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Phase II Study of Paclitaxel Plus Carboplatin in Recurrent and/or Metastatic Cervical Carcinoma

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ABSTRACT

Objective To assess the therapeutic efficacy and toxicities of paclitaxel and carboplatin in treatment of recurrent and/or metastatic cervical carcinoma.

Design Phase II trial.

Setting Multicenters.

Subjects and Method Between December 1997 and April 1999, 32 patients with recurrent and/or metastatic cervical cancer were treated with paclitaxel 175 mg/m^2 and carboplatin at AUC 5 every 3 weeks for 6 cycles.

Main outcome Response rate, drug toxicity, time to progression and survival.

Results Paclitaxel 175 mg./m^2 plus carboplatin AUC 5 achieved overall response rate of 62.6% with 31.3% complete response and 31.3% partial response. The median progression free survival was 26.86 weeks and median survival was 58.57 weeks. The major toxicities were hematologic toxicity with 13.8% of grade 3 and 4 leucopenia, 48.3% grade 3 anemia and 3.5% of grade 3 thrombocytopenia. Overall, the toxicities were moderate and manageable with no serious adverse effect.

Conclusion Paclitaxel and carboplatin achieved promising response in recurrent and metastatic cervical carcinona with modest toxicity. Phase III randomized trial on this combination should be performed to confirm the efficacy of this regimen.

Key words: paclitaxel plus paraplatin, cervical cancer, cervical carcinoma

Chemotherapy plays an important role in management of several groups of the patients including those with advanced (stage III and IV) tumors.[1,2] Generally lower response rates are seen in the patients who have received prior chemotherapy or recurred in the previously irradiated sites. The duration of response ranged from 4 to 6 months and survival ranged from 6 to 9 months. Among the chemotherapeutic agents used for the treatment of cervical cancer, platinum agent has demonstrated the most consistent activity as single agent. Cisplatin 100 mg/m^2 has been shown to have a higher response rate (31%) than 50 mg/m^2 (21%), however the higher dose was associated with more toxicity and no significant difference in overall survival.[3] A phase II study by the Southwest Oncology Group[4-6] comparing the carboplatin 400 mg/m^2 every 4 weeks with cisplatin and 5-FU, the activity of carboplatin was comparable with that of cisplatin, but carboplatin had better toxicity profile. Paclitaxel has been also shown to have some activity, producing reponse rate of 28% in squamous cell carcinoma of the uterine cervix.[7] Both platinum

and paclitaxel have promising activities in the treatment of cervical cancer and this combination is well established in many types of solid carcinoma. In GOG phase II study,[8,9] paclitaxel and cisplatin were used as first line therapy in recurrent or advanced squamous cell carcinama of the cervix. This regimen appeared highly active with an overall response rate of 46.3% and a complete response of 12.2%. This study was conducted to evaluate the response rate and toxicities of paclitaxel plus carboplatin in the treatment of recurrent/metastatic cervical cancer.

Patients and Methods

Patient eligibility criteria

Patients were required to have the histologically or cytologically confirmed diagnosis of squamous cell carcinoma of the cervix. The recurrent and/or metastatic disease were measured by clinical examination or radiolography. Eligible patients had age < 65 years, ECOG performance status 0-2, adequate bone marrow (leukocyte count greater than 3,000/cu.mm, a platelet count greater than 100,000/cu.mm, hemoglobin level greater than 10 gm/100 ml), adequate liver function (SGOT level less than 2x normal), normal renal function (serum creatinine level less than 1.5 mg/100ml), no serious medical or psychiatric illness, and signed the consent form.

Treatment plan and dose modification

Patients received paclitaxel at a dose of 175 mg/m^2 by intravenous infusion over 3 hr. Premedication consisted of dexamethasone 20 mg intravenously 12 and 6 hours before paclitaxel, cimetidine 400 mg IV or PO before treatment half and hour, granisetron 3 mg. PO 30-60 minutes before treatment. The dose of carboplatin was calculated following Calvert formula, with AUC 5 and was given in 5% dextrose in water 300 ml. infused intravenously for 2 hours. Treatment was repeated every 3 weeks for 6 cycles, except in patients who showed disease progression after 2 cycles would be treated by second line drug. Patients who achieved CR were added 2 more cycles. For subsequent courses of treatment, unresolved or repeated grade III and IV toxicity or intolerable adverse effect were the conditions for withdrawal from this study. The toxicity was recorded according to ECOG classification.

Response assessment and further treatment

Patients were evaluated by physical and gynecological examination every 2 cycles of treatment. Chest radiography and abdomino-pelvic ultrasonogram were used as necessary. The clinical response and toxicities grading were assessed using the standard criteria of WHO.[10] A complete response was defined as no appearance of all disease on radiographic finding and physical examination for 2 occasions at least 3 weeks apart. Partial response was defined as a greater than 50% reduction in the sum of the products of the perpendicular diameters of all measurable lesions documented on 2 occasions at least 3 weeks apart. Stable disease was defined as smaller than 25% or no detectable change in tumor volume of all the lesions. Progressive disease was describes as a greater than 25% increase in the sum of the products of the perpendicular diameters of all measurable lesions or appearance of new lesion.

Statistical analysis

All patients enrolled were monitored for overall response, duration of response, time to progression, overall survival and treatment-related toxicity.

Event-free survival and overall survival were estimated using the method of Kaplan and Meier and groups were compared by log-rank test.

Table 1. Patient characteristics and treatment

Patient characteristic	
Eligible for Study	32
Age - range (yrs)	32-62
- median (yrs)	45.5
ECOG performance	
0	21 (66%)
1	11(34%)
Histology	
Squamous cell	27 (84%)
Adenocarcinoma	4 (13%)
Unknown	1 (3%)
Previous treatment	
RT alone	13 (40.6%)
RT / chemo	13 (40.6%)
Surgery alone	1(3.1%)
RT/surgery/chemo	2 (6.2%)
No previous treatment	3(9.3%)
Metastatic sites	
SPC	6 (19%)
Lung	6 (19%)
Liver	2 (6%)
Para-aortic	4 (12%)
Bone	1 (3%)
SPC/lung	1 (3%)
SPC/bone	1 (3%)
SPC/para-aortic	1 (3%)
Bone/lung	2 (6%)
Bone/liver	1 (3%)

(RT = Radiation Therapy , SPC = Supraclavicular Node)

Table 2. Response of treatment

Response	n	%
Complete response (CR)	10	31.3%
Partial response (PR)	10	31.3%
Stable disease (SD)	2	6.3%
Progressive Disease	10	31.3%

Table 3. Response of treatment according to metastatic site

Response	n	%
Lung	5/6	83%
SPC	5/6	83%
Para-aortic	1/4	25%
Liver + bone	1/2	50%
SPC + bone	1/1	100%
Lung + bone	1/1	100%

Table 4. Toxic effects

Toxicities		percentage n = 32
1. Hematologic		
Grade 3	Anemia	48.3 %
Grade 3 /4	Leukopenia	13.8 %
Grade 3	Thrombocytopenia	3.5 %
2. Non-hematologic Grade 3 / 4		-

Results

From December 1997 to April 1999, the evaluable 32 patients from three centers entered this study. Patient characteristics and treatment are summarized in Table 1. All 32 were assessed for response, survival and toxicity.

The response of treatment is summarized in Table 2. The objective response rate was 62.6% with 10 complete (31.3%) and 10 partial response (31.3). Stable disease was observed in 2 patients (6.3%).

According to the metastatic sites, complete response was obtained in 4 of 6 lung (67%), 3 of 6 supraclavicular (SPC) node (50%) and 1 of 1 SPC/bone metastatic patients. The objective response of treatment according to metastatic site is summarized in Table 3. Overall response occurred in 5 of 6 lung (83%), 5 of 6 SPC (83%), 1 of 4 paraaortic (25%), 1 of 2 liver/bone (50%), 1 of 1 SPC/bone and 1 of 1 lung/ bone metastic patients.

The toxicity of this regimen was generally well tolerated. The major toxicity was hematologic toxicities as shown in Table 4.

Non-hematologic toxicities such as neuropathy, myalgia or arthralgia are generally mild with no grade 3 or 4 occurrence in this group of patients.

Discussion

From this study, the chemotherapy regimen, paclitaxel 175 mg/m^2 3 hour infusion with carboplatin AUC 5 every 3 weeks six cycles, has shown the promising efficacy with high tolerable toxicity. Severe hematologic toxicity was infrequent and manageable whereas non hematologic toxicity was unobserved and the efficacy and toxicities in this regimen can be comparable with the study of Rose et al.[8] The number of paclitaxel cycles should be considered and explored in further study. Due to less toxicity, paclitaxel and carboplatin may be continued to delay the onset of disease progression and lengthen the overall survival for this group of cancer patients. The further study on this regimen should be encouraged.

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References

1. Chao KC, Perez CA, Brady LW. Radiation Oncology Management Decisions: 2nd.Lippincott Williams & Wilkins 2002; 489-509.
2. Vincent TD, Samuel H, Steven A. Clinical Trails in Cancer. Cancer :Principles & Practice of Oncology 1997; 513-27.
3. Bonami P, Blessing JA, Stehman F, Disaia PJ, Walton L, Major FJ. Randomized trial of three cisplatin dose schedules in squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Clin Oncol 1985;3:1079-85.
4. Muggia FM, Muderspach L. Platinum compounds in cervical and endometrial cancers: focus on carboplatin. Semin Oncol 1994; 2(suppl2)5.
5. Go RS, Adjei AA. Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 1999;17:409-22.
6. Weiss GR, Green S, Hannigan EV, Boutselis JG, Surwit EA, Wallace DL, et al. A phase II trial of carboplatin for recurrent or metastatic squamous carcinoma of the uterine cervix: a Southwest Oncology Group study. Gynecol Oncol 1990;39:332-5.
7. Kudelka AP, Winn R, Edward CL, et al. Advanced squamous cell cancer of the cervix: An update of a multicenter phase II study of paclitaxel (Taxol) 250 mg/m2 administered over 3 hours every 21 days with G-CSF support. Proc Am Soc Clin Oncol 1997, Abstract 1327.
8. Rose PG, Blessing JA, Gershenson DM, McGehee R. Paclitaxel and cisplatin as first-line therapy in recurrent or advanced squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. J Cin Oncol 1999; 17: 2676-80.
9. Piver MS, Ghamande S, Eltabbakh GH. First line chemotherapy with paclitaxel and platinum for advanced and recurrent cancer of the cervix. A phase II study. Gynecol Oncol 1999; 75: 334-7.
10. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. Cancer 1981; 47: 207-14.