IMPACT OF RADIATION AND CHEMORADIATION WITH MITOMYCIN-C ON CELLULAR IMMUNITY OF PATIENTS WITH LOCALLY ADVANCED CERVICAL CANCER

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ABSTRACT

OBJECTIVE: To evaluate the impact of chemoradiation therapy with Mitomycin-C (MMC) on the cellular immunity of patients with locally advanced cervical cancer compared with radiation therapy alone.

MATERIALS AND METHODS: Fifty-six patients with locally advanced cervical cancer were divided into two groups, 34 patients treated with radiation alone and 22 patients with chemoradiation. Chemoradiation was performed by adding 15 mg MMC/ m^2 body surface through intravenous bolus injection on the first day of external radiation and on the first day of intracavitary radiation during the radiation routinely administered. In all patients, lymphocyte transformation test was performed after completion of external radiation, in one month, and three months after full-course treatment.

RESULTS: In radiation group, a significant decrease of lymphocyte transformation index was evident after external radiation compared with pre-treatment values, i.e., from 25.82 ± 14.30 % to 19.02 ± 10.54 % ($p = 0.08$). These parameters were further decreased to 17.85 ± 9.63 % in one month after full-course radiation. Although there was an increase to 18.97 ± 9.29 % at three months after full-course radiation, these values were still significantly lower than the values before radiation ($p = 0.015$). In chemoradiation group, there was an insignificant decrease of lymphocyte transformation index after external radiation and first MMC administration, compared with the values before radiation, i.e., 19.09 ± 12.66 % to 21.72 ± 12.68 %. A significant decrease of these parameters to 13.68 ± 8.23 % ($p= 0.038$) was noted at one month after full-course chemoradiation compared with the values before treatment. There was an increase of the parameters to 17.31 ± 11.32 % after full-course chemoradiation, such that they were not significantly different from the values before treatment.

CONCLUSIONS: Chemoradiation with MMC in patients with locally advanced cervical cancer did not result in greater impact on cellular immunity than radiation alone; the parameters would even improve rapidly in three months after treatment. The factors that possibly played a part in such condition were working mechanism and interval of MMC administration, as well as rebounded overshoot phenomena of lymphocyte transformation after cytotoxic treatment.

Keywords: Cervical cancer, chemoradiation, cellular immunity, lymphocyte transformation.

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INTRODUCTION

Chemoradiation therapy is frequently applied for locally advanced cancers with the purpose of providing better responses to both modalities than the separate treatment.[1] Each modality can decrease immunity of patients particularly cellular immunity which is the function of the important immune cells in cancer patients in coping with and eradicating tumor cells developing in their body. The decreased cellular immunity due to radiation is associated with a number of typical diseases, such as herpes zoster,[2] and even with the decreased survival rate in cancer patients receiving postoperative radiation.[3] Cellular immunity may also decrease as a result of chemotherapy such that infectious and fungal diseases may occur.[4] There is a possibility that the combined radiation and cytotoxic drug can result in synergism of immunosupressive effects that lead to infection, increased metastasis, and development of secondary tumor.[5] This is even more likely when chemoradiation is performed in patients with advanced stage whose cellular immunity generally tends to decrease because of the progress of the disease and malnutrition.[6]

Thus, even though chemoradiation may provide better therapeutic effects than the administration of radiation alone, it may cause toxicity to the extent that its benefits and risks should be carefully considered.

The examination of immunoblastic transformation is one of the qualitative tests for cellular immunity through the determination of the functional abilities of lymphocytes in vitro, i.e. the abilities to provide responses to mitogen.[7] Lymphocyte transformation test is basically aimed to show responses of T- lymphocyte to stimulation by mitogen.[8] Although not a single immunologic test in vitro can explain the functional abilities of lymphocytes in vitro appropriately, since there are other numerous functions in body at work, the results of this test are considered to have a correlation with the biologic expression of lymphocyte in the body.[9]

The examination of lymphocyte transformation as an immunologic parameter has been performed in various studies in cancer patients who were treated by radiation or other modalities.[10, 11]

Chemoradiation therapy was a method of treatment in locally advanced cervical cancer and one of cytotoxic agents used was Mitomycin-C (MMC). This agent was indicated as a hypoxic radiosensitizer although its application was limited due to bone marrow supression.[12] However, the impact of chemoradiation using MMC on cellular immunity, particularly in cervical cancer patients, has not been reported yet.

In this study, analysis of the impact of radiation therapy and chemoradiation with MMC of locally advanced cervical cancer on cellular immunity was examined with lymphocyte transformation test. The objective of the study was to evaluate the extent to which the combined therapy exerted its impact on patients' cellular immunity compared with radiation therapy alone.

MATERIALS AND METHODS

The study was performed in locally advanced cervical cancer patients referred for radiation therapy at Department of Radiotherapy, Dr Ciptomangunkusumo Hospital. Patients were from Department of Obstetrics and Gynecology, Faculty of Medicine University of Indonesia who had undergone routine examinations and biopsy to determine clinical stage and histopatological type in accord with the prevailing protocols.[13] The determination of clinical stage was performed using the 1976 FIGO system. Patients with locally ad-

vanced stage, i.e., stage IIb to stage IIIb meeting the inclusion criteria i.e., performance status of 50-100 according to Karnofsky scale, hemoglobin ≥10 g%, leucocyte > 4000/mm^3, thrombocyte > 100,000/mm^3, normal renal and heart functions, and having not received radiation and chemotherapy were included in this study.

Biospy specimen was sent for routine histopathologic and immunostaining examinations using Ki-67 monoclonal antibody,[14] to Department of Anatomic Pathology, Faculty of Medicine University of Indonesia. Routine histopathologic examinations were performed to identify histopathologic type and differentiation specified in the protocol of routine histopathologic examinations. Immunostaining using Ki-67 monoclonal antibody was performed to determine growth fraction of tumor[15] those were assumed to be associated with hypoxic state of the tumor.[16]

Patients receiving the treatment were divided into two groups, i.e., those with Ki-67 index ≥ 40 (high growth fraction) and those with Ki-67 index < 40% (low growth fraction). Each group was randomized into two treatment arms i.e chemoradiation with MMC and radiation alone. Written informed consent was obtained as needed after the subject of the study and her family were counseled on the objectives and steps of the study.

RADIATION THERAPY

Radiation therapy was performed in the form of external radiation administered in whole pelvis, and intracavitary radiation was followed 1-2 weeks afterwards. External radiation was administered using anterior-posterior radiation portals with superior border was between IV and V lumbar spines, inferior border was lower border of symphysis pubis, lateral border was 1. 5 cm from linea inominata. The dose administered was 180 cGy fraction per week, and a total dose of 5040 cGy in 5½ weeks with 10 MV linear accelerator or telecobalt-60 machine.

Intracavitary radiation was generally administered with HDR afterloading technique using Cobalt-60 sources with Selectron machine. Overall, it was performed twice with a one-week interval with Manchester system using RRTI (Rotterdam Radiotherapeutisch Instituut) applicator. A dose of 850 cGy was given at point A in each application such a way that the bladder and and rectal doses did not exceed 700 and 800 cGy, respectively. In small number of patients after loading technique was performed manually with Low Dose Rate (LDR) system using Cs-137 source. This technique was performed twice in the same interval as HDR system with a dose of 1300 cGy at point A and with bladder and rectal doses equivalent to HDR system.

CHEMORADIATION THERAPY

The radiation technique performed was similar to that applied in the radiation group. MMC was adminstered simultaneously on day one of external radiation and on day one of intracavitary radiation, with a dose of 15 mg/m^2 of body surface through intravenous bolus injection.

CLINICAL AND LABORATORY EXAMINATIONS

In each patient, clinical examinations were performed prior to the treatment, every week during the treatment, after external radiation with or without MMC, at one month and 3 months after overall treatment. Routine peripheral blood examinations were performed at the same periods except 3 months after treatment. The examinations of liver and renal functions were performed before treatment, after external radiation with or without MMC and at one month after completion of overall treatment. Lymphocyte transformation tests were performed at the same periods and also three months after completion of the overall treatment.

EXAMINATIONS OF LYMPHOCYTE TRANSFORMATION

Culture medium was made in accordance with Suharso's method, 1978.[17] The study of cell morphology of the culture could be done if the culture had lasted for 72 hours, and culture medium was separated with centrifugation of 600 gravitation during 10 minutes. Furthermore, the following steps were done:

(a) Deposit obtained was rinsed twice with BBS pH 7.2 Hanks solution. Then it was poured into hypotonic solution (KCI 0,075 M KCI solution) for 15 minutes such that its cells become lysis.

(b) Fluid was separated by re-centrifugating at the speed of 600 gravitation for 10 minutes. The deposit was fixated with Carnoy fixation. Fixations were changed several times until the deposit had the color of clean white.

(c) A suspension was made from the last deposit, scattered on the object glass and stained with Giemsa solution. After it has dried, the specimen was covered with Canada balm.

Microscopic examination was performed by dividing each specimen into 75 selection areas, in which each selection area measured 1 x 1 cm^2. Within the selection area chosen, 100 cells were counted and classified according to their morphology observed under a 10 x 45 magnified microscope. Classifications of the cells observed under microscope were as follows:

(a) Cells that did not transform: also called as the usual lymphocytes; small, round cells of dark and solid color with a diameter of 1.k. 8 m.

(b) Cells that transformed, consisting of:
- Lymphoblasts or blastocytes: 12-50 m diameter round-shaped cells, red-bluish color with Giemsa staining. Occasionally blue cytoplasm was observed around the nucleus
- Mitotic phase: Lymphoblast would enter mitotic phase when nuclear membrane was unobserved, and chromosome threads began to appear clearly. In advanced mitotic phase, only the scattered chromosome had a long and short size. The degree of lymphocye transformation was stated in transformation index according to **Matangkasombut** and **Tharavanich**, 1972.[18]

DATA IDENTIFICATION AND STATISTICAL ANALYSIS

Data of the study were identified manually and entered into computer to be analyzed statistically with SPSS program. Data were processed with independence T-test for unpaired groups, paired test, and X^2 - test for comparability among groups.

RESULTS

The study was carried out from October 1994 to September1996. The examinations of lymphocyte transformation were performed in 114 patients; however, only 56 patients were able to undergo regular lymphocyte transformation tests up to three months after radiation. In other patients, analysis could not be performed because of incomplete data, technical errors, and untimely admission of the patients.

From the same patients examination results of leukocyte number were obtained prior to the treatment, after external radiation with or without MMC and one month after completion of treatment except at three months after completion of treatment. Of 56 patients, 24 were included in the group receiving radiation alone, while the other 22 received chemoradiation with MMC (Table 1).

Table 1. Charateristics of patients

	Radiation therapy	Chemoradiation group
Stage		
II b	20	13
III b	14	9
Histology		
Squamous cell ca	32	20
Adeno	2	2
Differentiation		
Well/moderate	27	17
Undifferentiated	7	5
Tumor size		
< 4 cm	17	9
≥ 4 cm	17	13
Hemoglobin		
< 12 g %	20	12
≥ 12 g %	14	10
Ki -67 index		
< 40 %	7	12
≥ 40 %	27	10
Response		
complete	28	18
partial	6	4
Total patients	34	22

INDEX OF LYMPHOCYTE TRANSFORMATION

In the group of radiation alone (n = 34) index values of lymphocyte transformation were obtained, i.e., before radiation in the range of 00.00 to 53.00%, mean 25.82 ± 14.30 % and after external radiation 5040 cGy from 00.00 to 51.00%, mean 19.02 ± 10.54%. One month after complete radiation, the values ranged from 00.00 to 38.00%, mean 17.85 ± 9.63%, and three months after complete radiation from 00.0 to 36.00%, mean 18.97 ± 9.29%.

A significant decrease in lymphocyte transformation index was evident after 5040 cGy radiation compared with the index prior to radiation ($p = 0.008$). In the period of three months after complete radiation, the index was still significantly low compared with that before radiation ($p = 0.015$), even though the values had improved (Table 2).

Table 2. Mean values of lymphocyte transfromation in radiation group

Period of examination	Transformation index	p
Before radiation	25.82 ± 14.30	
After external radiation	19.02 ± 10.54	0.008
One month post radiation	17.85 ± 9.63	
Three months post radiation	18.97 ± 9.29	0.015

In the group of chemoradiation (n = 22) the following index values of lymphocyte transformation were obtained: before chemoradiation ranged from 00.00 to 40.00%, mean 21.72 ± 12.68%, after external radiation of 5040 cGy + MMC from 00.00 to 52.00%, mean 19.09 ± 12.66%. One month after complete chemoradiation, the values obtained ranged from 00.00 to 28.00%, mean 13.68 ± 8.23, and three months after complete chemoradiation from 00.00 to 35.00%, mean 17.31 ± 11.32% .

It was evident that after the first MMC administration and 5040 cGy radiation, there was no significant difference from the values prior to chemoradiation. However, after one month of the second administration of MMC and complete chemoradiation, there occurred a significant decrease compared with the values before therapy ($p = 0.038$). Lymphocyte transformation values at three months after completion of combined therapy showed an increase to the extent that there was no significant difference ($p = 0.192$). from the values prior to treatment (Table 3).

Table 3. Mean values of lymphocyte transfromation in chemoradiation group

Period of examination	Transformation index	p
Before treatment	21.72 ± 12.68	
Post external radiation + MMC	19.09 ± 12.66	
One month post treatment	13.68 ± 8.23	0.038
Three months post treatment	17.31 ± 11.32	

The comparison of index values between the two groups in various periods of examination was as follows: means before therapy ranged from 25.82 ± 14.30% to 21.72 ± 12.68% and after 5040 cGy radiation from 19.02 ± 10.54% to 19.09 ± 12.66%. After one month of complete radiation, the comparison between means of index values was from 17.85 ± 9.63% to 13.68 ± 8.23%, and after three months of complete radiation from 18.97 ± 9.29%, to 17.31 ± 11.32% .

If the index values in each period of examination were compared, there would be no significant difference between both groups ($p > 0.05$). However, there was a trend of slow decrease and then followed by rapid increase of lymphocyte transformation values during treatment in chemoradition group compared with radiation group (Figure 1).

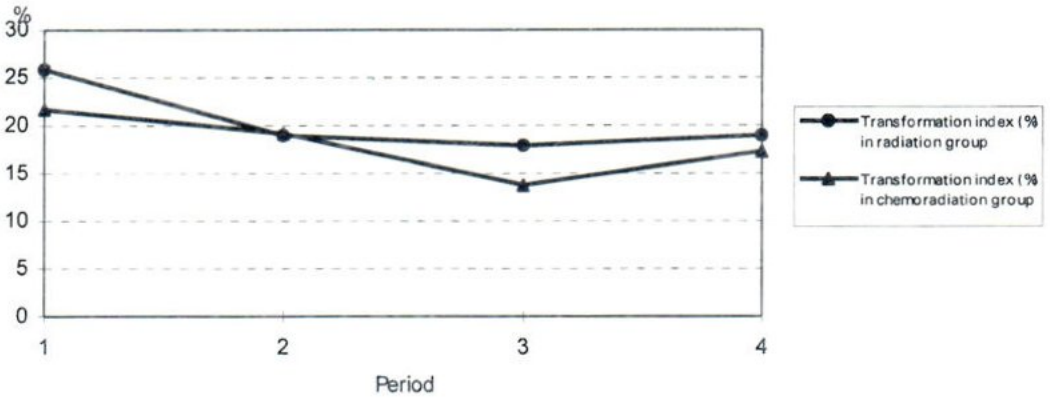

Fig. 1 Mean values of lymphocyte transformation index in both groups of treatment

NUMBER OF LEUKOCYTES

The average number of leukocytes before radiation was obtained in radiation group was between 1100/mm^3 and 16600/mm^3, mean 8756 ± 3920/mm^3. After external radiation, the number of leukocytes was 1000/mm^3 to 9500/mm^3, mean 5615 ± 1786/mm^3. After one month of complete radiation, the number of leukocytes was 2500 / mm^3 to 10800 /mm^3, mean 5836 ± 1825/ mm^3 (Table 5).

Compared with the number of leukocytes before therapy, there occurred a significant decrease after external radiation ($p = 0.000$) and at one month after complete radiation ($p = 0.001$). Although there was an increase in the number of leukocytes at one month after completion of therapy; however, this was not significant compared with the number of leukocytes after the completion of external radiation therapy ($p = 0.643$). These results showed that although there was a decrease, mean of leukocytes number remained within normal limit (4500-10,000/mm^3).

Table 4. Number of leukocytes before and after treatment in radiation group

Period of examination	Number of leukocytes /mm^3	p
Before radiation	8756 ± 3920	
Post external radiation	5615 ± 1786	0.000
One month post radiation	5836 ± 1825	0.001

The average number of leukocytes before chemoradiation was 1000 /mm^3 to 11700/mm^3, mean 7382 ± 3035/mm^3. After external radiation, the number of leukocytes was 3200/mm^3 to 9000/ mm^3, mean 5482 ± 1542. After one month of complete radiation, the number of leukocyte was 1000/ mm^3 to 7800 /mm^3, mean 5187 ± 1590/mm^3 (Table 5). Compared with the number of leukocytes before treatment, there was a significant decrease after external radiation ($p = 0.024$) and at after one month of complete treatment ($p = 0.002$). There was an increase in the number of leukocyte in one month after complete treatment (table 5) however, this was not significant compared with the number of leukocytes after completion of external radiation ($p = 0.531$). These results showed that although there was a decrease, mean of leukocyte number was still within the normal limit (4500 - 10,000/mm^3).

Table 5. Number of leukocytes before and after treatment in chemoradiation group

Period of examination	Number of leukocytes /mm^3	p
Before treatment	7382 ± 3035	
After ERT	5482 ± 1542	0.024
One month after treatment	5187 ± 1590	0.002

In addition, the results revealed that either before, after treatment, or at one month after treatment, there was no significant difference between the number of leukocytes in radiation group and in chemoradiation group. Nevertheless, there was milder decrease of leukocytes in chemoradiation group after external radiation + MMC compared with radiation group (Figure 2).

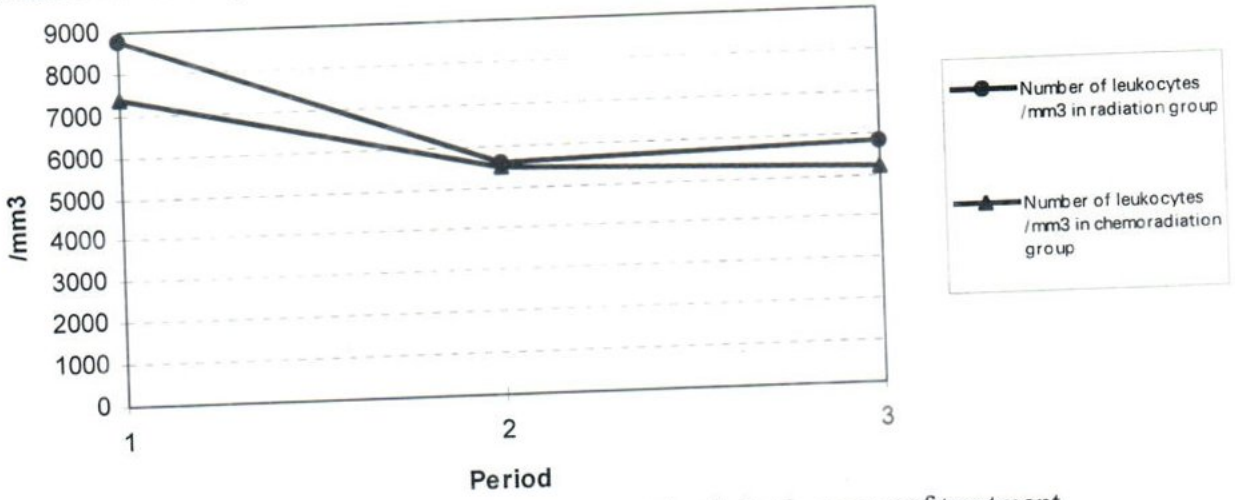

Fig. 2 Mean values of leukocyte number in both groups of treatment

It was evident that in each group there was a comparable distribution in age, stage, histopathologic type, differentiation degree, tumor size, Haemoglobin value, Ki-67 index, and responses to radiation (Table 7)

Table 7. Comparability of two treatment group

		Radiation (n)	Chemoradiation (n)	p
Age	Mean	48.09	48.73	0.810
Stage	IIb	20	13	0.985
	IIIb	14	9	
Histopathologic type	Squamous cell	2	2	0.656
carcinoma				
	Adenocarcinoma	32	20	
Differentiation degree	Well/moderate	27	17	0.705
	Undifferentiated	7	5	
Tumor size	< 4 cm	17	9	0.514
	≥ 4 cm	17	13	
Hemoglobin value	< 12 g %	20	12	0.757
	≥12 g	14	10	
Ki-67 index	< 40 %	7	12	0.089
	≥ 40 %	27	10	
Tumor response	Complete	28	18	0.960
	Partial	6	4	

DISCUSSION

Immunodeficiency in cancer patients is likely to occur as a result of multiple factors correlated with the patient, tumor, and environment.[19] It has been known that tumor occurred more frequently in people with suppression of immune system than in normal people.[20] Malnutrition will cause defects in cellular immune response and antibody formation.[21] Immunecompetence in cancer patients correlates with disease stage and prognosis[22] and may decrease with the progress of disease and metastasis.[23] In the present study, the possibility of decreased immune response was higher in patients with locally advanced stages, and presumably with malnutrition indicated by low Hemoglobin value before treatment (mean 11.72g%). It was obvious that lymphocyte transformation index before radiation or chemoradiation was lower than the normal values, i.e., 24.23 ± 13.72% compared with 37.18 - 45.26 %.[17]

Immunosuppression resulting from treatment contributing to the immunodeficiency of cancer patients was also demonstrated in this study; there was a significant decrease in lymphocyte transformation index in patients receiving either radiation or chemoradiation compared with the values before treatment, i.e., 25.82 ± 14.30 mm^3 versus 17.85 ± 9.63 mm^3 and 21.72 ± 12.68 mm^3 versus 13.68 ± 8.23 $mm,^3$ respectively.

Immunologic abnormalities generally occurred in local and regional radiation; however, the length and severity of such disorder usually were neither quite obvious nor specific.[24] Restoration of mitogen response may occur in six months or even longer[25] after local radiation in various body organs. Radiation in mediastinum or pelvic region resulted in rapid decrease of T and B cell, with disorder in mitogen reaction; however, a recovery may occur in three weeks after radiation.

In present study it was evident that in radiation group there was decreased in leukocytes number that presumably indicated the decreased of lymphocyte number during external radiation. One month after full - course radiation the number of leukocytes was increased although this was not significant compared with the leukocyte number before radiation. It should be noted that the leukocyte number at 3 months after treatment was not available.

It was evident that in radiation group there was a decrease in lymphocyte transformation at the end of radiation and it tended to recover at one to three months after radiation completion although the value was still less than before radiation. Another data showed that loco-regional radiotherapy resulted in a decreased lymphocyte transformation to approximately 50 % of the initial value, with a partial recovery to 80 % of pretreatment level 3 months after therapy.[26] These data are similar to our results.

The pattern of changes of lymphocyte transformation as well as the leukocyte number in radiation group could be observed in figure 3.

In general, the combined radiation and cytotoxic drug could reduce more lymphocytes than cytotoxic drug alone. In prophylactic radiation of the cranium in the treatment of acute lymphocytic leukemia which had remission after chemotherapy induction, it revealed that the decrease of lymphocytes and reduced reaction of lymphocytes toward mitogen stimulation were more evident.[27] Impact to cellular immunity is primarily because of stem cell death in the bone marow and in part of peripheral lymphoctye.[28]

In this study, there was a significant decrease of leukocyte number of patient in chemoradiation group after external radiation and first

administration of MMC and at one month of after complete treatment. Although there was an increase of leukocyte number at one month after complete treatment, this was not significant as compared with the number after completion of external radiation + MMC. These results also showed that even though there was a decrease, mean of leukocyte number was still within the normal limit.

In chemoradiation group, lymphocyte transformation values after external radiation + first administration of MMC were not significant difference from the values prior to the treatment. However, after one month of the second administration of MMC, there occurred a significant decrease compared with values before therapy ($p = 0,038$). Lymphocyte transformation values at three months after completion of chemoradiation showed an increase to the extent that there was no significant difference from the values prior to treatment.

The pattern of lymphocyte transformation changes as well as the leukocyte number in radiation group could also be observed in figure 4.

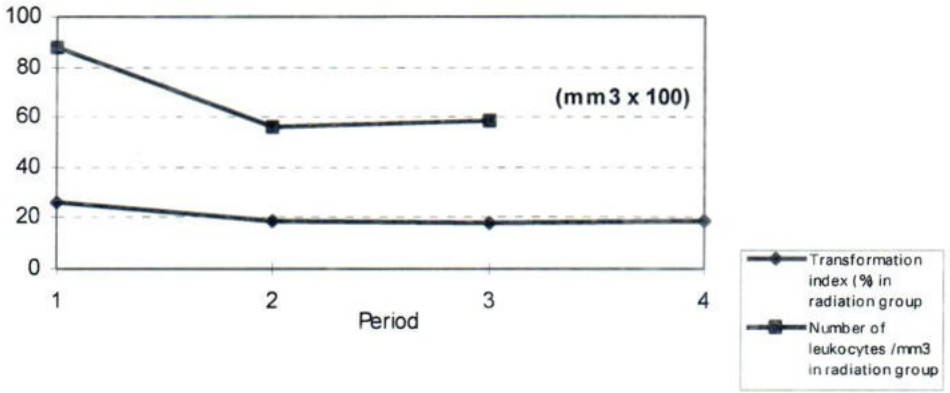

Fig. 3 Mean values of lymphocyte trasformation index and leukocyte number in radiation group

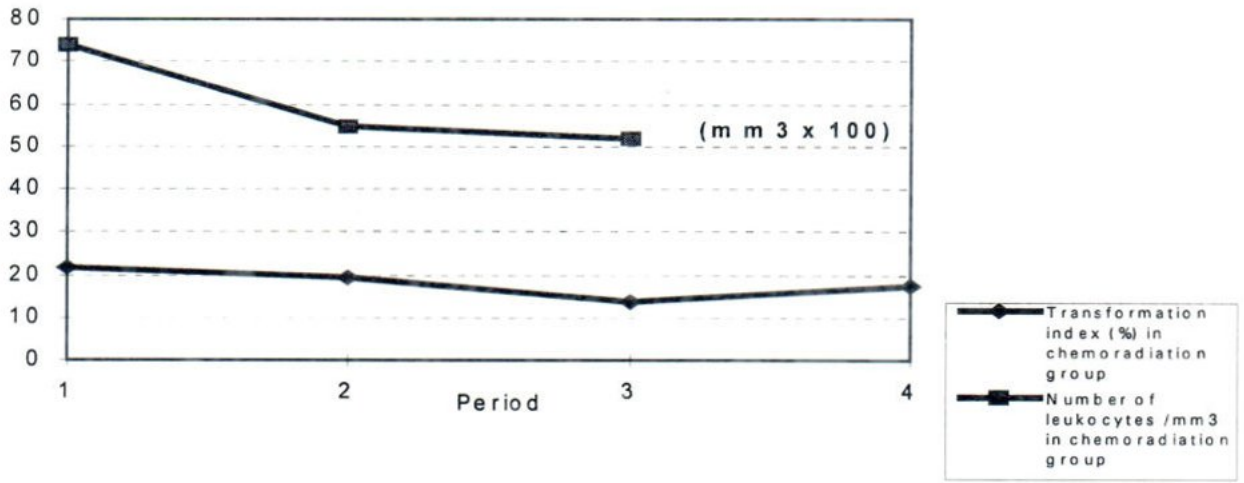

Fig. 4 Mean values of lymphocyte trasformation index and values of leukocyte number in chemoradiation group

The use of MMC as single cytotoxic agent in this study presumably did not much affect lymphocyte transformation since it did not much affect T cell. The impact of cytotoxic drug on peripheral lymphocytes was relatively lower than that of radiation since T cells those constituting the majority in peripheral lymphocyte cells, were at phase G_0 as such that they were not vulnerable to the treatment with MMC.[29]

The treatment of combined radiation and MMC could potentially enhance the impact on cellular immunity. However, the increased toxicity due to MMC would affect temporarily since the death of the main cells in bone marrow could be compensated if MMC was administered in sufficient intervals.[30]

In this study, lymphocyte transformation test performed at the end of the fifth week after radiation did not show any significant decrease, presumably because MMC was administered on the first the day of radiation and had compensated after five weeks. However, lymphocyte transformation values appeared to decrease in one month after chemoradiation because the second MMC administration was performed five weeks before the examination during which no complete recovery had occurred. The MMC administration performed in large dose would cause depression of bone marrow which would recover after six weeks.[31]

Although radiation and chemoradiation had the suppressive effect on immune system, the important difference was that in radiation such effects lasted in a long time and may depend on blood volume passing the radiation field. Suppressive effects of cytostatics were generally short-lived. Complete or nearly complete restoration of immune parameter may occur after completion of systemic chemoradiation, and many parameters could show overshoot phenomena.[32] This phenomena was observed following short, intensive courses of chemotherapy in patients with solid tumor. It was demonstrated that recovery of lymphocyte transformation beginning approximately 3 days after treatment and rebounding frequently to the level of function greater than those before treatment by 9 days after cessation of treatment.[33]

In addition to exerting possible adverse impacts, chemoradiation may be beneficial in enhancing immune response. The enhanced response may be caused by sensitivity of suppressor cells that if their functions were disrupted due to radiation an enhanced immune response would occur. It will be likely to occur when using alkylating agents[35] whereas MMC is one among them.[34]

A number of factors called for attention in the administration of chemoradiation to avoid cumulative toxicity effects, particularly on cellular immunity includes:

1. Types of chemoradiation

Combination of both modalities will therefore depend on the type of cytostoxic drug being used. With chemoradiation there may exist different effects on cellular immunity due to the different type and mechanism of cytotoxic agents. The effects of MMC on cellular immunity was minimal because T cell was at G_0 phase such that it was not sensitive to MMC [35]; although there was some effect of MMC on bone marrow, this impact was reversible.

2. Single or combined chemotherapy

In general, the administration of single cytotoxic agent less suppressive impacts on the number of lymphocytes compared with combined chemotherapy. B cell was more sensitive to single cytotoxic agent than was T cell, while combined chemoterapy had equal impact on both of them [36].

3. Timing of chemoradiation administration

The main toxicity limiting the use of MMC was slowed and cumulative myelosuppressive effect. The peak value of leukopenia and thrombocytopenia would be achieved in more than 28 days after the administration of single dose.[37] Thus, the accumulated suppressive effects may be prevented if the subsequent administration of MMC could be performed after four weeks. In the present study, MMC was adiministered in a minimum interval of six weeks to the extent that its suppressive effects in the first administration had been restored.

4. Sequence of radiation and chemoradiation administration

Several studies demonstrated that a number of cytotoxic drugs required functional immune response to enable it to be effective in killing the tumor.[38] The reduced immunocompetency by radiation administered before and after chemotherapy may reduce the potency of chemoradiation clinically to the extent that its use should be reconsidered in designing a combined treatment.

A drawback in this study, among others, was that lymphocyte examination was not performed, particularly of T- cell which exerted enormous effects on cellular immunity.

One of the indicators of chemoradiation effects on cellular immunity was the slowed-type hypersensitvity reaction. This reaction was produced by lymphokin released by T- lymphocyte already stimulated by the antigen working in macrophage as a final mediator. Thus, examination of skin test could be performed to enhance the reliability of cellular immunity test. In addition, other qualitative examinations, such as mixed lymphocyte reaction, should be performed to corroborate the results obtained.[39]

Examinations by way of lymphocyte transformation test in this study were performed with index calculation based on somewhat subjective morphologic descriptions of lymphocyte cells. The other method to measure the sensitivity of the stimulated lymphocyte activity was by measuring the activity of DNA synthesis. This could be performed by incubating the stimulated lymphocytes by mitogen with radioactive thymidine.[40] The activity of DNA formation was proportionate with the extent to which thymidine was incorporated into the cells calculated with measuring tool of radioactivty.

CONCLUSIONS

Chemoradiation with MMC in patients with locally advanced cervical cancers did not result in greater impact on cellular immunity than radiation alone ; it would even improve more rapidly at three months after treatment compared with patients treated with radiation alone. The factors that possibly played a part in such condition were working mechanism and interval of MMC administration, as well as rebounded overshoot phenomena of lymphocyte transformation after chemotherapy.

ACKNOWLEDGEMENT

The author is indebted to Professor M. Djakaria M.D, Professor Nana Suhana Ph.D., Santoso Cornain M.D., D.Sc, for their assistant during the studies and preparation of this manuscript.

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