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The Close Follow-up of Immunosuppressed Renal Recipient Women through Colposcopy, Cervical Biopsy and FCM DNA Content Analysis

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IN 1971, Tallent *et al.* reported a first renal transplant patient who had developed primary cervix cancer during immunosuppresive treatment [1]. In this study we aimed to emphasise the imperativeness of the use of cytology and colposcopy during preoperative checks and postoperative controls and further to determine the significance of the DNA content changes in the cell suspensions taken from one yearly interval cervix biopsies, by flow cytometric (FCM) DNA measurement.

Between December 1988 and March 1989, 20 renal recipient female patients were subjected to routine gynaecological examination, cervico-vaginal smear, colposcopy and colposcopy directed biopsy. The same procedure was repeated after a year between February–March 1990. The biopsy samples were analysed at the Norwegian Radium Hospital Flow cytometry laboratory. We used the preparation method described by Hedley [2].

The ages of the patients were 28–52, with an average of 35.4 years. Renal transplantations were carried out between minimum 2 and maximum 37 months before the date of the first biopsy, with an average of 10.8 months. Only 14 patients presented for the second examination, with respective transplantation periods as above, of between 14 and 49 months, with an average of 21 months.

In the first biopsy, results showed 13 cases of chronic cervicitis, 4 cases of metaplasia and 2 cases of parakeratosis while only 1 patient exhibited mild dysplasia (CIN I). The second biopsy results of the above were as follows: 7 cases of chronic cervicitis, 3 cases of metaplasia and 4 cases of parakeratosis. The CIN I case of the first biopsy was now observed as regressive subepithelial cervicitis.

Preinvasive lesions can be diagnosed by FCM analysis of biopsy specimens [3, 4]. As the method is not suitable for screening, however we therefore used this technique for high-risk immunosuppressed renal recipient patients. The analysis results in the DNA content levels could not point to the potential significance of this technique in the early diagnosis of CIN. We also could not find any progressive changes in histopathological classification in our study.

It is considered that, given the insufficiency of data presented in this preliminary report for statistical generalisation, further study of wider ranging and long-term followed-up cases will yield more significant results.

It should, however, be realised that histopathological classification is partly based on subjective criteria while flow cytometry is an objective method. Therefore we believe that the FCM technique study of the DNA content level changes in the high-risk renal recipient cervix biopsy materials is an important tool in long term follow-up premalign cervical lesions, in addition to the post-transplantation smear, virus, colposcopy and histopathological controls.

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Comparison of Ondansetron with Dexamethasone and Domperidone in the Prophylaxis of Non-cisplatin Chemotherapy Induced Emesis Refractory to Dexamethasone

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WE HAVE previously shown that both high dose dexamethasone and domperidone, which are widely used as anti-emetic prophylaxis for cytotoxic therapy, are effective in 60% and 40% of patients receiving non-cisplatin regimens, respectively, on their first course [1]. Ondansetron, a novel selective 5HT3 antagonist,

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has been shown to be effective in controlling emesis refractory to conventional antiemetics [2, 3].

We describe a randomised double blind comparison of ondansetron with the combination of dexamethasone and domperidone in patients receiving a variety of outpatient non-cisplatin chemotherapy regimens who had emesis refractory to treatment with dexamethasone alone.

31 patients (26 women, 5 men, mean age 57 [range 21–84]) who had experienced more than 2 emetic episodes or severe nausea on their previous chemotherapy cycle despite prophylactic high dose dexamethasone (4 mg intravenously, 4 mg orally immediately prior to chemotherapy followed by 4 mg orally 6 hourly for 2 days, 2 mg orally six hourly for 2 days, 1 mg 6 hourly for 1 day) were entered into this study. Additional entry criteria were that there should be no reduction in chemotherapy dose, no nausea and vomiting in the 12 h prior to chemotherapy, no concomitant antiemetic therapy and no steroids as part of the chemotherapy regimen. Patients were randomised to treatment with either ondansetron plus placebo or dexamethasone plus domperidone for one chemotherapy treatment. 15 patients received ondansetron at a dose of 8 mg (4 mg intravenously, 4 mg orally) immediately prior to chemotherapy followed by 4 mg orally 6 hourly for 5 days together with placebo capsules. 16 patients were given domperidone 20 mg orally immediately prior to chemotherapy followed by 20 mg orally 6 hourly for each of the 5 days in addition to the same dexamethasone dosage regime that was used on the previous chemotherapy cycle.

Patients filled out a diary for each day of the study period. The following were recorded: the number of vomits and retches, the severity of nausea on a 4 point scale and upsetting symptoms from antiemetic treatment. Treatment was considered to be a "success" if there were no vomits and no retches, and either mild or no nausea. Success rates were compared between the two groups using the Mantel–Haenzsel χ^2 test [4].

Patient characteristics in the two groups were comparable with respect to sex distribution, age, weight and body surface area. The composition of chemotherapy regimens were similar in both groups.

5 patients (2 in the ondansetron group and 3 in the dexamethasone plus domperidone group) were unevaluable for entry into the study because of inconsistent chemotherapy regimens (previous and study chemotherapy). Results were analysed for 26 patients (13 in each group).

The number of episodes of vomits and retches and distribution of nausea are shown in Table 1. Treatment was considered to be a success during the first 24 h with 10 patients (77%) in the ondansetron group and 2 patients (15%) in the dexamethasone plus domperidone group ($P = 0.002$). When the worst 24 h period during the 5 days of study for each patient was evaluated, treatment was considered to be a success with 8 patients (62%) in the ondansetron group and 1 (8%) in the dexamethasone plus domperidone group ($P = 0.005$). The number of patients who experienced more than 5 emetic episodes during the first 24 h was 1 for ondansetron vs. 8 for the combination dexamethasone and domperidone ($P = 0.005$). Adverse events in both groups were mild.

When results of the 5 excluded patients were added to the 26 study patients, treatment was considered to be a success in the ondansetron group (15 patients) for 80% (first 24 h) and 67% (day 1–5), compared to 19% (first 24 h) and 13% (day 1–5) for the dexamethasone and domperidone group (16 patients).

Table 1. Control of refractory emesis

	Day 1		Days 1–5 (worst day)	
Control of symptoms	Ond	Dex/Dom	Ond	Dex/Dom
Emesis (vomits/retches)				
Complete (0 episodes)	10	2	8	1
Major (1–2 episodes)	2	2	3	2
Minor (3–5 episodes)	0	1	1	1
Failure (>5 episodes)	1	8	1	9
Nausea				
None	9	2	7	1
Mild	2	3	2	1
Moderate	2	3	2	4
Severe	0	5	2	7

Ond = ondansetron ($n = 13$); Dex/Dom = dexamethasone plus domperidone ($n = 13$).

Of the 12 patients who failed over the 5 day period with dexamethasone and domperidone as antiemetic, 10 were given ondansetron only as antiemetic with their subsequent course of chemotherapy (the remaining 2 patients received no further chemotherapy). Treatment was considered to be a success during the first 24 h with 8 out of 10 patients (80%) according to the study criteria. 6 of these patients received the same dose of chemotherapy as their previous cycle, 1 patient had a smaller dose of chemotherapy and 1 patient received additional chemotherapy. The remaining 2 patients experienced more than five emetic episodes.

Our results show that ondansetron is considerably more effective than the combination of dexamethasone and domperidone in the prophylaxis of non-cisplatin chemotherapy induced emesis refractory to high dose dexamethasone. Ondansetron was also effective in controlling non-cisplatin induced emesis in patients who had failed on dexamethasone and dexamethasone plus domperidone.

In this study ondansetron was given 4 mg every 6 h, however a subsequent study in patients receiving non-cisplatin chemotherapy has shown that 8 mg given 12 hourly is also efficacious [5]. This simplified dosing schedule should be studied further as it should lead to a greater patient acceptance.

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