, 217-21.

Guthrie TH Jr, McElveen LJ, Porubsky ES, et al (1985). Cisplatin and doxorubicin. An effective chemotherapy combination in the treatment of advanced basal cell and squamous carcinoma of the skin. *Cancer*, **55**, 1629-32.

Guthrie TH Jr, Porubsky ES, Luxenberg MN, et al (1990). Cisplatin-based chemotherapy in advanced basal and squamous cell carcinomas of the skin: Results in 28 patients including 13 patients receiving multimodality therapy. *J Clin Oncol*, **8**, 342-6.

Han A, Ratner D (2007). What is the role of adjuvant radiotherapy in the treatment of cutaneous squamous cell carcinoma with perineural invasion? *Cancer*, **109**, 1053-59.

Hao ZF, Ao JH, Zhang J, et al (2013). ATF3 activates Stat3 phosphorylation through inhibition of p53 expression in skin cancer cells. *Asian Pac J Cancer Prev,* **14**, 7439-44.

Ikegawa S, Saida T, Obayashi H, et al (2013). Cisplatin combination chemotherapy in squamous cell carcinoma and adenoid cystic carcinoma of the skin. *J Dermatol*, **16**, 227-30.

Jambusaria-PahlajaniA, Miller CJ, QuonH, et al (2009). Surgical monotherapy versus surgery plus adjuvant radiotherapy in high-risk cutaneous squamous cell carcinoma: A systematic review of outcomes. *Dermatol Surg*, **35**, 574-85.

Joseph MG, Zulueta WP, Kennedy PJ, et al (1992). Squamous cell carcinoma of the skin of the trunk and limbs: The incidence of metastases and their outcome. *Aust NZ J Surg*, 62, 697-01.

Khansur T, Kennedy A (1991). Cisplatin and 5-fluorouracil for advanced locoregional and metastatic squamous cell carcinoma of the skin. *Cancer*, **67**, 2030-32.

Lippman SM, Parkinson DR, Itri LM et al (1992). 13-cis-retinoic acid and interferon alpha-2a: effective combination therapy for advanced squamous cell carcinoma of the skin. *J Natl Cancer Inst*, **84**, 235-41.

Merimsky O, Neudorfer M, Spitzer E, et al (1992). Salvage cisplatin and adriamycin for advanced or recurrent basal or squamous cell carcinoma of the face. *Anticancer Drugs*, 3, 481- 4.

Miller AB, Hoogstraten B, Staquet M, et al (1981). Reporting results of cancer treatment. *Cancer*, **47**, 207-14.

Miller DL, Weinstock MA (1994). Nonmelanoma skin cancer in the United States: Incidence. *J Am Acad Dermatol*, **30**, 774-8.

Minton TJ (2008). Contemporary Mohs surgery applications. *Curr Opin Otolaryngol Head Neck Surg*, **16**, 376-80.

Mohs F (1978). Chemosurgery: Microscopically Controlled Surgery for Skin Cancer. Springfield, IL: Charles C. *Thomas*, 153-64.

Nakamura K, Okuyama R, Saida T, et al (2013). Platinum and anthracycline therapy for advanced cutaneous squamous cell carcinoma. *Int J Clin Oncol,* **18**, 506-9.

Sadek H, Azli N, Wendling JL, et al (1990). Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. *Cancer*, **66**, 1692-6.

Shin DM, Glisson BS, Khuri FR, et al (2002). Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer. *J Clin Oncol*, **20**, 364-70.

Veness MJ, Morgan GJ, Palme CE, et al (2005). Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: Combined treatment should be considered best practice. *Laryngoscope*, **115**, 870-5.

Wang SQ, Li J, Tang WR, et al (2013). Note of clarification of data in the meta-analysis of XPC 939A>C and 499C>T polymorphisms in skin cancer. *Asian Pac J Cancer Prev*, **14**, 2687-8.

Wu Q, Zhao YB, Sun ZH, et al (2013). Clinical application of endoscopic inguinal lymph node resection after lipolysis and liposuction for vulvar cancer. *Asian Pac J Cancer Prev,* **14**, 7121-6.