Concomitant Application of Cyclooxygenase-2 Inhibitor and Whole Brain Radiotherapy in Patients with Brain Metastasis

Beyin Metastazlı Hastalarda Eşzamanlı Siklooksigenaz-2 Inhibitörü ve Tüm Beyin Radyoterapi Uygulaması

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ABSTRACT

Objective: Brain metastasis is one of the important causes of morbidity and mortality in cancer patients. One approach for improving local control is applying agents such as cyclooxygenase-2 inhibitor (celecoxib) that enhance radiosensitivity. This study was aimed to evaluate the safety and efficacy of the celecoxib which is delivered concomitant to whole brain radiotherapy in patients with unresectable brain metastasis.
Methods: Thirty patients with brain metastasis, who received whole brain radiotherapy (30 Gy in 10 fractions over 2 weeks) alone or with celecoxib (a dose of 400 mg/day) were evaluated prospectively. Seventeen of 30 patients were in the celecoxib+radiotherapy group compared to 13 patients who were in the radiotherapy only group. The radiological response, neurological and performance status with neurological and hematological toxicities were assessed at the 60th day following radiotherapy.
Results: Mean tumor volume was reduced from 7.9 mm^3 to 3.5 mm^3 in the celecoxib+radiotherapy group. In the radiotherapy only group, we did not observe any changes in mean tumor volume (8.9 mm^3) compared to pretreatment values. The difference of mean tumor volumes between treatment groups was statistically significant (p=0.001). Moreover, objective response ratios were higher in the celecoxib and radiotherapy group (p=0.002). However, the addition of celecoxib to radiotherapy did not improve neurological and performance status significantly. No hematological and neurological toxicities were observed in patients.
Conclusion: Concomitant application of celecoxib with whole brain radiotherapy was found effective and safe in the treatment of brain metastasis. However, further studies are required to validate our results.
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Key Words: Brain metastasis, cyclooxygenase-2 inhibitor, celecoxib, radiotherapy

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ÖZET

Amaç: Beyin metastazı, kanser hastalarında morbidite ve mortalitenin en önemli nedenlerinden biridir. Lokal kontrolü artırmak için yaklaşımlardan biri siklooksigenaz-2 inhibitörü (selekoksib) gibi radyoduyarlılığı artıran ajanları kullanmaktır. Bu çalışma rezeke edilemeyen beyin metastazlı hastalarda tüm beyin ışınlaması ile eşzamanlı kullanılan selekoksibin güvenirliliğini ve etkinliğini değerlendirmeyi amaçlamaktadır.
Yöntemler: Selekoksib (400 mg/günlük doz) ile birlikte veya tek başına tüm beyin ışınlaması (10 fraksiyonda 30 Gy, 2 haftada) alan beyin metastazlı 30 hasta prospektif olarak değerlendirildi. Selekoksib+radyoterapi grubunda olan 30 hastanın 17'si, sadece radyoterapi alan gruptaki 13 hasta ile karşılaştırıldı. Radyoterapi bitiminden sonraki 60'ıncı günde radyolojik yanıt, nörolojik ve performans durumu ile birlikte nörolojik ve hematolojik toksisiteler değerlendirildi.
Bulgular: Selekoksib+radyoterapi grubunda ortalama tümör hacimi 7.9 mm^3'ten 3.3 mm^3'e azaldı. Sadece radyoterapi alan grupta tedavi öncesi değerler ile karşılaştırıldığında ortalama tumor haciminde bir değişiklik gözlenmedi. Tedavi grupları arasındaki ortalama tümör haciminin farkı istatistiksel olarak anlamlıydı (p=0.001). İlaveten, objektif

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yanıt oranları selekoksib ve radyoterapi grubunda yüksek bulundu (p=0.002). Ancak, radyoterapiye selekoksib eklenmesinin nörolojik ve performans durumunu önemli ölçüde düzeltmediği izlendi. Hastalarda hematolojik ve nörolojik toksisite gözlenmedi.
Sonuç: Tüm beyin radyoterapisi ile eşzamanlı selekoksib uygulamasının beyin metastazlarının tedavisinde etkili ve güvenli olduğu bulundu. Ancak, sonuçlarımızı doğrulamak için daha ileri çalışmalara ihtiyaç vardır. *(Gazi Med J 2012; 23: 70-6)*

Anahtar Sözcükler: Beyin metastazı, siklooksigenaz-2 inhibitörü, selekoksib, radyoterapi

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INTRODUCTION

Brain metastasis (BM) is an important cause of morbidity and mortality in cancer patients. At least 60% of patients with BM have neurological deficits that are responsible for poor survival (1-4). Outcomes of patients can be improved by increasing local control of BM (5). There are different treatment options depending on various prognostic factors. The Radiation Oncology Group (RTOG) constituted a classification that was derived from a recursive partitioning analysis (RPA) and three groups of patients were defined according to prognostic factors related to tumor and patient characteristics (6). Patients with Karnofsky performance status (KPS) of ≥70, <65 years with no extracranial metastasis and controlled primary tumor were defined as class I ,with a median survival of 7 months. Patients with KPS <70 were included in class III with a median survival of 2 months; all other patients were in class II having a median survival of 4 months (7-9). The validity of RTOG-RPA prognostic parameters for treatment decision had been confirmed in several studies (7, 9, 10). Patients with a single BM in RPA class I are treated with surgical resection and WBRT. Patients with multiple BM from any RPA classes receive WBRT alone. Patients with two or three BM in RPA class 1 or 2 are treated with single or multiple modalities. Unfortunately, treatment options for these patients are limited. Although surgery and radiosurgery are available for selected patients, whole brain radiotherapy (WBRT) remains the standard therapy option for most of the patients. Median survival is poor with WBRT alone (11). Therefore, clinicians are keenly interested in new target molecules enhancing the sensitivity of tumor cells to radiation, which is needed to improve the outcome.

The prostaglandin signaling pathway is one of the important targets in which modulation of its synthesis can ameliorate the response of tumors to radiation (12). Cylooxygenase (COX) is the key enzyme for synthesis of prostaglandin and it has two forms such as COX-1 and COX-2 (13). COX-2 is over-expressed in malignant and inflamed tissue but it is not detectable in normal tissue (14). In the cell models, it was shown that COX-2 inhibitors has roles in blocking inflammation and the growth of tumor by inhibiting angiogenesis, which has an important role in tumor progression and metastasis (15-19). COX-2 enzyme inhibitors have been used to prevent the development of cancer in several clinical studies (20-21). Moreover, targeting of COX-2 may potentially improve the effects of radiotherapy, chemotherapy or radiochemotherapy (22). In several experimental trials, it was shown that interaction between RT and anti-angiogenic agents might have additive effects on cell death and inhibition of cell growth (23-25). Celecoxib, a selective COX-2 inhibitor, is a member of a new group of anti-inflammatory drugs commonly used in the treatment of arthralgia (26). Recently, it has been demonstrated that it acts as a radiosensitizer in in vivo and in vitro models (23-26). However, its anti-tumor effect has not been studied well in cancer patients. In this study, we aimed to assess the effectiveness and safety of celecoxib in patients with BM via comparing the treatment groups of concomitant use of celecoxib+WBRT and WBRT.

METHODS

Patient Selection

Thirty patients were prospectively randomized into two treatment groups. Seventeen (56%) of 30 patients were in the celecoxib+WBRT treatment group and 13 (44%) patients were in the WBRT treatment group. The inclusion criteria for both groups were as follows: Patients older than 18 years old with histologically confirmed cancer diagnosis and radiologically demonstrated BM. Patients who had not had surgery/radiosurgery for BM or patients who did not receive cranial RT before. All patients were required to have Eastern Cooperative Oncology Group [ECOG] performance status ≤3. Requirement of blood tests for applying celecoxib included the following: granulocyte count $\geq 1.5 \times 10^9$/L, thrombocyte count $\geq 100 \times 10^9$/L, serum creatinine and total serum billurubin <1.5 times the upper limit of normal, alanine amino transferase and aspartate amino transferase <2 times the upper limit of normal.

Patients with small cell lung carcinoma were excluded from both treatment groups. The exclusion criteria for the Celecoxib+WBRT group were as follows: patients who had deep venous/arterial thrombosis, active infection, uncontrolled hypertension or peptic ulcer, cardiovascular or pulmonary disease and chronic hepatic and renal failure.

The data were obtained from patients' files and they were reviewed for gender, age, performance status, neurological function status, primary tumor site, features of brain and other site metastasis, treatment response and patients' outcome. The ethical approval for this study was obtained from Gazi University Clinical Investigations Ethics Committee and all patients signed informed consent form.

Treatment

Radiotherapy was applied to the whole brain in the supine position after immobilization of the patient via a thermoplastic mask. All patients were irradiated with Co60 device at a dose of 30 Gy in 10 fractions, five days per week. Two parallel and opposed fields were used and the reference dose was chosen in the central axis with respect to the middle line. The 400 mg/day celecoxib (Celebrex® capsule, 100-200 mg celecoxib, Pfizer) was delivered concomitant to WBRT and continued with the dose of 200 mg/day following the WBRT until assessment of radiologic response at the 60th day. In the WBRT only group, RT was delivered with the same device, fractionation schedule and treatment planning. Supportive treatment such as anti-convulsions, steroids and anti-emetics were used if they were indicated in both treatment groups.

Evaluation of the Patients

All patients had a baseline assessment including complete physical and neurological examination, evaluation of performance status with ECOG and routine laboratory analysis. Magnetic resonance imaging (MRI) of the whole brain was performed for all patients at least two weeks before WBRT. Physical and neurological examination and assessment of toxicity were performed once a week during WBRT. Two months after completion of WBRT, patients underwent physical and neurological examinations, performance status evaluation and hematological and radiological tests, the same as those obtained at baseline. Additionally, scoring of acute neurological toxicity was performed according to RTOG/EORTC toxicity criteria (27).

According to criteria, there were 4 levels. Level 1 neurological status: Fully functional status with minor neurological finding, no medication needed. Level 2 status: Neurological findings apparent requiring home care/nursing, assessment may be required, medication including steroids or anti-seizure agent may be required. Level 3 status: Neurological finding requiring hospitalization for initial management. Level 4 status: Serious neurological impairment that includes paralysis, coma or seizure >3 per week despite medication/ hospitalization required. Adverse effects other than neurologic toxicity were graded according to the World Health Organization (WHO) criteria (28). Brain tumor response was measured on MR by using the visual metric system (29). Greatest diameter of the tumor gross section and its longest perpendicular diameter were taken into consideration. The area of the lesion(s) was obtained by multiplying the greatest diameter by its longest perpendicular diameter. This area (or sum of the areas if there were multiple lesions) was then used to classify the response into one of four classes. 1) Complete response (CR) was defined as the disappearance of all evidence of active tumor 2) Partial response (PR) was defined as at least a 50% decrease of the cross sectional diameters. 3) Stable disease (SD) was defined as patients with less than 50% decrease or a 25% increase of diameters. 4) Progressive disease (PD) was defined as an increase of more than 25% of the cross sectional diameters, or the appearance of new lesions (29, 30). Tumor volume before treatment was assessed as the reference volume and it was calculated with $\pi/6(xyz)$ ellipsoid where the longest width (X) and lengths (coronal (y) and sagital (z)) in the plane perpendicular to it in axial T1-weigthed MRI images (31).

Statistical Method

Statistical analyses were performed with SPSS (Statistical Package for Social Science) 12.0 version. The x^2 and Fischer exact tests were used to compare the qualitative data and Wilcoxon rank sum test was used to compare the quantitative data. The primary end point of the study was to evaluate the radiological response of BM after treatment. The secondary end point was overall survival (OS). The OS was estimated from the first date of treatment to date of death or last follow-up. The survival analysis was performed by using the Kaplan-Meier method and survival curves were compared by long rank test. P value of ≤0.05 was assessed as statistically significant.

RESULTS

There was no difference between the two groups in terms of patient characteristics. The clinical characteristics of the patients were shown in Table 1.

Radiological Response of Brain Lesions to Treatment

Mean pretreatment tumor volume was 7.9 (minimum 0.56-maximum 27.1) mm^3 for the celecoxib+WBRT group and 8.9 (minimum 0.6-maximum 29.8) mm^3 for the WBRT only group. At the 60^{th} day following completion of RT, a significant shrinkage was observed for the celecoxib+WBRT group. The mean tumor volume was reduced from 7.9 mm^3 to 3.5 (minimum 0.9-maximum 14.6) mm^3. However, no significant improvement was observed in the WBRT group. The mean tumor volume was 8.6 (minimum 0.8-maximum 14.6) mm^3 after treatment. The amount of tumor volume reduction between Celecoxib+WBRT and WBRT groups was found significant (p=0.001). According to radiological response criteria, CR and PR were observed in 3 and 8 patients in the Celecoxib+WBRT group. In the WBRT only group, PR was observed in one patient and CR was observed in none of the patients; most of the patients had stable and progressive disease. Therefore, CR and PR were combined and objective responses (OR) were constituted. Accordingly, OR was observed in 11 (64.7%) patients in the Celecoxib+WBRT group and it was observed in one (7.7%) patient in the WBRT only group. The difference between treatment groups was found significant (p=0.002). The distribution between groups according to responses was shown in Table 2.

Clinical Assessment

For the Celecoxib+WBRT group, level 1 neurological status was observed in 9 (53%) patients and in 14 (82.5%) patients; level 2 neurological status was observed in 4 (23.5%) patients and in 1 (5.8%) patient and level 3 neurological status was observed in 4 (23.5%) patients and in 2 (11.7%) patients at pre- and post-treatment evaluation, respectively. For the WBRT group, level 1 neurological status was observed in 6 (46%) patients and in 8 (61.5%); level 2 neurological status was observed in 5 (38.4%) patients and in 4 (30.7%) patients and level 3 neurological status was observed in 2 (15.6%) patients and in 1 (7.8%) patient at pre and post-treatment evaluation, respectively. Improvement of level 1 neurological status was found significant for the Celecoxib+WBRT group compared to the WBRT group (29.5% vs 15.5%). However, comparison of level 1, 2 and 3 neurological function status between two treatment groups was not significant (p>0.05). Results of neurological function status were summarized in Table 3.

For the Celecoxib+WBRT group, ECOG 0 performance status was observed for none of the patients and for 5 (29.4%) patients; ECOG 1 status was observed for 6 (35.3%) patients and for 4 (23.5%) patients; ECOG 2 status was observed for 7 (41.2%) patients and 8 (47.1%) patients and ECOG 3 status was observed for 4 (41.2%) patients and for none of the patients at pre- and post-treatment assessment, respectively. For the WBRT only group, ECOG 0 performance status was not observed. ECOG 1 status was observed for 3 (23.1%) patients and 4 (30.8%) patients and ECOG 2 status was observed for 9 (69.2%) patients and 8 (61.5%) patients and ECOG 3 status was observed for 4 (41.2%) patients and none of the patients at pre- and post-treatment evaluation, respectively. Improvement of ECOG 0 status was found significant for Celecoxib+WBRT group compared to the WBRT group (29.4% vs 0%). However, comparison of ECOG 0, 1, 2 status between the two treatment groups was not significant (p>0.05). Results of ECOG performance status were summarized in Table 4.

Both in the Celecoxib+WBRT group and in the WBRT only group no difference was observed for biochemical and hematological values before and after the treatment (data was not shown).

Table 1. Patients' characteristics

Characteristics	Celecoxib +WBRT (n=17) n, (%)	WBRT (n=13) n, (%)	p
Median age (years)	57	55	0.44
Sex			
Male	12 (70.5)	8 (61.5)	0.7
Female	5 (29.5)	5 (38.5)	
ECOG performance status			
0	-	-	0.88
1	6 (35.3)	3 (23.1)	
2	7 (41.2)	9 (69.2)	
3	4 (23.5)	1 (7.7)	
Primary tumor site			
Lung (Non-small cell)	8 (47.1)	7 (53.8)	0.63
Breast	5 (29.4)	2 (15.4)	
Colon	1 (5.9)	-	
Head&Neck	1 (5.9)	2 (15.4)	
Unknown	2 (11.8)	2 (15.4)	
Brain metastases			
Single	5 (29.4)	4 (30.7)	0.94
Multiple	12 (70.6)	9 (69.3)	
Other organ metastases			
Hepatic	3 (17.6)	3 (23.1)	0.3
Bone	4 (23.5)	3 (23.1)	
Lung	2 (11.8)	-	
RPA classification			
I	4 (23.5)	6 (46.2)	0.3
II	9 (53)	6 (46.2)	
III	4 (23.5)	1 (7.6)	
Neurological function evaluation			
Level I	9 (53)	6 (46.2)	0.65
Level II	4 (23.5)	5 (38.5)	
Level III	4 (23.5)	2 (15.3)	

WBRT: Whole brain radiotherapy, ECOG: Eastern Cooperative Oncology Group, RPA: Recursive partitioning analyses

Table 2. Radiological response of brain lesions

Radiological Response	Celecoxib+WBRT	WBRT
Complete response	3(17.6)	-
Partial response	8(47)	1(7.8)
Objective response*	11(64)	1(7.8)
Stable disease	5(29.4)	5(38.4)
Progressive disease	1(6)	7(53.8)

WBRT: Whole Brain radiotherapy
*Objective response was constituted by including complete and partial response

Table 3. Evaluation of neurological function status

Treatment Group	Neurological function status					
	Level I		Level II		Level III	
	n	%	n	%	n	%
Celecoxib +WBRT						
Pre-treatment	9	53	4	23.5	4	23.5
Post-treatment	14	82.5	1	5.8	2	11.7
WBRT						
Pre-treatment	6	46	5	38.4	2	15.6
Post-treatment	8	61.5	4	30.7	1	7.8

WBRT: Whole brain radiotherapy

Table 4. Evaluation of ECOG performance status

	ECOG Performance Status							
	Score 0		Score 1		Score 2		Score 3	
Treatment Group	n	%	n	%	n	%	n	%
Celecoxib.+WBRT								
Before Treatment	-	-	6	35.3	7	41.2	4	23.5
After Treatment	5	29.4	4	23.5	8	47.1	-	-
WBRT								
Before Treatment	-	-	3	23.1	9	69.2	1	7.7
After Treatment	-	-	4	30.8	8	61.5	1	3.9

WBRT: Whole Brain Radiotherapy

Overall Survival

Median survival was 8 months (95% Confidence Interval: 6.21-9.79) for the patients in the Celecoxib+WBRT group and it was 6 months (95% Confidence Interval: 4.02-7.98) for the patients in the WBRT only group. Even though the survival result was better for the Celecoxib+WBRT group compared to the WBRT only group, this difference was not statistically significant (p>0.05, Figure 1).

DISCUSSION

Whole brain radiotherapy continues to be the standard treatment of BM. There is still no agreement on the dose-fractionation schedule despite several randomized studies (26). Today, a total of 30 Gy in 10 fractions seemed to be the standard dose-fractionation scheme (32). The local control ratios were reported between the range of 30-50% with this regimen (33). However, the outcome is still poor; 50% of the patients die due to the neurological deterioration and median survival is reported as 3 to 5 months after WBRT (2-4). It is known that if the systemic disease is under control, the controlled intracranial disease increases patient survival (33-36). For this reason, various radiosensitizer agents have been studied for improving local control via increasing the effectiveness of RT, but the findings are variable. In the studies of the RTOG group, no survival advantage was shown by adding radiosensitizer agents such as misonidazol (37) and BudR (38) to RT. A similar result was observed when motexafin gadolinium -redox modulator increasing the apoptosis- had been used (39). In the treatment with temozolomide, which is an alkylating agent used concomitantly with RT, the response rates were found to be higher, however, the result did not have an influence on survival (40). RT plus RSR13-synthetic allosteric (modifying agent of hemoglobin) application provided a decrease in deaths due to BM

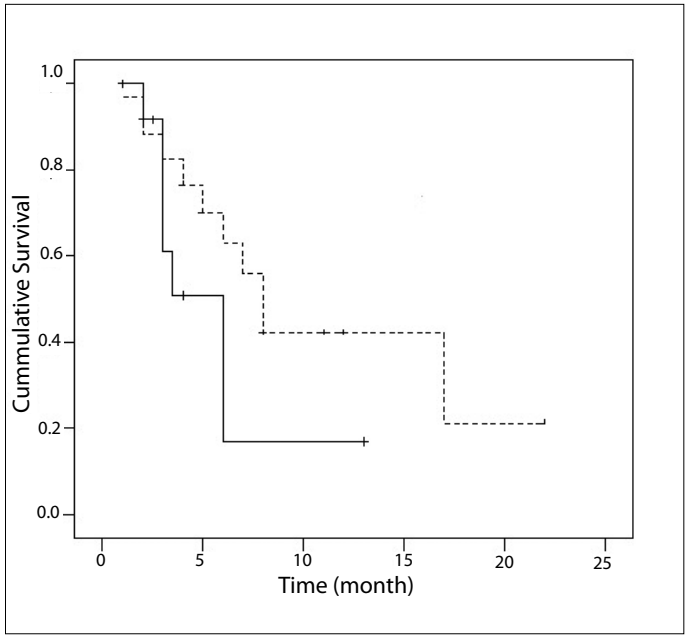

Figure 1. The overall survival curves in the groups of Celecoxib+WBRT and WBRT alone. Dotted line represents the overall survival of Celecoxib+WBRT group and straight line represents the overall survival of WBRT only group

and an increase in survival ratios when compared with class II RTOG BM (41). Based on these data, it is obvious that the benefits of the radiosensitizers has attracted the clinicians and further studies are needed for validating the results and finding new agents.

Recently, COX-2 inhibitors have become the focus of interest for enhancing the effects of radiation, because COX-2 is over-expressed in many types of malignant tumors and their metastasis (15, 42). On the other hand, COX-2 mediates the synthesis of prostaglandin E2- the intermediate product of prostaglandin- which may be associated with radio resistance (42). In the studies which evaluated the non-selective or selective COX-2 inhibitors, it was shown that adding COX-2 inhibitors increases the effectiveness of radiation (23-25, 43, 44). However, there are few preclinical and clinical data that establish the efficiency and safety of concomitant use of selective COX-2 inhibitor and RT in human tumors. Moreover, the most effective dose scheme for celecoxib and radiation is currently unknown (45).

In the animal study by Milas et al. (25), a single dose (25-80 Gy) of gamma radiation and COX-2 inhibitor at a dose of 6 mg/kg was used. It was shown that adding COX-2 inhibitor increased the efficiency of radiation. In the phase I clinical trial by Liao et al. (46), celecoxib at doses of 200 to 800 mg was applied to the patients with non-small cell lung cancer, starting 5 to 7 days before the first fraction of thoracic RT and continuing throughout the course of RT. Although the doses of celecoxib were used as 200, 400, 600, 800 mg/day and given in two equally divided doses; they did not find a difference in toxicity or tumor response among different dose levels of celecoxib. In the phase I/II study by Chercietti et al. (45), 27 patients with measurable BM by CT or MRI and unresectability criteria by a neurosurgeon and RPA-RTOG class II were eligible. During the entire course of RT, celecoxib was applied as 400 mg, once a day, 3 hours before radiation. The WBRT dose was 32 Gy (20 fractions of 1.6 Gy each two times a day) followed by a 22.4 Gy boost (same fractionation schedule) over evident lesions. Radiological responses developed in 72% of the patients with 5 CR. The OR was 66.7%. Their results supported the safety of concomitant use of RT and celecoxib. Although the study was not designed to evaluate the OS, the 8.7 months of median survival time was encouraging (45). Similarly, we found the OR ratio 64.7% and OS time 8 months in the Celecoxib+WBRT treatment group. However, in our study, the WBRT fractionation and dose schedule (a total of 30 Gy in 10 fractions, 3 Gy daily fraction dose) was quite different from Chercietti et al. (45) study. They preferred to use a hyperfractionation regimen to maximize the potential radiosensitizer effect of celecoxib. Hyperfractionated RT increases the antiangiogenic effects of celecoxib, which is a key mechanism in maximizing radiation response. Using this mechanism, the enhanced effects on sublethal cellular repair, redistribution, repopulation, and angiogenesis may result in a therapeutic gain (45). In the results of several RTOG studies, 30 Gy in 10 fractions over 2 weeks became the standard practice and it was shown that there was no survival benefit of accelerated regimen compared with conventionally fractionated WBRT (32, 47). According to RTOG findings, the conventional WBRT regimen was preferred in our department. Additionally, there was a difference between daily application schemes of celecoxib. We applied the same dose of celecoxib (400 mg), but twice a day during WBRT. Although it was reported that the plasma concentration of celecoxib reaches its maximum level 3 hours later after taking the drug, there was no correlation between radiation efficiency and plasma concentration (48, 49). There is insufficient evidence regarding the observation of maximum radiosensitivity when the plasma concentration was at maximum. With these results, in order to provide a constant plasma drug concentration, we preferred to apply the dose every 12 hours.

In this study, the adding of COX-2 inhibitor to WBRT in the treatment of unresectable BM resulted in the increase of radiological responses when compared to WBRT alone. The OR was assessed in 39 lesions of 17 patients in the celecoxib+WBRT group and 30 lesions of 13 patients in the WBRT only group. Although OR rates (CR 17.6%+PR 46%) were higher and statistically significant in the celecoxib+WBRT group, the subjective improvement tendency (neurological and ECOG performance score) was observed but it did not reach statistical significance in the WBRT only group. As in other studies, when RT and drug combination was used, it was seen that this improvement in objective and subjective responses did not improve OS. This finding shows that other parameters, such as the progression of other metastases or primary diseases, have an important effect on determining the survival of patients. Nevertheless, we could not perform a study to examine the survival and response with respect to primary tumor type.

The daily addition of celecoxib to RT was well tolerated. . Although it is known that celecoxib is well tolerated, since it causes several cardiologic problems, its use has been restricted recently (50). We did not encounter any complaint that could be a symptom of cardiologic disease or any sudden death that could not be explained during the therapy. The skin reactions and gastric problems are the other side effects that are observed (48). In the Cerchietti et al. (45) study, they reported that the simultaneous use of a similar dose rate resulted in generalized skin reaction with a rate of 11%. In our patients included into study group, no serious side effect that would lead us to interrupt the therapy was observed. With these data, concomitant use of 400 mg celecoxib with WBRT and maintainance celecoxib dose of 200 mg during 2 months were well tolerated.

CONCLUSION

Celecoxib was effective in the treatment of BM as well as the other studied agents. Although promising, our results need to be interpreted with caution since this study has several limitations. The number of patients in each group was small, limiting the statistical power of the study. Moreover, we did not have long-term results of concomitant use of celecoxib with WBRT in terms of treatment response and side effects. Therefore, additional studies are warranted to confirm our results.

Conflict of Interest

No conflict of interest was declared by the authors.

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