The Differences of Apoptosis Effects Between Combination of Meloxicam with Gemcitabine-Carboplatin Chemotherapy Compared To Gemcitabine-Carboplatin Chemotherapy Alone In Urothelial Carcinoma Culture C

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THE DIFFERENCES OF APOPTOSIS EFFECTS BETWEEN COMBINATION OF MELOXICAM WITH GEMCITABINE-CARBOPLATIN CHEMOTHERAPY COMPARED TO GEMCITABINE-CARBOPLATIN CHEMOTHERAPY ALONE IN UROTHELIAL CARCINOMA CULTURE CELLS

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ABSTRACT

Objective: *To determine the differences of apoptosis effect between the combination of meloxicam and gemcitabine-carboplatin compared to gemcitabine-carboplatin alone as the standard of chemotherapy care in urothelial carcinoma culture cells.* ***Material & Methods:*** *This research is an in vitro experimental using human bladder cell carcinoma type 5637 which was cultured in the laboratory. In this study, the study group was divided into 3 groups: untreated control group, gemcitabine-carboplatin group, and the meloxicam-gemcitabine-carboplatin combination group, each group consist of 5 replications. To determine the dose of meloxicam, gemcitabine, carboplatin used and the time of apoptosis evaluation, cytotoxic tests were carried out using the MTT assay method. The time of apoptosis evaluation is carried out for 24 hours. Apoptosis was assessed using the Apoptotag reagent from Trevigen®. Observation of apoptosis characterized by a positive reaction (the color turning brown) against DNA strand damage using the TUNEL assay method. One Way ANOVA was used for comparative analysis of apoptosis between the group with a significant value of $p<0.05$. The analysis was continued with a post hoc test, to determine the differences in each group.* ***Results:*** *The mean of apoptosis in the control group, gemcitabine-carboplatin group, apoptosis and the meloxicam-gemcitabine-carboplatin combination group was 0.748%, 80.336%, and 83.312%, respectively. Post hoc Bonferroni analysis showed that the results had significant difference between the meloxicam-gemcitabine-carboplatin combination group compared to the gemcitabine-carboplatin group ($p=0.026$) and the control group ($p=0.000$).* ***Conclusion:*** *Meloxicam-gemcitabine-carboplatin combination therapy has a significantly higher apoptotic effect than gemcitabine-carboplatin alone.*

Keywords: *Meloxicam, gemcitabine, carboplatin, apoptosis.*

ABSTRAK

Tujuan: *Mengetahui perbedaan efek apoptosis pemberian kombinasi meloksikam dan kemoterapi gemcitabin karboplatin dibandingkan kemoterapi gemcitabine karboplatin saja sebagai standard of care pada sel kultur karsinoma urothelial.* ***Bahan & Cara:*** *Jenis penelitian ini adalah eksperimental in vitro menggunakan sel kultur karsinoma urothelial human bladder cell carcinoma tipe 5637 yang dibiakkan di laboratorium. Pada penelitian ini, kelompok penelitian dibagi menjadi 3 dengan 5 replikasi pada tiap kelompok, yaitu kelompok kontrol tanpa perlakuan, kelompok gemcitabine-karboplatin, dan kelompok kombinasi meloksikam gemcitabine-karboplatin. Untuk menentukan dosis meloksikam, gemcitabine, karboplatin dan waktu evaluasi apoptosis, dilakukan uji sitotoksik dengan metode MTT assay. Waktu pengamatan apoptosis dilakukan selama 24 jam. Apoptosis dinilai menggunakan reagen Apoptotag dari Trevigen®. Pengamatan apoptosis yang ditandai dengan reaksi positif (berwarna coklat) terhadap kerusakan strand DNA dengan menggunakan metode TUNEL assay. Analisis data dilakukan dengan studi komparasi apoptosis antar kelompok menggunakan One Way ANOVA dengan nilai signifikan bila $p<0.05$. Analisis dilanjutkan dengan uji post hoc, untuk mengetahui perbedaan pada tiap kelompok.* ***Hasil:*** *Rerata apoptosis pada kelompok kontrol adalah 0.748%, kelompok gemcitabine-karboplatin rerata apoptosis 80.336% dan kelompok kombinasi meloksikam gemcitabine-karboplatin rerata nilai apoptosis 83.312%. Analisis post hoc Bonferroni antara menunjukan hasil yang perbedaan yang signifikan antara kelompok kombinasi meloksikam gemcitabine-karboplatin dengan kelompok gemcitabine-karboplatin ($p=0.026$) dan kelompok kontrol ($p=0.000$).* ***Simpulan:*** *Terapi kombinasi meloksikam gemcitabine-karboplatin memiliki efek apoptosis yang signifikan lebih tinggi dibandingkan dengan gemcitabine-karboplatin saja.*

Kata kunci: *Meloksikam, gemcitabine, karboplatin, apoptosis.*

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INTRODUCTION

Bladder cancer is the 9th most malignancies in both gender, and 2nd most malignancies in the urinary tract.[1,2] In 2008, more than 150.000 deaths from bladder cancer occurred. The average incidence of bladder cancer is 10.1 per 1.000.000.[3,4] In Indonesia, there were 10.000 patients with bladder cancer in 2012, the number was increasing almost 15% every year.[5] In general the management of bladder cancer is divided into two groups, Non-Muscle Invasive Bladder Cancer (NMIBC) group treat with intravesical instillation therapy,[6] and Muscle Invasive Bladder Cancer (MIBC) group treat with radical cystectomy, radiotherapy and chemotherapy.[7,8] In the patients who are inoperable, refuse to do surgery and in the case of metastatic bladder cancer chemotherapy are preferred.[9]

Gemcitabine-Cisplatin (Gem-Cis) becomes the standard chemotherapy regimen for urothelial carcinoma bladder. Another chemotherapy regimen, Gemcitabine-Carboplatin (Gem-Carbo) is used if there are contraindications to cisplatin.[9] The Gem-Carbo chemotherapy regimen has lower effectiveness compared to Gem-Cis.[10] But the Gem-Carbo chemotherapy has an advantage of safer for kidney function, so this regimen is more widely used in patients with renal insufficiency conditions.[11,12]

Selective Cyclooxygenase-2 inhibitors (COX-2 inhibitors) have proven to be an alternative therapy for malignancy that can be used alone or in combination with other therapies, such as chemotherapy.[13] COX-2 inhibitors have also proven to increase apoptosis effect, decrease cell proliferation, inhibits angiogenesis and also could increase the cytotoxic effect of anticancer drugs.[14] Meloxicam also has a significant anti-carcinogenic effect on urothelial carcinoma bladder through inhibition of cell proliferation, increased apoptosis and also DNA damage cancer cells.[15] The most often used COX-2 inhibitors as non-steroidal anti inflammation drugs (NSAIDs) are meloxicam. But, in-vitro studies which aims to evaluate synergistic effects of gemcitabine, carboplatin, and meloxicam on the bladder cancer have not yet been studied so far.

OBJECTIVE

To determine the differences of apoptosis effect between the combination of meloxicam and gemcitabine-carboplatin compared to gemcitabine-carboplatin as the standard of chemotherapy care in urothelial carcinoma culture cells.

MATERIAL & METHODS

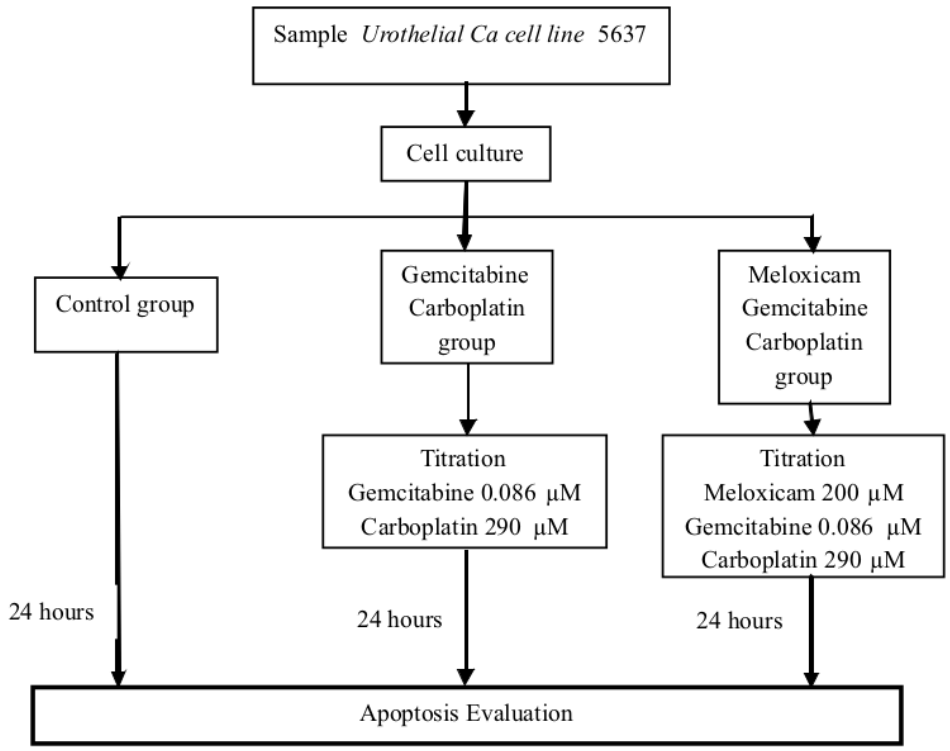
This research is an in vitro experimental using human bladder cell carcinoma type 5637 which was cultured in the laboratory. 5637 cell lines was provided by American Type Culture Collection (ATCC). The culture process starts by placing the cell into the RPMI-1640 medium. The 10% bovine fetal serum, 2 µM L-glutamine and 1% penicillin/streptomycin were added into the media. After that, the cells were centrifugate and passages repeatedly.

In this study, the study group was divided into 3 groups: untreated control group, gemcitabine-carboplatin group, and the combination group of meloxicam-gemcitabine-carboplatin.

MTT (thiazolyl blue tetrazolium bromide, from Bio Basic, Canada) was performed to determine meloxicam (Ostelox®) dose given and the time for apoptosis evaluation. From the MTT result, the optimal dose of meloxicam chosen based on IC50 was 200 µM, and the dose of gemcitabine was 0.086 µM, and the dose of carboplatin was 290 µM, with 24-hour of apoptosis evaluation.

In this study, 5 sample replicant was used in each group and observed at 24 hours. Apoptosis was assessed using the apoptotag from Trevigen®. Morphological criteria were used to detect the apoptosis. Observation of apoptosis characterized by a positive reaction (the color turning brown) against DNA strand damage using the TUNEL assay method, then the number of apoptotic cell measured and divided by the total number of cells then multiplied by 100%.[16] In this study, cell culture were treated and interpreted by two different experts. The apoptotag results were interpreted by pathologist who did not know the previous sample identify.

In the control group, urothelial carcinoma culture cells were only observed for 24 hours without any treatment. In the gemcitabine-carboplatin group, the gemcitabine and carboplatin titration dose used were 0.086 µM and 290 µM, respectively. In the combination group of meloxicam-gemcitabine-carboplatin, the gemcitabine and carboplatin titration dose used were 0.086 µM and 290 µM, respectively, with the addition of 200 µM meloxicam. Then, all research samples in all groups were given apoptotag® reagents. The apoptosis of urothelial carcinoma cell was observed using a light microscope with 400x magnification at 24 hours.



The results from the research were collected in a data collection sheets, then grouped and presented in the tables and diagrams. Data analysis was performed using the SPSS 22 program. One Way ANOVA was used for comparative analysis of apoptosis between the group with a significant value of $p<0.05$. The analysis was continued with a post hoc test, to determine the differences in each group.

RESULT

The results of apoptosis calculation from the three urothelial carcinoma cell groups were as follows: in the control group, the culture cell apoptosis percentages from five replicates were 0.87%, 0.25%, 1.15%, 0.98%, and 0.49% with an average of 0.748%. In the gemcitabine-carboplatin group, the culture cell apoptosis percentages were 78.29, 82.74%, 81.45%, 79.05%, and 80.15% with an average of 80.336%. In the meloxicam-gemcitabine-carboplatin combination group, apoptotic percentages were 80.83%, 82.4%, 83.46%, 84.08%, and 85.79% with an average of 83.312% (Figure 1 & 2).

The results of the Post hoc Bonferroni test showed a significant difference in the mean apoptosis between the control group and the two other groups, gemcitabine-carboplatin group and also the meloxicam-gemcitabine-carboplatin combination group after 24 hours of treatment (Table 1). In this study, it was clear that in the gemcitabine-carboplatin group and the meloxicam-gemcitabine-carboplatin combination group had a significant apoptotic effect ($p<0.05$). The results of the Post hoc Bonferroni analysis also showed that the apoptotic index was significantly difference between the gemcitabine-Carboplatin group and the meloxicam-gemcitabine-carboplatin combination group ($p<0.05$), where the apoptotic index in the meloxicam-gemcitabine-carboplatin combination group was higher than the gemcitabine-carboplatin group. This study showed that the meloxicam-gemcitabine-carboplatin combination group had higher capability for induced bladder TCC apoptosis compared to the gemcitabine-carboplatin group after 24 hours treatment.

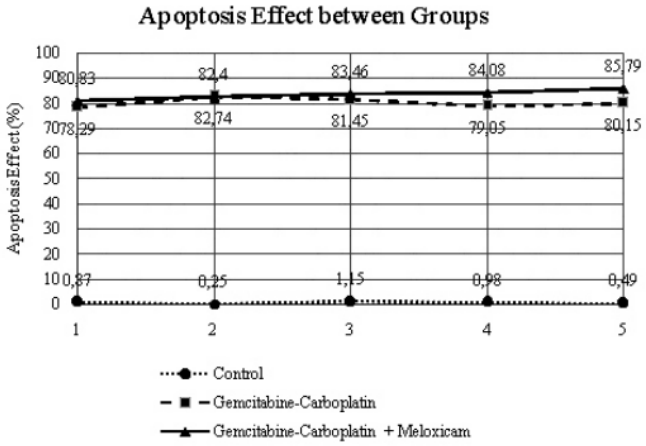


Figure 1. Apoptosis effect between groups.

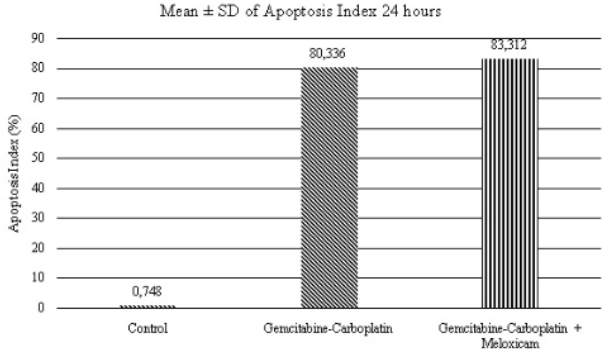


Figure 2. Mean ± SD of apoptosis index.

Table 1. Bonferroni post-hoc of apoptosis index between groups after 24 hours.

Groups	Mean Difference	95% CI		p
		Lower Bound	Upper Bound	
Gemcitabin & Carboplatin vs Control	79.588	76.942	82.233	0.000*
Gemcitabin, Carboplatin, & Meloxicam vs Control	82.564	79.918	85.209	0.000*
Gemcitabin, Carboplatin &Meloxicam vs Gemcitabin & Carboplatin	2.976	0.330	5.621	0.026*

*p<0.05: statistically significant

DISCUSSION

COX-2 can trigger carcinogenesis, tumor proliferation, angiogenesis, prevention of apoptosis and immunosuppressants. Therefore, the addition of COX-2 inhibitors is expected to have a good effect as an anti-cancer therapy.[15] The most often used COX-2 inhibitors as non-steroidal anti-inflammation drugs (NSAIDs) is meloxicam. Several studies suggest that meloxicam as a COX-2 inhibitor can prevent cancer cell proliferation in osteosarcoma, colorectal, hepatocellular, ovarian and glioma cell cancers. Some studies state that meloxicam has a mechanism that prevents the proliferation of cancer cells and

also induces cancer cell apoptosis, DNA damage to cancer cells and increases the cytotoxic effects of anti-cancer regimens.[15,17] Expression of COX will increase the synthesis of prostaglandin E2 (PGE2) and synthesis of bcl-2.[18] The result of that study underlies this study, that meloxicam as COX-2 inhibitor have a role in inhibiting the synthesis of PGE2 and bcl-2 so the apoptosis of cancer cells may occurs.

The combination of several types of drugs that have different working mechanisms as chemotherapy regimens is expected to be more effective and efficient therapeutic protocol. The expected positive synergistic effects are as follow: increasing the efficacy of therapy, finding the optimal dose and reducing the toxicity of the previous chemotherapy regimen, and minimizing drug resistance.[19]

The 5637 cell line was used in this study because 5637 subtype is one of the most commonly found human's bladder cell carcinoma subtype besides T24 type cells. Also, these cells originate from invasive and metastatic bladder cancer.[20] This study discussed about apoptosis index of urothelial carcinoma culture cells using gemcitabine-carboplatin combined with meloxicam. According to Wang et al., study the gemcitabine and carboplatin dose that used based on IC50 were 0.086 µM and 290 µM, respectively,[21] while the meloxicam dose used was 200 µM. The time for apoptosis evaluation was 24 hours because the number of cells that still alive at 48 hours was less than 10%.

MTT was performed to determine the meloxicam dose and the time for apoptosis evaluation. MTT is useful to evaluate the amount of living cells after treatment in percentage. MTT assessment was using Spectrophotometry to determine the optical density. Based on the MTT result, 200 µM meloxicam dose and the time for apoptosis evaluation at 24 hours was chosen. From the result data of the MTT, the number of living cells was 50% (IC50) at a dose of 200 µM meloxicam within 24 hours. The evaluation of apoptosis was not carried out more than 48 hours because the number of alive cells was estimated to be small and difficult to assessed.

This study used 5 cell lines type 5673 replications as control, 5 replications of gemcitabine-carboplatin group, and 5 replications of meloxicam-gemcitabine-carboplatin group on a 24-hour observation. Apoptosis was assessed using TACS 2 TdT DAB, an In Situ Apoptosis Detection Kit from Trevigen® using morphological criteria. Morphological data obtained from microscopes and histochemistry must always be considered in addition to biochemical assessments to assess apoptosis. Methyl green makes the cell specimens can be visualized. The cells that condensate will show an uptake of methyl green. But cells that the chromatin core were fragmented will stained blackish suggesting an apoptosis.

According to several studies, the incidence and the risk of bladder cancer can be reduced by COX-2 inhibitors.[22,23] COX-2 inhibitor also had the effect of increasing apoptosis, decreasing cell proliferation, inhibiting angiogenesis, and increasing the cytostatic effect of anticancer drugs also.[14] This is consistent with this study where the apoptotic index in meloxicam-gemcitabine-carboplatin combination group was higher compared to the gemcitabine-carboplatin group.

This study is also in accordance with the research conducted by De Nardi et al., in 2011 that meloxicam was also shown to be effective in inhibiting malignant cell growth in bone where the study was carried out involving experimental animals.[13,24] Meloxicam also had a significant anti-carcinogenic effect on urothelial carcinoma bladder through the process of inhibiting cell proliferation, increasing apoptosis and also cancer cells DNA damage.[15] All the study above supported this study because meloxicam could increase the apoptosis induce effect and also has anti-carcinogenic effects.

COX-2 inhibitors such as celecoxib, piroxicam and meloxicam can reduce tumor volume associated with increased apoptosis of bladder tumor cells.[25]

Research that conducted on 11 cats with bladder TCC who received meloxicam showed a better clinical outcome compared to the control group. The antineoplastic mechanism in meloxicam as a COX-2 inhibitor works through the apoptotic pathway, inhibits the cycle of cell progression, stimulates immunity and decreases carcinogen activity.[26]

Based on invitro research, the administration of meloxicam to bladder cancer culture cells 5637 can suppress proliferation and increase apoptosis cell count of bladder significantly.[15]

The studies above support that meloxicam can increase the effectiveness of gemcitabine and carboplatin chemotherapy. It was proven by the higher apoptotic effect on the meloxicam-gemcitabine-carboplatin combination group and

differed significantly with the apoptosis index of gemcitabine-carboplatin group.

This study also has several limitations. This study is an in vitro study that not has examined the effect on normal bladder cells, did not use pure drugs, and there has been no research on the combination of meloxicam and gemcitabine-carboplatin before. Therefore, other studies need to be developed to obtain more significant data and evaluate therapeutic, efficacy, and the possible side effects.

CONCLUSION

The combination therapy of meloxicam-gemcitabine-carboplatin has a significantly higher apoptotic effect compared to gemcitabine-carboplatin only.

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