The Efficacy of Chemically-Stabilized Chlorite-Matrix (TCDO*) in the Management of Late Postradiation Cystitis†

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Abstract

Carcinoma of the uterine cervix is the most common cancer of women in Thailand. The most frequent complication after pelvic radiation for uterine cancer is radiation cystitis. The management of severe late postradiation cystis is far from satisfactory. The objective of this study was to evaluate the efficacy of chemically-stabilized chlorite-matrix (TCDO) in patients with severe radiation cystitis. This study was conducted at the Department of Obstetrics and Gynecology, Ramathibodi Hospital and the Department of Radiology, Siriraj Hospital between September 1997 and September 1998. Twenty patients with grade 3 radiation cystitis after radiotherapy were enrolled into this study. TCDO was administered at a dose of 0.5 ml/kg body weight per day on 5 consecutive days as intravenous infusion over 4 hours. The response rate after the first cycle was 80 per cent with 30 per cent of the patients showing complete response. The follow-up time (13 patients) ranging from 1-9 months revealed no recurrent bleeding. There were no side effects from TCDO therapy. The result suggests good efficacy of TCDO in the treatment of post-radiation cystitis.

Key word : Radiation Cystitis, TCDO

Carcinoma of the uterine of cervix is the most common cancer of women in Thailand with an estimated 5593 new cases in 1990(1). Most patients present with locally advanced disease (FIGO stage II - III) and radiotherapy is the standard treatment. The most frequent complications after pelvic irra-

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† The chemically-stabilized chlorite-matrix, in the literature referred to as tetrachlorodecaoxygen anion complex or TCDO, has been registered in Thailand under the name IMMUNOKINE®

diation are chronic inflammatory and necrotic processes in rectosigmoid, small bowel, urethra and bladder.

The scoring scheme[2] developed by the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC) is used to classify the severity of the complication (grading). Grade 1 and 2 complications are characterized as mild to moderate and treatment is non-aggressive or deferred. Grade 3 complications, the incidence of which has been described as 2.6 per cent[3], are associated with severe, persistent bleeding. The management of grade 3 complications, however, is supportive at best, and the results are far from satisfactory. Some cases will develop repeated episodes of bleeding from postradiation cystitis and proctitis which eventually requires colostomy, or formalin instillation into the bladder to control bleeding.

Basically, postradiation cystitis is a chronic inflammatory process. To date no safe and effective therapy for regeneration of chronic irradiation damage is known. Chemically-Stabilized Chlorite-Matrix (TCDO) pharmacological action comprises of the promotion of immune functions and tissue repair by targeting macrophages[4]. There is evidence that TCDO has a positive effect in several inflammatory conditions including postradiation damage. In Thailand Uttaravichien T, et al[5] reported that 10 out of 12 patients with postradiation cystitis were symptom free and without macroscopic hematuria within 4 weeks of treatment with TCDO.

The objective of this study was to evaluate the efficacy of TCDO in patients with grade 3 radiation cystitis presenting with repeated episodes of bleeding and failure to respond to standard consevative therapy.

MATERIAL AND METHOD

This study was conducted at the Department of Obstetrics and Gynecology, Ramathibodi Hospital and the Department of Radiology, Siriraj Hospital between September 1997 and September 1998. Twenty patients were included in this study. All patients had completed radiation therapy for carcinoma of the cervix or the endometrium. All patients were diagnosed with grade 3 radiation complication according to the RTOG / EORTC scoring system with recurring symptoms which could not be controlled with the usual conservative management. The patients were experiencing excessive and uncontrollable bleeding which required continuous bladder irrigation, intravesicular clot evacuation or blood transfusion.

The daily dose of TCDO (as 1:10 aqueous solution equivalent to 62 mM ClO_2) was 0.5 ml per kg body weight diluted in 500 to 1000 ml of 5 per cent D/W or normal saline (NSS) for intravenous infusion in 4-6 hour. Infusions were given on 5 consecutive days (= 1 cycle). This solution was freshly prepared and protected from sun light. The protocol allowed the use of systemic antibiotics if urinary tract infection was present. Bladder irrigation with normal saline and blood transfusions were given when indicated.

Evaluation of efficacy of TCDO in this study was done according to the following response criteria:-

1. Complete response :- no gross hematuria
2. Partial response :- gross hematuria without blood clot in the urine
3. No response :- gross hematuria with blood clot

The evaluation was done 7-14 days after TCDO treatment. Patients who showed only partial or no response after the first cycle were administered a second cycle of TCDO with the same regimen after a rest period of 7-14 days.

RESULTS

The time from completion of radiotherapy to the development of grade 3 clinical symptoms is shown in Table 1. The duration ranged from 5 to 115 months with a mean duration of 50.3 months. Forty per cent (40%) of the patients had developed grade 3 complications 60 months after completion of radiotherapy. Fifteen out of 20 patient (75%) had

Table 1. Duration of severe complications after radiotherapy

Duration (month)	Number	Per cent
1-12	2	10
13-24	5	20
25-36	2	10
37-48	2	10
49-60	1	5
Over 60	8	40
Total	20	100

Table 2. Data summary the effect of TCDO.

No.	Age	Diag.	Radio-therapy (m/y)	Complica-tion (m/y)	Response 1st cycle	Response 2rd cycle	Previous Bl. Tx.	Follow-up month
1.	57	Cx 3B	5/88	10/97	CR		11 u	9 mo.
2.	65	Corpus IB	4/90	10/97	NR	PR	13 u	10 mo.
3.	62	Cx 3B	3/91	11/96	CR		14 u	2 mo.
4.	60	Cx 3B	3/96	9/97	CR		4 u	Loss FU
5.	49	Cx 2B	3/96	10/97	PR		2 u	3 mo.
6.	66	Cx 3B	4/96	1/97	NR	PR	4 u	Loss FU
7.	67	Cx 3B	12/90	6/96	PR		8 u	8 mo.
8.	60	Cx 3B	4/96	2/98	NR		7 u	
9.	53	Cx 2A	3/90	11/97	NR	NR	10 u	
10.	65	Cx 2B	4/95	8/97	PR		9 u	7 mo.
11.	53	Cx 2A	4/92	9/97	PR		2 u	1 mo.
12.	54	Cx 3B	10/90	6/97	PR		4 u	3 mo.
13.	60	Cx 3B	8/94	2/98	PR	CR	-	1 mo.
14.	47	Cx 2B	9/94	3/98	CR		-	7 mo.
15.	44	Cx 2B	8/96	3/98	CR		-	Loss FU
16.	32	Cx 2B	1/94	4/95	PR	CR	-	7 mo.
17.	55	Cx 2B	8/97	5/98	PR	CR	4 u	Loss FU
18.	57	Cx 3B	10/93	5/98	PR	PR	-	CR at 4th course
19.	69	Cx 3B	10/96	6/98	PR	PR	6 u	CR at 4th course 2 mo.
20.	72	Cx 3B	1/89	7/98	CR		-	1 mo.

Table 3. Type of response to TCDO treatment.

	Complete response	Partial response	No response	Total
First course				
Number	6	10	4	20
Per cent	30	50	20	100
Second course				
Number	3	4	0	7
Per cent	43	57	-	100

received blood transfusion before TCDO treatment. Blood transfusions ranged from 2 to 14 units with a mean of 4.9 units of blood. Data summary, number of cycles and the response to TCDO treatment in all 20 patients are shown in Table 2. Nineteen patients had a history of carcinoma of the cervix and one had a history of endometrial carcinoma. The age of the patients ranged from 32 to 72 years with the mean age of 57 years. The results of TCDO treatment of grade 3 radiation cystitis and the type of response are shown in Table 3. After the first course of treatment, 6 patients or 30 per cent showed complete response within 5-10 days, ten patients (50%) showed partial response and 4 patients (20%) showed no response. Seven patients who had shown partial response (5 of 10) or no response (2 of 4) after the first cycle of treatment received a second cycle of treatment. Of these 7 patients, 3 (43%) showed complete response and 4 (57%) showed partial response.

Two patients who had shown no response after the first cycle and no response after the second cycle underwent transurethral fulguration and silver nitrate intravesicle instillation.

At 9-month follow-up, of the 18 patients who had shown complete and partial response after TCDO treatment, it was revealed that 13 patients did not develop recurrent bleeding. Five patients were lost to follow-up. Side effects of TCDO such as palpitation or phlebitis were not found in this study.

DISCUSSION

Post radiation syndrome involves a side effect pattern characterized by damage to the tissues and blood vessels of organs after direct interaction with ionizing radiation and secondary free oxygen radicals leading to inflammation and necrosis[6,7]. The most deleterious effect in terms of overall healing is obliterating endarteritis, which results in acute and chronic ischemia of the vesical wall. Endarteritis obliterans from radiation is an inflammatory process driven by T-cell dependent inappropriate antigen-response[8].

Various drugs and techniques have been introduced to treat postradiation syndrome. These treatments, however, do not repair late effects of radiation, but rather provide transient, palliative benefit. The most successful treatments are aggressive and have again serious side effects. Many patients, once stabilized, ultimately require surgery, for instance, urinary diversion or bladder augmentation because of bladder contraction due to radiation fibrosis coupled with effects of formalin treatment.

New modalities to treat late postradiation syndrome (cystitis or proctitis), avoiding aggressive and radical therapies which significantly diminish the patients' quality of life, are urgently being developed. The novel drug TCDO has recently been approved in Thailand (1997) and tested in phase II and III clinical trials in the United States and Germany, resets macrophages, set in an "inflammatory mode", back into an anti-inflammatory, phagocytic mode. TCDO reduces antigen-presentation and thereby interrupts persistent proliferation of T-cells that drive inflammatory processes such as endarteritis[9,10]. Evidence for the efficacy of TCDO in the treatment of postradiation cystitis was accrued several years ago : pilot experience has been reported from Germany[11,12], where the drug was developed and manufactured, and from Thailand[5,13] where the first controlled studies were conducted

In this study (30% of the patients showed complete response and 50% showed partial response) after the first cycle of TCDO treatment. The healing process seems to predominantly take place on the level of the epithelial lining, which may explain the early improvement after TCDO treatment. In this study, the response to TCDO treatment was noted 5-10 days after treatment began. Regarding duration of response, no recurrence of symptoms within 1-9 months after treatment was observed. The follow-up should be continued in this group of patients for 1-2 years, to confirm the long-term efficacy of TCDO.

The results of the study suggest good efficacy of TCDO in the treatment of postradiation cystitis. The safety of TCDO therapy at the current regimen was confirmed.

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ผลการรักษากระเพาะปัสสาวะอักเสบ ภายหลังรังสีรักษาด้วยเตตระคลอโรเดคาออกซิเจน

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มะเร็งปากมดลูกเป็นมะเร็งที่พบบ่อยที่สุดของอวัยวะสืบพันธุ์สตรีไทย ภาวะแทรกซ้อนภายหลังรังสีรักษามะเร็งปากมดลูกคือ กระเพาะปัสสาวะอักเสบ วัตถุประสงค์การศึกษาเพื่อศึกษาการรักษากระเพาะปัสสาวะอักเสบภายหลังรังสีรักษาด้วย Tetrachlorodecaoxygen (TCDO) โดยทำการศึกษาที่ภาควิชาสูติศาสตร์-นรีเวชวิทยา โรงพยาบาลรามาธิบดี และภาควิชารังสีวิทยา คณะแพทยศาสตร์ศิริราชพยาบาล ระหว่างเดือนกันยายน 2540 ถึงเดือนกันยายน 2541 ผู้ป่วยที่ทำการศึกษาทั้งหมด 20 คน ซึ่งเป็นมะเร็งปากมดลูกและมะเร็งเยื่อบุโพรงมดลูก ที่เคยได้รับการรักษาโดยรังสีรักษาและมีภาวะแทรกซ้อนกระเพาะปัสสาวะอักเสบอย่างรุนแรง การรักษาโดย TCDO 0.5 มิลลิเมตร/กิโลกรัม/วัน โดยให้ทางหลอดเลือดดำเป็นเวลา 5 วัน พบว่าผลการรักษาโดยเลือดออกน้อยลง 80% และ 30% พบว่าเลือดหยุดภายใน 5-10 วัน จากการติดตามผู้ป่วยภายหลังการรักษา 1-9 เดือน ไม่พบมีอาการเลือดออกจากกระเพาะปัสสาวะ ในการศึกษาครั้งนี้ไม่พบภาวะแทรกซ้อนจากการรักษา

คำสำคัญ : กระเพาะปัสสาวะอักเสบภายหลังรังสีรักษา, ทีซีดีโอ

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