Original Article
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The Long-Term Effects on Recurrence and Progression of Bladder Tumors of Chemotherapeutic Agents Used After Transurethral Resection

Mesane Tümörlerinde Transüretral Rezeksiyondan Sonra Kullanılan Kemoterapötik Ajanların Nüks Ve Progresyon Üzerindeki Uzun Vadeli Etkileri

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ABSTRACT

Objective: Early single dose chemotherapy may have a reducing effect on recurrence and progression. In this study, we aimed to compare non-muscle invasive patients diagnosed with bladder cancer who did not receive early single dose chemotherapy and those who received intravesical Epirubicin or Gemcitabine in terms of recurrence and progression.

Material and Methods: 116 patients were followed up for 48 months (May 2020-June 2022) with diagnosis of primary non-invasive bladder cancer. After transurethral resection of the bladder, patients were followed up with 3 groups: who received intravesical epirubicin, who received gemcitabine, who did not receive any chemotherapeutic agent.

Results: The mean age was 63. There were no statistically significant difference in age and, body mass index. Recurrence was determined 57.1% (n=20), 40% (n=18), and 41.7% (n=15) (p=0.263) of the patients, respectively who were not administered any intravesical agent, were administered Epirubicin and, Gemcitabine. While recurrence rates were observed 50%, 25%, 0% (p=0.177) respectively, in low-risk, no progression was detected. In intermediate risk group, 66.7%, 33.3%, 42.8% (p=0.378) recurrence, and 33.3%, 22.7%, 6.7% (p=0.282) progression were detected, respectively. High-risk group, recurrence was found in 56%, 64.2%, 56.2% (p=0.866) of the patients and progression 8%, 14.3%, 6.3% (p=0.723) respectively. In low-grade group, 35.7%, 42.9%, 21.4% (p=0.045) recurrence, and 16.6%, 12.1%, and 4.3% (p=0.164) progression were determined , respectively. In the high-grade group, 58.8%, 50%, 69.2% (p=0.982) recurrence, 5.9%, 16.6% and 7.7% (p=0.581) progression were detected, respectively.

Conclusion: These findings demonstrated that intravesical chemotherapeutics can delay or prevent recurrence and progression, should therefore be administered in early postoperative period. Gemcitabine is not in widespread use and has been found to be a good alternative.

Keywords: bladder cancer, recurrence, progression, epirubicin, gemcitabine

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ÖZET

Amaç: Erken tek doz kemoterapinin nüks ve progresyonu azaltıcı etkisi olabilmektedir. Çalışmamızda mesane kanseri tanısı almış, erken tek doz kemoterapi almayan ve intravezikal Epirubisin veya Gemcitabin alan kasa invaziv olmayan hastaların nüks ve progresyon açısından karşılaştırılmasını amaçladık.

Gereç ve Yöntemler: Primer non-invaziv mesane kanseri tanısı almış 116 hasta 48 ay (mayıs 2020-haziran 2022) boyunca takip edildi. Mesanenin transüretral rezeksiyonundan sonra hastalar 3 grupta takip edildi: intravezikal epirubisin alanlar, gemcitabin alanlar ve herhangi bir kemoterapi ajanı almayanlar.

Bulgular: Olguların ortalama yaşı 63 idi. Hastalarda yaş ve vücut kitle indeksi arasında istatistiksel olarak fark yoktu. Herhangi bir intravezikal ajan uygulanmayan, Epirubisin, Gemcitabine uygulanan hastalarda sırasıyla %57,1 (n=20), %40 (n=18) ve %41,7 (n=15) (p=0,263) oranında nüks saptandı. Düşük riskli grupta nüks oranları sırasıyla %50, %25, %0 (p=0,177) olarak gözlenirken, progresyon saptanmadı. Orta riskli grupta ise sırasıyla %66,7, %33,3, %42,8 (p=0,378) nüks, %33,3, %22,7, %6,7 (p=0,282) oranında progresyon saptandı. Yüksek riskli grupta ise hastaların sırasıyla %56, %64,2, %56,2'sinde nüks (p=0,866), %8, %14,3, %6,3'ünde (p=0,723) progresyon saptandı. Düşük dereceli grupta sırasıyla %35,7, %42,9, %21,4 nüks (p=0,045) ve %16,6, %12,1 ve %4,3 (p=0,164) progresyon saptandı. Yüksek dereceli grupta sırasıyla %58,8, %50, %69,2 nüks (p=0,982), %5,9, %16,6 ve %7,7 (p=0,581) progresyon belirlendi.

Sonuç: Bu bulgular, intravezikal kemoterapötiklerin nüks ve progresyonu geciktirebileceğini ve/veya önleyebileceğini, bu nedenle erken postoperatif dönemde uygulanması gerektiğini göstermiştir. Gemsitabin yaygın kullanımda olmayıp alternatif olarak iyi bir tercih olduğu görülmüştür.

Anahtar Kelimeler: mesane kanseri, nüks, progresyon, epirubisin, gemcitabine

INTRODUCTION

All types of cancers are known to be increasing all over the world depending on lifestyles and environmental conditions. Bladder cancer is the tenth most commonly diagnosed cancer in all genders (1). Approximately 75% of transitional epithelial cancer of the bladder is a disease with mucosa (stage Ta or carcinoma in situ) or submucosa (stage T1) involvement and is defined non-muscle invasive bladder cancer (NMIBC) (2).

Tumor resection is the main treatment approach in superficial bladder cancers, and recurrence or progression is relatively common during follow-up according to grade and stage. There is a risk of frequent recurrence in NMIBC. Moreover it can advance to a life-threatening disease (3). Therefore, a scoring system developed by the European Organization for Research and Treatment of Cancer (EORTC) defining risk groups to be able to monitor patients and facilitate the treatment process. Risk factors for recurrence and progression are multifocality, tumor size, number of previous recurrences, grade, stage, and presence of carcinoma in situ (CIS) (4). It has been well known for many years that various intravesical chemotherapeutic agents are used and different protocols are applied after resection of superficial bladder tumors. The current guidelines recommend that early single-dose intravesical chemotherapy should be administered after resection to prevent or delay recurrence and progression. Intravesical chemotherapy has an ablative effect on small tumors that remain in the resection area, which have been missed following transurethral resection of the bladder (TURB) (5).

In this study it was aimed to compare progression and recurrence rates of patients with bladder tumor who were administered intravesical Epirubicin or Gemcitabine or who did not receive any early single-dose chemotherapy.

MATERIAL AND METHODS

This was a prospective, cross sectional study. It was conducted at Sivas Cumhuriyet University from May 2020 to June 2022 after obtaining the local ethics committee's approval, with decision number 2020-05/02.

Between 2020 and 2022, a total of 116 primary consecutive patients with the diagnosis of superficial bladder cancer were followed up for 48 months. All patients diagnosed with superficial bladder cancer who were eligible for the study between the specified dates were included. All patients were evaluated by cystoscopy. The data were evaluated according to the pathology results and included in the study.The patients were separated into 3 groups randomly: Those who did not receive any intravesical chemotherapy (n:35), those who received Epirubicin (n:45), and those who received Gemcitabine (n:36). Also a subdivision made to the patients into 3 groups as low, intermediate, and high risk, and 2 groups according to the degree of invasiveness as high grade and low grade. These groups were formed based on the risk scale of the EORTC. Follow-up of the patients was done by cystoscopy at 3-month intervals.

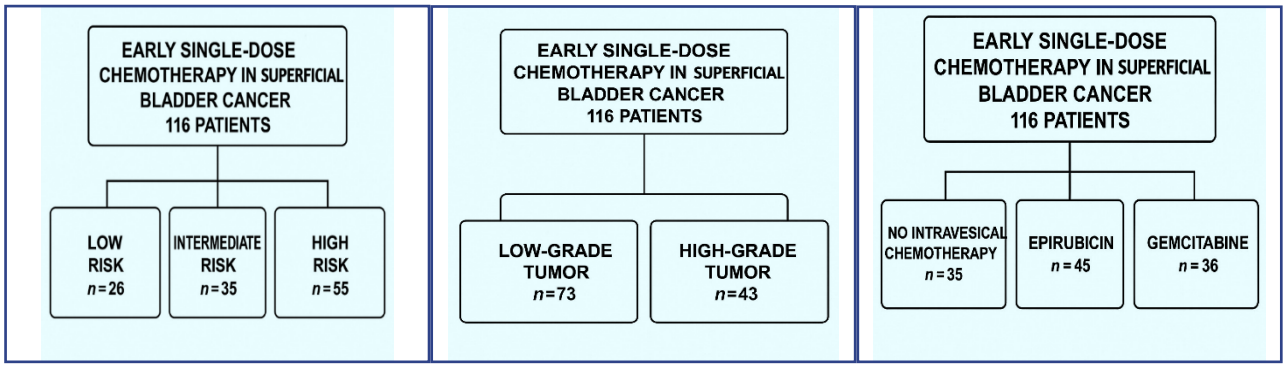

Figure 1. Classification of 116 patients receiving early single-dose chemotherapy according to risk groups, grade and whether they received treatment or not

Inclusion Criteria of Patients

We included patients in whom we performed resection with the TUR method and did not deepen the resection too much, patients whose hematuria was not very intense after resection, and patients who allowed intravesical chemotherapy in our study.

Exclusion Criteria of Patients

We did not include patients with previous bladder tumor surgery and variant pathology, patients with a history of chemotherapy and radiotherapy applied to the bladder, and patients with T2 or higher pathology in 59 of the 175 patients in whom we performed resection with the TUR method.

Approximately 1 hour after the bladder tumor resection which was performed with the conventional method: 50 mg of Epirubicin was prepared with 50 ml of saline and then administered intravesical via a 22f Foley catheter. 2000 mg of Gemcitabine was prepared with 100 ml of saline and then administered intravesical via a 22f Foley catheter. Intravesical chemotherapeutic agent was not administered to patients who had grade 2 or grade 3 perforation during TURB according to the Depth of Endoscopic Perforation (DEEP) scale, had extensive hematuria, or did not accept intravesical early single-dose chemotherapy treatment. These patients who did not administered any intravesical chemotherapeutic agent were included in the 1st group.

Statistical Analysis

Statistical analysis of the data obtained in the study was performed using SPSS vn. 22.0 software. The categorical variables were presented as numbers (n) and percentages (%). All the continuous variables were analysed and expressed by mean ± standard deviation. Conformity of continuous data to normal distribution was examined with the Shapiro-Wilk test and the results showed that the disstribution of continuous variables was not normal ($p<0.05$). The Kruskal-Wallis H test was applied in multiple comparisons. The Mann-Whitney U-test was used again in posthoc

analyses. Categorical data were examined with Chi-square analysis. At the same time, Breslow test results were interpreted to interpret the tests on the survival of patients**.** All the analyses were interpreted at 95% confidence level. A value of p below 0.05 was accepted as statistically significant.

RESULTS

Evaluation was made of patients who did not receive early single-dose intravesical chemotherapy, patients who were administered intravesical Epirubicin, and those who were administered intravesical Gemcitabine in terms of progression and recurrence in bladder tumors. The groups were compared in respect of the time to recurrence and progression. The difference between the groups were not statistically significant. (Table 1).

Table 1. Comparisons of the treatments of bladder tumor in terms of recurrence(63) and progression (12), and the time elapsed (months) in patients with recurrence and/or progression

	No IV Treatment	Epirubicin	Gemcitabine	p Value
Recurrence (+ / n) %	15/35 42.90%	27/45 60.00%	21/36 58.30%	0.263[a]
Time To Recurrence (Median) (Min / Max Months)	 3.8 3/5	 5.3 3/7	 18.1 3/24	0.234[b]
Progression (+ / n)	4/35 11.40%	6/45 13.30%	2/34 5.60%	0.505[a]
Time To Rogression (Median) (Min / Max Months)	9.1 4/13	11.9 9/16	21.2 3/42	0.486[b]

a: Chi-Square Test

b: Kruskal-Wallis H Test

Recurrence times were compared with the Breslow test and recurrence times were not statistically different according to intravesical use or intravesical type (p=0.095). For the whole patient group, the time to recurrence was 6.698 months (hazard ratio (HR): 0.40; 95% confidence interval (CI), 4.100-9.296; p<0.001), as 4.059 months (HR: 0.41; 95% CI, 2.977-5.141; p<0.001) in Group 1, patients not administered intravesical agents, 5.188 months (HR: 0.25; 95% CI, 3.234-7.141; p<0.001) in Group 2, patients administered Epirubicin, and 13.6 months (HR: 0.30; 95% CI, 3.865-23.335; p<0.001) in Group 3, patients administered Gemcitabine.

The patients were separated into three groups as low risk, intermediate risk, and high risk. The groups with and without chemotherapeutic agents were compared in terms of progression and recurrence. No statistically significant difference was found. (Table 2).

Table 2. Comparisons of the patient risk groups in terms of recurrence and progression in patients with and without IV agents, time to recurrence (months), and time to progression (months)

Risk Groups	Recurrence			p value (recurrence) p value (time)	Risk Groups	Progression			p value (progression) p value (time)
	No IV Treatment	Epirubicin	Gemcitabine			No IV Treatment	Epirubicin	Gemcitabine	
Low Risk					Low Risk				
(+ / n)	2/4 50%	4/16 25%	0/6 0%	0.177[a]	(+ / n)	0/4 0%	0/16 0%	0/6 0%	-
Time to recurrence (min-max month)	3/9	4/18	0	0.248[b]	Time to progression (min-max month)	0	0	0	-
Intermediate Risk					Intermediate Risk				
(+ / n)	4/6 66.6%	5/15 33.3%	6/14 42.8%	0.378[a]	(+ / n)	2/6 33.3%	4/15 26.6%	1/14 7.1%	0.282[a]
Time to recurrence (min-max month)	3/8	3/9	4/21	0.462[b]	Time to progression (min-max month	6/15	9/13	42	0.325[b]
High Risk					High Risk				
(+ / n)	14/25 56%	9/14 64.2%	9/16 56.2%	0.866[a]	(+ / n)	2/25 8%	2/14 14.2%	1/16 6.2%	0.723[a]
Time to recurrence (min-max month)	2/5	3/9	4/24	0.241[b]	Time to progression (min-max month	2/11	16/27	3	0.223[b]

a: Chi-Square Test

b: Kruskal-Wallis H Test

The compare means kruskal-wallis h test and chi-square test was applied

Then compared in terms of progression and recurrence. Low-grade bladder tumor patients were compared with and without intravesical chemotherapy, and a statistically significant difference was determined between these subgroups in terms of recurrence and progression ($p<0.05$). The comparisons between the other groups demonstrated no statistically significant difference (Table 3).

Table 3. Comparisons of patients histologically classified as low grade and high grade, who received and did not receive IV chemotherapeutic agents in terms of recurrence and progression, time to recurrence (months), and time to progression (months)

	RECURRENCE				PROGRESSION			
	NO IV TREATMENT	EPIRUBICIN	GEMCITABINE		NO IV TREATMENT	EPIRUBICIN	GEMCITABINE	
GRADE of INVASION				p value (recurrence) p value (time)				P value (progression) p value (time)
LOW GRADE					LOW GRADE			
(+ / n)	9/18 50%	10/33 30%	3/22 13.6	0.045[a]	(+ / n)	3/18 16.6%	4/33 12.1%	1/22 4.5%	0.164[a]
Time to recurrence (min-max months)	3/7	3/9	6/36	0.091[b]	Time to progression (min-max months)	6/15	9/13	(4/2)	0.999[b]
HİGH GRADE					HİGH GRADE			
(+ / n)	9/17 5.2%	6/12 50%	7/14 50%	0.982[a]	(+ / n)	1/17 5.8%	2/12 16.6%	1/14 7.1%	0.581[a]
Time to recurrence (min-max months)	3/3	3/4	3/9	0.301[b]	Time to progression (min-max months)	2/2	12/27	3/3	0.368[b]

a: Chi-Square Test
b: Kruskal-Wallis H Test

The compare means kruskal-wallis h test and chi-square test was applied

The Breslow test was applied to compare the times to recurrence times, and a statistically significant difference was determined according to grade (low/high), intravesical use, and intravesical type ($p=0.029$). The time to recurrence in all low-grade patients was calculated to be 7.864 months (HR: 0.32; 95% CI, 4.463-11.264; $p<0.001$), as 5.111 months (HR: 0.33; 95% CI, 3.529-6.693; $p<0.001$) in Group 1, (no intravesical chemotherapy), as 6.100 months (HR: 0.30; 95% CI, 3,260-8,940; $p<0.001$) in Group 2 (Epirubicin), and as 22.0 months (HR: 0.33; 95% CI, 4.913-39.087; $p<0.001$) in Group 3 (Gemcitabine).

The time to recurrence in all high-grade patients was found to be 5.476 months (HR: 0.19; 95% CI, 1.508-9.444; $p<0.001$), as 2.875 months (HR: 0.62; 95% CI, 1.865-3.885; $p<0.001$) in Group 1 (no intravesical chemotherapy), as 3.667 months (HR: 0.33; 95% CI, 1.796-5.538; $p<0.001$) in Group 1 (Epirubicin), and as 10.0 months (HR: 0.14; 95% CI, 0.00-21.564; $p<0.001$) in Group 3 (Gemcitabine).

DISCUSSION

The global age-standardised incidence rate is 9.5 for males and 2.4 for females (per 100,000 person/years). These rates are 20 for males and 4.6 for females in the European Union. Despite significant advances and changes in the field of molecular and technology science, TURB remains the first approach in the treatment and diagnosis of primary bladder cancers. The most prominent clinical features of NMIBC are that it is progressive and recurrent. After TURB, the probability of recurrence within 1 year in low-risk patients is 15%, and 31% within 5 years. In high-risk patients, the

probability of recurrence is 61% within 1 year and 78% within 5 years. For high-risk NMIBC the probability of 1-year progression patients is 3.5% and probability of annual progression is 9.6%. For very high-risk NMIBC the probability of 1-year progression patients is 16.5%, and probability of annual progression is 40% (6).

Epirubicin, one of the anticancer agents of the anthracycline group, is a periodic, non-specific anticancer agent. Its mechanism of action is to prevent DNA replication and transcription by controlling polymerase (7). Due to powerful anticancer activity, low drug resistance, rapid diffusion, and low toxicity, Epirubicin is a highly preferred intravesical chemotherapeutic agent (8). In a study of a total of 512 patients by Oosterlink et al., intravesical Epirubicin was administered to 50.2% of the patients after TURB, and not to 49.8%. In the cystoscopic examination performed on the patients 4 weeks later, recurrence was observed in 3.9% of the patients, and it was seen that only one of the patients who developed recurrence was from the Epirubicin group (9). In the current study, intravesical Epirubicin was administered to 38.7% of patients after TURB, while intravesical treatment was not applied to 30% of patients. In the cystoscopic examination performed 3 months later, recurrence was seen to have developed in 15.5% of the patients who received Epirubicin and in 17.2% of the patients with no intravesical treatment. The reason for the higher recurrence rate in the current study in the group treated with Epirubicin was thought to be the earlier performance of first cystoscopy by Oosterlink et al., or that the majority of patients who received Epirubicin in the current study were at moderate or high risk.

In contrast, Masters et al.'s clinical study stated that a 42% complete response was obtained in 122 patients in 3 months with a single Epirubicin administration on a 0.5 cm tumor (10). That study demonstrated that early single-dose intravesical chemotherapy prevents recurrences by both chemoresection and preventing implantation. In the present study, patients with bladder tumors of a small size (<3 cm) and those with a single tumor were in the low-risk group, constituting 22.4% of the total patients. Epirubicin was administered to 61.5% of these patients, and no intravesical treatment was applied to 15.4%. Recurrence developed in 25% of the patients who received Epirubicin and in 50% of the patients with no intravesical treatment, thereby demonstrating that Epirubicin administration reduced the likelihood of recurrence proportionally.

Sylvester et al.'s study examined 13 publications with 2278 patients. Of the 1161 patients treated with TURB only, and 1117 patients with Pirarubicin, Epirubicin, Thiotepa, or Mitomycin C, recurrence was seen in 1128 patients. ($p<0.001$). Single-dose chemotherapy was administered IV to 42.5% of the patients with recurrence, and no intravesical treatment was administered to 56.2% of the patients. A single dose of chemotherapy which administered intravesically reduced the likelihood of recurrence by 35% (11). In the current study, Epirubicin or Gemcitabine was administered to 86 of 116 patients, and recurrence occurred in 36% of the patients. No intravesical agent was administered to 30.1% of the patients and recurrence developed in 57.1%. These results can be interpreted as Epirubicin and other IV chemotherapeutics being very advantageous in terms of preventing recurrence compared to patients not administered with intravesical chemotherapeutic agents.

Gemcitabine is anticancer agent a pyrimidine antimetabolite, which replication disrupts cell by acting on the cell cycles S phase (12). Although Gemcitabine and Epirubicin differ in terms of the mechanism of action, both show antitumor activity through interference in the division of tumor cells. Gemcitabine, which is widely used in many different types of cancer, is also used in the treatment of urological cancers. In a clinical study of 86 patients followed up for 36 months, Ye HB et al. compared Epirubicin and Gemcitabine. Of the total patients, 48.9% were administered Gemcitabine and 51.1% received Epirubicin. The results from a 2-year follow-up period showed that recurrence developed in 33.3% of the patients who received Gemcitabine and in 40.1% of the patients who received Epirubicin (13). In the final of the 4-year follow-up period of the current study, recurrence was seen to have developed in 40% of the patients administered Epirubicin and in 41.6% of the patients administered Gemcitabine. Both studies showed no statistically significant difference.

Gemcitabine and physiological saline application were compared 406 patients in a study by Messing et al. Gemcitabine was administered as a single dose to 49.5% of the patients, and intravesical irrigation with saline solution was applied to 50.5% of the patients. Tumor recurrence occurred within 4 years in 33.3% of the patients administered Gemcitabine and in 44.4% of the patients treated with saline irrigation ($p<0.001$). Of the 215 patients with low-grade tumors who had undergone TURB, recurrence developed in 33.3% of the patients in the Gemcitabine group and in 52.2% of the saline solution group ($p=0.001$) (14). In the current study, 36 patients were administered Gemcitabine, and recurrence developed in 41.6% of these patients during the 4-year follow-up period ($p<0.001$).

Of the 73 patients with low-grade NMIBC in the current study, 8.2% of those who received Gemcitabine developed recurrence. It was determined that Gemcitabine administered to patients with low-grade bladder tumors statistically significantly reduced the probability of recurrence compared to those who were not administered any intravesical agents. These results were consistent with findings of Messing et al. ($p<0.001$), and Gemcitabine administration was shown to be beneficial, especially in patients with low-grade NMIBC.

NMIBC is a heterogeneous group of tumors, each exhibiting different behavior. To predict the behavior of these heterogeneous groups, namely tumor recurrence, and progression, the EORTC developed a scoring system with risk groups defined accordingly. Patients are classsified as low risk, intermediate risk, or high risk according to the probability of progression and recurrence. Zhang et al. followed up 335 patients for 4 years, with Epirubicin administered to 32.5%, Gemcitabine to 34%, and Pirarubicin to 33.5%. The patients were separated into high risk and intermediate risk groups according to the risk of NMIB tumor. Of the patients treated with Epirubicin, 38.5% were classified as intermediate-risk and 61.5% as high-risk, 28.9% of the patients treated with Gemcitabine were classified as intermediate-risk and 71.1% as high-risk, and 33.9% of the patients treated with Pirarubicin were classified as intermediate-risk and 66.1% as high-risk. The intermediate risk groups recurrence was 7.1% of patients with Epirubicin treatment, 6% of patients with Gemcitabine treatment, and 7.8% of patients with Pirarubicin treatment. In the high-risk group, recurrence developed in 10.4% of patients treated with Epirubicin, 3.7% of patients treated with Gemcitabine, and 13.1% of patients treated with Pirarubicin. The intermediate-risk groups recurrence after administration of all three chemotherapeutic agents was not statistically significant. The high-risk groups rate of recurrence in the Gemcitabine treatment group was determined to be lower statistically significantly compared to the other chemotherapeutic agents ($p<0.017$) (15). In the current study, the intermediate-risk group included 35 patients and the high-risk group included 55. Epirubicin was administered to 42.9% and Gemcitabine to 40% of the intermediate-risk patients, and Epirubicin was administered to 25.5% and Gemcitabine to 29.1% of the high-risk patients. In the intermediate-risk group, recurrence developed in 38.5% of patients administered Epirubicin and in 30.8% of patients administered Gemcitabine. In the high-risk group, 33.3% of patients administered Epirubicin and 22.2% of patients administered Gemcitabine developed recurrence. In terms of recurrence between the intermediate-risk and high-risk groups no statistically significant difference was determined. However, it was observed that administration of Gemcitabine decreased the recurrence probability proportionally.

Early single-dose intravesical chemotherapy does not change the progression and cancer-related death rate (11). Messing et al. compared the administrations of Gemcitabine and saline in terms of progression. A single dose of intravesical chemotherapy with Gemcitabine was administered to 201 patients, and intravesical irrigation with saline was applied to 205 patients. Progression developed in 5.9% of the patients administered Gemcitabine and in 8.8% of those administered saline irrigation. No statistically difference significant was determined in terms of the effect of early single-dose intravesical chemotherapy on progression ($p=0.25$) (14). In the current study, 31% of 116 patients were administered Gemcitabine, 38.9% were administered Epirubicin, and 30.1% received no intravesical chemotherapy. Progression developed in 5.6% of the patients who received Gemcitabine, in 13.3% of the patients who received Epirubicin, and in 11.4% of those who did not receive any intravesical chemotherapy. Intravesical single-dose chemotherapy was not found to be statistically significant in terms of progression, and similar results were obtained

in the other groups (p=0.244). Sylvester et al.'s meta-analysis from 13 publications of 2278 patients demonstrated that 1161 patients were treated with only TURB, and 1117 patients were administered Epirubicin, Mitomycin C, Pirarubicin, or Thiotepa, and progression developed in 4.8% of the total patients (11). The advantage of intravesical chemotherapeutic agent administration in preventing progression has not been proven, but it appears to reduce the probability of progression proportionally. In the current study, it was observed that Gemcitabine administration reduced the probability of progression more proportionally than Epirubicin.

There is a relatively limited number of comparative studies in the literature. Epirubicin, Gemcitabine, and Pirarubicin administered to 335 patients were compared over a 4-year follow-up period by Zhang et al., and the results showed complications of 8.7% of the patients with hematuria, 2.7% with fever, and 11% with bladder irritation symptoms (15). In the current study, no major complications developed in any of the patients. Of the patients treated with Epirubicin, 6.7% had hematuria and 11.1% had bladder irritation symptoms (urgent urination sensation, detrusor hyperactivity, pain due to contraction). In the patient group treated with Gemcitabine, 2.8% had hematuria and 2.8% had bladder irritation symptoms. No patient had a fever. A clearer evaluation would be able to be made with data obtained from more patients, but the possibility of complication development in patients who received Gemcitabine was seen to be reduced.

In comparison with patients not receiving any intravesical chemotherapy, there are clear benefits of single-dose chemotherapy administered intravesically after TURB. To be able to decide which patients will benefit most or least from intravesical chemotherapy and to reveal clearer results, the keeping of optimal records regarding intravesical chematheraputic agents used immediately after resectıon, reporting the known risk factors for the progression and recurrence of bladder cancer, classifying the study results according to risk groups, studying more patients and collecting data more systematically are necessary.

Limitations of this study can be said to be the relatively short time to follow up for recurrence and progression, and the low number of patients. Despite these limitations, the strength of the study is that it shows that gemcitabine is more effective in low-grade, non-muscle-invasive tumors and should be used more widely. Patients continue to be followed up in our clinic, and a further study is planned in which more precise results will be able to be obtained by including new patients.

CONCLUSION

A single dose of early postoperative intravesical chemotherapy is effective against circulating tumor cells and residual tumors in the resection area after TURB. Even if the lesion is completely resected after TURB, intravesical chemotherapeutic agents delay and even prevent short-term recurrence and progression, and should be applied in the early postoperative period.

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Conflicts of Interest: The authors declare no conflicts of interest.

Ethical Consideration: The study was authorized by the Ethics Committee at the Faculty of Medicine, Cumhuriyet University, on the date of 05/20/2020 With ethical number: 2020-05/02.

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