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Research Article

Carboplatin and Paclitaxel as an Initial Treatment in Patients with Stage IV A & IVb Cervical Cancer: A Report of 16 Cases and a Review of the Literature

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Abstract:

Objective: Ca Cervix in 2nd most common malignancy in India and worldwide. NACT is not standard treatment in Advanced Ca Cervix. In this study we try to see the response rate of P+C NACT and to see if patients are able to complete definitive RT in advanced CA Cervix pt. Stage IVA and IV B post NACT. Methods: Am bidirectional study to see the demographic profile and treatment response when patients receive P+C NACT. We reviewed the demographic data and treatment details of patients who has received NACT for advanced Ca Cervix from our prospectively maintained database from 2019 till 2022.

Results: Out of 386 number of registered pt. Of ca cervix , 156 number of patients were of advanced ca cervix malignancy registered in this time period 17number of pt. Received NACT with P+C , median age of these patients was 52.2(39-71yrs) 16% of patients who were planned for NACT received 3.number of cycles. Overall, the treatment of PC was well tolerated. The overall response rate was 75%.(2 complete response, 10 partial response). Although grade 3-4 hematologic toxicities were observed in 4 out of 16 patients (25%), 3 patients experienced grade 3-4 non-hematologic toxicities,2 neurotoxity ,1 nephrotoxicity. Out of 14 ,who completed NACT and underwent definitive CRT , 8 (57.14 %) achieved complete response

Conclusion: PC is having response and efficacy and well tolerated in patients FIGO stage IVa & IVb cervical cancer. This combination can be considered as an initial treatment regimen in locally advanced cervical cancer patient population.

Key Words: Cervical cancer, Neoadjuvant chemotherapy (NACT), Paclitaxel (P) and cisplatin (C)

Introduction

Patients according to the International Federation of Gynecology and Obstetrics (FIGO) stage IV A & IVB cervical cancer have a poor and bad prognosis.1,2 Systemic chemotherapy or concurrent chemoradiation and individualized radiotherapy have been proposed as initial treatments for these patients.3 Based on data obtained from phase III clinical trials, cisplatin-containing combination chemotherapy; i.e., cisplatin plus paclitaxel (TP), has become the standard treatment for recurrent or advanced cervical cancer. People who cant tolerate toxicity profile of ciplastin , there carboplation has been used as replacement with comparable results.4 Although the combination of carboplatin-paclitaxel (PC) was demonstrated to be equally effective as and less toxic than TP in ovarian cancer,5 information on the use of PC in patients with advanced cervical cancer is limited. We herein describe our experiences with 16 cases of stage IVa & IVb cervical cancer that were primarily treated with P+C.NACT will help to decrease tumor buden in stage IVA , will help to avoid complication like fistula formation due to local infiltration of disease in surrounding tissues, eg rectum and bladder , will decrease tumor volume so it can be easily encompassed in Rt portals on definitive treatment .

Materials and Methods

Required compulsary permission to proceed with consent of patients , along with data acquisition collection and analysis was obtained from the NTR University GSL Medical College and Hospital institutional review board.17 .number of patients with stage IA &IV B cervical cancer that were primarily treated with PC at the GSL Cancer Hospital under NTR University from 2019 to 2022 were identified and retrospectively reviewed. For all participant patients in study , clinical data on the following characteristics/ parameters were collected: initial stage, maximal tumor diameter, cell type, performance status, primary treatment, site of recurrent disease, disease free interval (DFI), chemotherapy regimen, response, and progression free survival (PFS). PFS was measured from the start of chemotherapy to the progression of disease. The maximal tumor diameter was measured three-dimensionally based on CT based images (RESIST 1.1). The longest diameter was considered valid as the maximal tumor diameter. PC was administered on a 3 weekly basis in all patients: Carboplatin at an area under the curve (AUC) of 5 given as a 1 hour infusion, and paclitaxel at 175 mg/m2 given as a 3 hours infusion every 21 days. The response to treatment was assessed according to the Response Evaluation Criteria in Solid Tumors after every three cycles of each regimen. A complete response (CR) was defined as the disappearance of all target and non-target lesions and no new lesions being documented after two assessments that were done after 3 cycles of PC and after completion of CRT. A partial response (PR) was defined as at least a 30% decrease in the sum of the longest dimension of the target lesions, which was also documented in two assessments that were at least 4 weeks apart. Progressive disease (PD) was defined as a 20% increase in the longest dimension of the sum of the target lesions or the development of new lesions. Stable disease (SD) implies that none of the above applies. Performance status (PS) was graded according to the Eastern Cooperative Oncology Group performance status criteria. Toxicity related to treatment was graded according to the NCI Common Terminology Criteria for Adverse Events, ver. 3.0.

Results

The study participant patient's characteristics and clinical data are summarized in Table A.

Age	Diagnosis	Stage	performance Status	Histology	Maximum Tumour Diameter	Site of Mets	Pelvic Side Wall Fixation	Courses Of Chemotherapy
57	ca cervix	IVA	2	Mod. Differntiated Sq. Cell Ca	4.2	nil	involved	3
45	ca cervix	IIIB	1	Squamous cell ca gr 2	5*5.3	ovarian	involved LPW	1
49	C cx	IVA	1	Suuamous	47*62*50	inguinal ln	involved B/L	3
43	Ca CX	iiic2	1	poorly differentiated squamous cell ca	4.6*4.3*5.4	paraoartic lap	involved B/L	3
60	Ca Cx	IIIC2	1	Squamous Cell Ca	4.3*5.1*4.2		rt side involved	3
50	Ca Cx	IVA	1	SquamousCell Ca	5.1*4.8*4.0	Bladder invasion	involved LT	3
45	CaCx	IVA	1	Squamous Cell Ca	5.4*4.9*4.6			1
55	CA Vault	IVA	1	adenocarcinoma	5.2*3.1*4.1	Non mets	B/L para involved	3
48	Ca Cx	IV B	1	SCC	3.3*4*4.8	Lt SCF LN	free	wkly P+C
48	Ca Cervix	IV A	1	SCC, HTN	3.5*2.2	Bladder Fat planes lost	B/L para	3
55	ca cervix	IIIB	1	scc,	5.2*4.8*5.4		Rt para involved LPW	3
70	CA CErvix	IBA	1	SCC	7.8*7.8*5.2	rectal wall	B/L para involved	3
59	CA Cervix	IVA	1	SCC	3.6*3.3*2.5	Bladder Infiltration	B/L para	3
57	CA Cervix	IV A	1	Scc	Large growth	Bladder Infiltration		3
39	Ca Cervix	IVA	1	SCC	6.4*4.6*4.8	Rt INGUINAL NODE	B/L para Lt. Pelivc Wall	3
60	Ca Cervix	IVA	1	SCC	7.2*8.5*7.6	Rectum	B/L to peliv wall involved	3

Response On Clinical Ex	Grade 3-4 Toxicity	RT portal eaily enpasses disease voume	Subsequent Treatment	Fistula formation	PFS in Months	Site Of Recurrence	Outcome
CR	Neuropathy Gr2	Yes	didnnt show up for ICBT 07-07-2021				
left treatment	Nephropathy creat 4.2						Left t/t 28/7/21
PR	Haematolgical	yes	on CRT	Nil			7/10/21 on CRT
progressive dis 1 monthlate as covid +, Supraclav LN. FNAC- sq cell ca	nil	yes	palliative gemcitabine + Cisplatin	Nil			26/8/21 on palliative cct
PR		yes	CRT copleted CR attained	Nil		Colon	1/18/2022
PR	neuropathy	yes	CRT copleted CR attained	NIL			3/24/2022
incomplete treatment							7/23/2021
PR. MRI size 2.5*2.5.3.5		yes	CRT completed PR	Nil			3/19/2021
PR at cervix. Necl lesion resolved		yes	CRT completed Progressive Disease	NIL		Cervical LN	7/5/2021
CR on USG		yes	CRT , CR	NIL			1/5/2021
PR		yes	CRT completed ,CR	NIL			3/7/2022
Progessive dis, paraoartic nodes , L5 vertebra involvement	hematological		Pallaitve RT 27.5	NIL			pt dischaege on request as not tollerating RT 3/7/2021
PR,	hematological	yes	CRT,CR	NIL			3/9/2022
PR		yes	CRT, CR	NIL			3/28/2022
PR	hematological	yes	CRT , CR	NIL			5/3/2022
PR		yes	CRT, CR	NIL			2/28/2022

The median age at the time of treatment was 52.5(39-70yr).93.75% (16)women had squamous cell carcinoma, and 6.25%had adenocarcinoma. All patients had stage IVA and IVb disease with metastasis to distant organs majority including the lungs, liver, peritoneal dissemination, para-aortic lymph node, or other distant lymph node. All patients received PC 3 cycles as an initial treatment. PC was administered on a three weekly basis and 3 cycles in all patients: Carboplatin at an AUC of 5 given as a 1-h infusion and paclitaxel at 175 mg/m2 given as a 3-h infusion every 21 days. Inj Peg GCSF was also Administered in patient on day two to avoid haematological toxicity and maintain good general condition of patient to complete planned treatment .The median courses of PC administered was 3, in 12.5%(2)number of patients we were not able to complete study treatment because of intolerability and left before completing NACT . As predicted, the administration of PC was generally well tolerated without any significant delays or dose reduction. Although grade 3-4 hematologic toxicities were observed in 4(25%) out of 16patients,No (0%) patients developed febrile neutropenia. 3 patients experienced grade 3-4 non-hematologic toxicities, 2 neuropathy (12.5%), 1nephropathy (6.25%). 2(12.5%)patients showed CR, 10(62.5%)showed PR, 0 showed SD, and 2(12.5%) demonstrated PD. The overall response rate was 75%. Patients who had achieved clinical CR to chemotherapy were further examined, and proven to be with no radiological evidence of disease in the primary site . 14 of patients who completed 3 NACT P+C underwent further received concurrent radiotherapy consisting of external beam radiotherapy and high dose rate-intracavitary brachytherapy with curative intent following treatment with PC. Out of 14 ,who completed NACT and underwent definitive CRT , 8 (57.14 %) achieved complete response which was only 2(12.5%) after NACT P+C .2(14.28) pt. showed progressive disease out of which 1 didnt received CRT and 1 pt.didnts showed up to receive ICRT after EBRT .At the time of writing of this study, 7out of 16 patients were alive and regular follow up, and rest 9 were lost to follow up .6 had not suffered recurrence after a median follow-up period of 7 months.

Discussion

Surgery and concurrent chemoradiotherapy (CCRT) have achieved significant success in the treatment of cervical cancer both in patients with early stage cervical cancer, and in those with locally advanced cervical cancer till IVA.Stage IVA and IVB are advanced diseases with almost having systemic spread component and poor prognosis.6 However, in patients with stage IVb disease, no standard treatment has been established. Although systemic chemotherapy and individualized radiotherapy have been proposed as initial treatments,2 the patients given these regimens showed a poor prognosis with a reported 5-year survival of less than 10%.7 Since stage IVA &IVB cervical cancer is a systemic disease, theoretically, chemotherapy is required for these patients. Based on previous phase III clinical trials, cisplatin-containing combination chemotherapy; i.e., cisplatin plus paclitaxel or topotecan, had become the standard treatment for recurrent or advanced cervical cancer.4,8 Subsequently, a Gynecologic Oncology Group (GOG) phase III clinical trial (protocol GOG 204) comparing the efficacy of four cisplatin-based combination chemotherapies including TP, cisplatin-topotecan, cisplatin-vinorelbine, and cisplatin-gemcitabine has been conducted. In this study, although not statistically significant, TP showed the most favorable clinical activity with regard to the response rate, progression free survival, and overall survival in patients with FIGO stage IVb, recurrent, and persistent cervical cancer.9 A

recent retrospective review of four randomized phase III GOG clinical trials suggested that advanced or recurrent cervical cancer patients who had been previously treated with radiosensitizing-cisplatin showed poorer response to platinum-based chemotherapy than those who had not.10 With the aim to investigate the effectiveness of non-platinum containing chemotherapy in the same population, GOG has recently initiated a phase III trial (protocol 240) comparing TP versus non-platinum doublet (paclitaxel- topotecan), with or without bevacizumab.11 Although the combination of PC was demonstrated to be equally effective as and less toxic than TP in ovarian cancer,5 information on the use of PC in cervical cancer is limited. Except for several case reports, to the best of our knowledge, only six retrospective studies on the value of PC in 3-48 recurrent or advanced cervical cancer patients have been reported.12-17 Since the vast majority of patients enrolled in these studies were treated for advanced atge IVA & IVB cancer, the effectiveness of PC against stage IV disease as an initial treatment is largely unknown before definitive treatment in form of surgery or concurrent chemo radiation . Of the six retrospective studies, the total number of patients treated for advanced stage IVA &stage IVb disease as an initial treatment was 9. Of these, detailed information regarding the treatment outcome was only available for 4 patients

(TABLE B)

Table 2. Paclitaxel-carboplatin as an initial treatment in patients with stage IVb cervical cancer

Article	Target disease	Dose of chemotherapy	Total no. of patients	Stage IVb patients	Response		
					No. of CR	No. of PR	Rate (%)
Piver et al.[15] (1999)	R or A	Paclitaxel: 135 m^2 Carboplatin: 300 mg/m^2 Every 4 wk	3	2	0	1	50
Tinker et al.[16] (2005)	R or A	Paclitaxel: 175 m^2 Carboplatin: AUC 5-6 Every 4 wk	25	2	0	1	50
Moore et al.[17] (2007)	R or A	NA	48	5	NA	NA	NA
Current study (2010)	A	Paclitaxel: 175 m^2 Carboplatin: AUC 5 Every 4 wk	7	7	2	3	71.4
Evaluable patients				11	2	5	63.6

CR: complete response, PR: partial response, R: recurrent cervical cancer, A: advanced-stage cervical cancer, AUC: area under the curve, NA: not available.

We have demonstrated that PC is effective in patients with stage IVA& IVb cervical cancer. Our overall response rate of75%. is very similar to previously reported response rates in medical literature.. As predicted, PC was well tolerated. Although grade 3-4 hematologic toxicities were observed in 4out of16 patients, no patients developed febrile neutropenia. This favorable toxicity profile of PC demonstrated in the current study may have been, at least in part, due to the treatment schedule employed in our institution: PC was administrated every 21 days as this dosing schedule had demonstrated significant clinical activity in patients with recurrent cervical cancer.12 However, on the basis of the concept of dose-density, we believe that we should try even try weekly administration of PC, which may result in better treatment outcome based on performance staus of patients. Although this study was retrospective and involved a relatively small number of patients, given the advantages of patient convenience and tolerance as well as the significant activity shown, we believe that PC is a reasonable treatment option for patients with stage IV A& IVb cervical cancer in NACT Setting . To address the clinical benefit of PC compared with TP in stage IVb, persistent, or recurrent cervical cancer, the Japan Clinical Oncology Group (JCOG) is currently conducting a randomized phase III trial of their JCOG 0505 protocol.18 In addition, since this combination chemotherapy demonstrated significant effectiveness as an initial treatment, PC may also hold promise in a CCRT or neoadjuvant chemotherapy setting in patients with cervical cancer leading to benefit in survival, but for that larger scale randomized studies are advocated in future. To establish a more effective and less toxic treatment strategy for patients with advanced cervical cancer, further studies are needed.

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