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BRCA1 mRNA expression and outcome to neoadjuvant cisplatin-based chemotherapy in bladder cancer

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Background: Neoadjuvant chemotherapy has shown a modest benefit in muscle-invasive bladder cancer patients; however, the subset of patients most likely to benefit has not been identified. BRCA1 plays a central role in DNA repair pathways and low BRCA1 expression has been associated with sensitivity to cisplatin and longer survival in lung and ovarian cancer patients.

Patients and methods: We assessed BRCA1 messenger RNA expression levels in paraffin-embedded pre-treatment tumor samples obtained by transurethral resection from 57 patients with locally advanced bladder cancer subsequently treated with neoadjuvant cisplatin-based chemotherapy. BRCA1 levels were divided into terciles and correlated with pathological response and survival.

Results: A significant pathological response (pT0-1) was attained in 66% (24 of 39) of patients with low/intermediate BRCA1 levels compared with 22% (4 of 18) of patients with high BRCA1 levels ($P = 0.01$). Median survival was 168 months in patients with low/intermediate levels and 34 months in patients with high BRCA1 levels ($P = 0.002$). In the multivariate analysis for survival, only BRCA1 expression levels and lymphovascular invasion emerged as independent prognostic factors.

Conclusions: Our data suggest that BRCA1 expression may predict the efficacy of cisplatin-based neoadjuvant chemotherapy and may help to customize therapy in bladder cancer patients.

Key words: bladder cancer, BRCA1 mRNA expression, cisplatin, customized chemotherapy, pathological response, prognostic marker

introduction

Cystectomy with pelvic lymph node dissection remains the mainstay of treatment of muscle-invasive bladder cancer. However, ~50% of patients will develop distant metastases after surgical treatment and die of the disease [1]. This prognosis worsens in tumors involving perivesical fat or adjacent organs (cT3b-4) and those with lymph node involvement. In these patients, cystectomy alone offers a cure rate of only 20%–30% [2–4].

Based on the proven efficacy of cisplatin-based chemotherapy in advanced bladder cancer [5], neoadjuvant chemotherapy has been explored in invasive bladder cancer [6]. In the largest neoadjuvant trial, carried out by European Organization for Research and Treatment of Cancer/Medical Research Council (UK), 976 patients with muscle-invasive bladder cancer were randomly assigned to receive either neoadjuvant chemotherapy with cisplatin, methotrexate, and vinblastine (CMV) or no chemotherapy, followed by local therapy (cystectomy or radiotherapy). An improvement of 6% (50% versus 44%) was observed in 5-year survival in patients treated with neoadjuvant chemotherapy [7, 8]. In a more recent Southwest Oncology Group randomized trial (SWOG 8710) in patients with muscle-invasive bladder cancer stage cT2–4N0M0, neoadjuvant chemotherapy with methotrexate, vinblastine, doxorubicin, and cisplatin (M-VAC) led to a significant improvement in median survival (77 versus 46 months), with a reduction in estimated risk of death of 25% compared with cystectomy alone [9]. Moreover, in two meta-analyses, each including >2600 patients from randomized trials, a positive but modest benefit for neoadjuvant chemotherapy was observed, with an absolute improvement in survival of 5%–6.5% with cisplatin-based chemotherapy [10, 11]. In spite of these results, neoadjuvant chemotherapy is not a standard approach in many institutions [12, 13] due to many factors,

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including treatment-related toxicity, the potential negative impact of delaying cystectomy in chemorefractory patients [14, 15], and the absence of predictive markers to identify patients who will respond to neoadjuvant chemotherapy. There are no baseline clinical characteristics that help us to predict response to neoadjuvant treatment, but it is well established that patients who obtain a pathological complete response (pCR) after chemotherapy have a higher probability of long-term survival than those with residual tumors in the cystectomy tissue [9]. Unfortunately, we are still not able to predict which patients will fall into each prognostic group.

The breast cancer susceptibility gene 1 (BRCA1) encodes a 220-kDa nuclear protein that responds to DNA damage by participating in multiple biological processes, including gene transcription, DNA damage repair, cell growth, and apoptosis [16]. In response to DNA damage, BRCA1 is recruited to the sites of DNA breaks, modulating radioresistance and chemoresistance through its important role in transcription-coupled nucleotide excision repair, homologous recombination repair, and nonhomologous end joining [17]. Decreased BRCA1 messenger RNA (mRNA) expression in breast cancer cell lines increases sensitivity to cisplatin and resistance to antimicrotubule agents, like paclitaxel, vinorelbine, and vincristine [18, 19]. Moreover, low BRCA1 levels were associated with a better prognosis to cisplatin-based chemotherapy in ovarian [20] and non-small-cell lung cancer (NSCLC) [21].

In order to investigate the predictive role of BRCA1 mRNA expression in invasive bladder cancer, we retrospectively analyzed tumor samples from bladder cancer patients treated with neoadjuvant cisplatin-based chemotherapy and correlated BRCA1 levels with pathological response to chemotherapy and overall survival.

patients and methods

patients

Between 1991 and 2007, 98 patients with muscle-invasive locally advanced bladder cancer were treated with neoadjuvant chemotherapy in our institution. After transurethral resection (TUR), all patients were clinically staged by chest X-ray and computerized tomography (CT) of the abdomen and pelvis. Only patients with locally advanced tumors with extravesical disease (T3–4 and/or regional lymph nodes) were candidates for neoadjuvant chemotherapy, and the final decision was based on the consensus of the attending urologist and medical oncologist. Patients were required to have no serious alteration in hematologic, renal, and hepatic functions and a performance status (PS) of zero to two. Patients received a median of three cycles of cisplatin-based chemotherapy. Patients were treated with CMV from 1991 to 2000 and with cisplatin plus gemcitabine from 2001 to 2007. After chemotherapy, patients were restaged with a CT scan of the abdomen and pelvis and a cystectomy was carried out if feasible. The study was approved by the institutional ethics review board for gathering all materials and patient data.

BRCA1 mRNA expression

Tumor tissue was obtained from TUR before the administration of neoadjuvant chemotherapy. BRCA1 mRNA expression was assessed in formalin-fixed paraffin-embedded tumor tissue from 57 patients; in the remaining 41 patients, tumor tissue was unavailable or insufficient for BRCA1 assessment. Intratumoral BRCA1 mRNA expression levels were assessed by real-time quantitative polymerase chain reaction (RT-PCR). Total RNA was isolated after laser-capture microdissection that ensured a minimum of 90% of tumor cells. In previous validation experiments (M. Taron, unpublished data), we had found that the minimum number of tumor cells required for BRCA1 expression analysis was 4400 cells, which corresponds to an average of 2.2 mm^2 of tumor tissue from a section of 4 μ. This was the median number of microdissected cells in the paraffin-embedded tumor tissues used in this study. After deparaffination with standard xylene and alcohol process, samples were subjected to lysis in a buffer containing Tris–chloride, EDTA, sodium dodecyl sulfate, and proteinase K. RNA was then extracted with phenol–chlorofrom–isoamyl alcohol followed by precipitation with isopropanolol in the presence of glycogen and sodium acetate. RNA was resuspended in diethyl pyrocarbonate water (Ambion Inc., Austin, TX) and treated with DNAse I to avoid DNA contamination. Complementary DNA (cDNA) was synthesized using M-MLV retrotranscriptase enzyme. Template cDNA was added to TaqMan Universal Master Mix in a 12.5-ml reaction with specific primers and probe for each gene. The endogenous reference gene was β-actin. Gene expression was quantified using the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, CA) [22].

statistical analyses

Median values and ranges were calculated for quantitative variables and gene mRNA expression. Qualitative variables were summarized by absolute frequencies and percentages. In order to provide an easily interpretable evaluation of the effect of BRCA1 mRNA expression, gene expression values were divided into terciles. Hazard ratios were calculated with the univariate Cox model, and Kaplan–Meier survival curves were compared with the log-rank test. All tests of statistical significance were two sided, with a statistical power of 80%, and significance was set at 0.05. For potential multiple comparisons, the *P* values were corrected with the Bonferroni correction. Analyses were carried out using Statistical Package for the Social Sciences (SPSS) for Windows version 17 (SPSS Inc., Chicago, IL) and S-Plus 6.1 for Windows.

results

patient characteristics

Table 1 shows the clinicopathologic characteristics for all patients (98), for the 57 patients in whom BRCA1 mRNA expression was analyzed, and for the 41 patients with insufficient tumor tissue for BRCA1 assessment. No differences were observed between patients in whom BRCA1 was assessed and those in whom it was not assessed. Thirty-six patients (63%) received CMV and the remaining 21 (37%) received cisplatin plus gemcitabine. The median number of cycles of chemotherapy given was 3 (range, 2–6). Cystectomy was carried out in 53 patients (93%), 5 of whom had positive surgical margins; these 5 patients received postoperative radiotherapy. Four patients were considered ineligible for surgery due to early death related to chemotherapy toxicity, poor PS, tumor progression, or patient refusal. A significant pathological response—defined either as no tumor found in the pathological analysis of the cystectomy (pCR) or only superficial residual tumor (pTis/pT1)—was observed in 28 patients (49%), including 15 patients (26%) with a pCR. Eleven patients (19%) were classified as pT2 and 5 (9%) as pT3–4N0. In the remaining nbine patients, regional lymph node involvement was observed in the pathological analysis of lymphadenectomy samples. With a median follow-up of

Table 1. Patient characteristics

Variable	Entire cohort	%	Patients with BRCA1 assessment	%	Patients without BRCA1 assessment	%	*P*
No. of patients	98		57		41		
Age (years)							0.61
Median	63		64		62		
Range	41–80		41–80		47–77		
Sex							1
Male	93	95	54	94	39	95	
Female	5	5	3	6	2	5	
Histology							0.46
TCC	76	78	46	81	30	73	
TCC with other	22	22	11	19	11	27	
Lymphovascular invasion							0.77
Present	14	14	9	16	5	12	
Absent	84	86	48	84	36	88	
Hydronephrosis							0.53
Yes	40	49	25	44	15	37	
No	58	60	32	56	26	63	
Clinical stage							0.27
T2N0M0	3	3			3	7	
T3N0M0	55	5	31	55	24	58	
T4N0M0	24	24	16	27	8	19	
T1–4N + M0	13	13	8	14	5	12	
TxNxM1	3	3	2	4	1	2	
Chemotherapy regimen							0.38
CMV	66	67	36	63	30	73	
Cisplatin/gemcitabine	32	33	21	37	11	27	
BRCA1 levels							
Low (<13.57)			21	36	NA		
Intermediate (13.57–26.77)			18	32	NA		
High (>26.77)			18	32	NA		

TCC, transitional cell carcinoma; CMV, cisplatin, methotrexate, and vinblastine.

45 months (range, 14–190 months), median disease-free survival was 49 months [95% confidence interval (CI) 6.2–91.7 months], median survival was 54 months (95% CI 0–120.8 months), and 5-year survival was 48% for all patients.

BRCA1 mRNA expression and outcome

BRCA1 was detected in all tumors, although there was considerable variation in expression levels, with values relative to the β-actin internal control ranging from 2.09 to 95.83. Patients were divided into terciles according to their BRCA1 levels (lowest tercile, 2.09–13.57; intermediate tercile, 13.67–26.77; and highest tercile, 29.29–95.83). No differences in clinical characteristics were observed according to BRCA1 mRNA expression levels (Table 2).

Median overall survival in patients with low levels was 124 months (95% CI 57.7–190.3 months), while it was not reached in patients with intermediate levels, and it was 34 months (95% CI 14.5–53.5 months) in those with high levels ($P = 0.008$). Because survival times were similar in patients with low and intermediate levels, these two groups of patients were combined for further statistical analyses. In patients with low/intermediate BRCA1 levels, median survival was 168 months (95% CI 54.9–281.1 months) and 5-year survival was 64%, whereas in patients with high levels, median survival was 34 months (95% CI 14.5–53.5 months) and 5-year survival was 12% ($P = 0.002$) (Figure 1). Patients with low/intermediate BRCA1 levels had a higher pathological response rate than those with high levels. Sixty-six percent (24 of 39) of patients with low/intermediate levels, compared with 22% (4 of 18) of those with high levels, attained a pathological response (pT0-1) ($P = 0.01$).

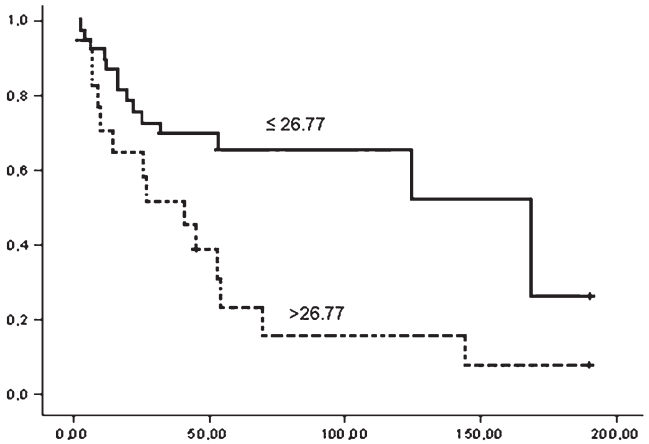
Among 36 patients treated with CMV, median survival was 168 months in those with low/intermediate BRCA1 levels and 41 months in those with high levels ($P = 0.03$). Among 21 patients treated with cisplatin plus gemcitabine, median survival in patients with low/intermediate BRCA1 levels was not reached, whereas in patients with high levels, it was 34 months ($P = 0.09$).

A univariate analysis of overall survival was carried out including the following variables: age, histology, lymphovascular invasion, hydronephrosis, clinical stage, chemotherapy regimen, resection, pathological stage, and BRCA1 expression. Low/intermediate BRCA1 levels, absence of lymphovascular invasion, absence of lymph nodes at baseline clinical staging, radical cystectomy, and pathological response (pT0-1) were associated with longer survival (Table 3). In the

Table 2. Characteristics of patients according to BRCA1 messenger RNA levels by terciles

Variable	BRCA1 mRNA expression levels			*P*
	≤13.57	13.57–26.77	>26.77	
Age, *n* (%)				0.985
≤64 years	10 (35)	9 (32)	9 (32)	
>64 years	11 (37)	9 (31)	9 (31)	
Histology, *n* (%)				0.563
TCC	16 (35)	16 (35)	14 (30)	
TCC with others	5 (45)	2 (18)	4 (36)	
Lymphovascular invasion, *n* (%)				0.789
Absent	17 (35)	16 (33)	15 (31)	
Present	4 (44)	2 (22)	3 (33)	
Hydronephrosis, *n* (%)				0.755
Yes	8 (32)	9 (36)	8 (32)	
No	13 (40)	9 (28)	10 (31)	
TNM, *n* (%)				0.576
T3N0	11 (35)	12 (38)	8 (26)	
T4N0	7 (44)	4 (25)	5 (31)	
T1–4N + M0–1	3 (30)	2 (20)	5 (50)	
Chemotherapy regimen, *n* (%)				0.439
CMV	12 (33)	13 (36)	11 (30)	
Cisplatin/gemcitabine	9 (45)	4 (20)	7 (35)	

TCC, transitional cell carcinoma; CMV, cisplatin, methotrexate, and vinblastine; mRNA, messenger RNA.



	N	Median	95% CI	5-yr survival (95% CI)	p
≤26.77	39	168	54.9-281.1	64.1 (48.2-80)	0.002
>26.77	18	34	14.5-53.5	12.1 (0-27.8)	

Figure 1. Overall survival according to BRCA1 messenger RNA levels (low/intermediate versus high). CI, confidence interval

Table 3. Univariate analysis for overall survival

Variable	*N*	Survival (months)	95% CI	*P*
Age (years)				0.92
≤64	28	53	0–117.9	
>64	29	70	0–140.2	
Histology				0.13
TCC	46	70	15.6–124.4	
TCC with other	11	32	0.7–63.3	
Lymphovascular invasion				<0.0001
Present	9	14	8.1–19.8	
Absent	48	124	30.2–217.8	
Hydronephrosis				0.08
Yes	25	45	22.7–67.2	
No	32	124	1.7–246.3	
Clinical stage				0.009
T3N0M0	31	124	31.5–216.5	
T4N0M0	16	144	0–306.6	
T1–4N + M0–1	10	22	0–44.8	
Chemotherapy regimen				0.73
CMV	36	54	0–135.6	
Cisplatin/gemcitabine	21	46	17.9–74.1	
Surgical results				0.002
Complete resection	48	142	24.1–223.8	
Incomplete/no surgery	9	12	6.2–17.8	
Pathological stage				<0.0001
T0–1N0M0	28	NR	–	
T2–4N0M0	16	45	6.9–99.1	
TxN+M0	9	11	8.1–13.9	
BRCA1 levels				0.008
Low (<13.57)	21	124	57.7–190.3	
Intermediate (13.57–26.77)	18	NR	–	
High (>26.77)	18	34	14.5–53.5	

CI, confidence interval; TCC, transitional cell carcinoma; CMV, cisplatin, methotrexate, and vinblastine; NR, not reached.

Table 4. Multivariate analysis for overall survival

	HR	95% CI	*P*
BRCA1 mRNA levels			0.02
≤26.77	1 ref.	1.16–6.39	
>26.77	2.73		
Lymphovascular invasion			<0.0001
No	1 ref.	2.35–15.91	
Yes	6.12		

HR, hazard ratio; CI, confidence interval; mRNA, messenger RNA.

multivariate analysis, only lymphovascular invasion and BRCA1 mRNA expression levels emerged as independent prognostic factors for overall survival (hazard ratios: lymphovascular invasion, 6.1, $P < 0.0001$; high BRCA1 expression, 2.7, $P = 0.02$) (Table 4).

discussion

In the present study, we have observed a significant correlation between BRCA1 mRNA levels and response and survival in locally advanced bladder cancer patients treated with neoadjuvant cisplatin-based chemotherapy. The subgroup of patients with low and intermediate BRCA1 levels obtained a significant benefit from preoperative chemotherapy, with a 5-year survival rate of 64%, in spite of the fact that the majority of patients had locally advanced disease and/or lymph node involvement. In contrast, the subgroup of patients with the highest levels of BRCA1 expression had a poor prognosis, with a 5-year survival rate of only 12%. In the multivariate

analysis, BRCA1 expression levels emerged as an independent prognostic marker of survival, while no baseline clinicopathologic characteristic except lymphovascular invasion had a prognostic impact on survival.

Few genetic markers have been proven to predict chemotherapy efficacy in bladder cancer. Expression of emmprin, a modulator of matrix metalloproteinases, and survivin have been identified as prognostic factors for response and survival in advanced bladder cancer patients treated with cisplatin-based chemotherapy [23]. In contrast, findings regarding alterations in p53 expression [22, 24–26] and other markers involved in cell cycle regulation and apoptosis [27, 28] have been contradictory. Although for practical reasons, studies have often concentrated on the assessment of one genetic marker, it seems likely that multiple markers can influence chemotherapy efficacy. While high MDR1 expression determined by RT-PCR was associated with a shorter survival in patients with locally advanced bladder cancer treated with adjuvant cisplatin/methotrexate [29], Takata et al. [30] used microarray analysis to identify a set of genes related to response to neoadjuvant chemotherapy. In another study of bladder cancer patients treated with neoadjuvant M-VAC, using multivariate gene expression models based on biomarkers of *in vitro* drug sensitivity, the 3-year overall survival for patients with favorable gene expression scores was 81% versus 33% for those with less favorable scores [31].

Several studies have shown that the analysis of DNA damage repair pathways can provide useful information for customizing therapy. For example, in a study of metastatic bladder cancer patients treated with a cisplatin-based regimen, ERCC1 expression was associated with improved outcome, although no differences in survival were observed according to BRCA1 expression [32]. However, in 75% of the patients, paclitaxel was administered in combination with cisplatin plus gemcitabine and the addition of taxanes may have counteracted the positive impact of low BRCA1 expression. More recently, these authors have shown that ERCC1 expression detected by immunohistochemistry can predict disease-specific survival in advanced bladder cancer patients treated with cisplatin-based chemotherapy [33]. In contrast, in a study of resected NSCLC patients, although a significant relationship between BRCA1 and ERCC1 expression was observed, only BRCA1 expression emerged as an independent prognostic factor [34].

The results of the present study are consistent with findings in preclinical studies in breast and ovarian cancer cells [18, 19] and in clinical studies [20, 21]. In patients with locally advanced NSCLC treated with cisplatin plus gemcitabine, low BRCA1 levels correlated with a longer survival in comparison with high BRCA1 levels [21]. In a retrospective study in ovarian cancer, among patients treated with platinum-based chemotherapy, those with low and intermediate BRCA1 levels had longer survival than those with high levels, whereas among patients treated with taxanes, a better outcome was attained by those with high BRCA1 levels [20]. In a study of 102 NSCLC patients, high BRCA1 mRNA levels were associated with better response and decreased risk of progression to docetaxel plus gemcitabine [35]. This differential modulating effect of BRCA1 mRNA expression was also observed in tumor cells isolated from malignant effusions of NSCLC and gastric cancer patients, where BRCA1 mRNA levels correlated negatively with cisplatin sensitivity and positively with docetaxel sensitivity [36].

Taken together, these studies suggest that BRCA1 may have a dual role as both a prognostic marker and a predictor of sensitivity to cisplatin and taxanes. The impact of BRCA1 expression on pathological response observed in the present study reinforces this predictive role as a marker of sensitivity to cisplatin-based chemotherapy, making it a useful tool for selecting bladder cancer patients who will benefit from neoadjuvant cisplatin-based chemotherapy. At the same time, early identification of potential nonresponders would allow us to consider alternative treatments and avoid ineffective therapies. Thus, the option of taxane-based therapy for patients with high BRCA1 expression could be explored, as has been suggested in studies of ovarian and lung cancer patients [20, 35].

In conclusion, although our findings should be interpreted cautiously due to the limited number of patients included, our data lead us to speculate that the assessment of BRCA1 mRNA expression can be used to customize therapy and improve outcome in bladder cancer patients. Further studies with a larger number of patients and other molecular markers are warranted to confirm these results.

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disclosure

None of the authors declare conflicts of interest.

references

1. Sternberg CN. The treatment of advanced bladder cancer. Ann Oncol 1995; 6: 113–126.
2. Soloway MS, Lopez AE, Patel J, Lu Y. Results of radical cystectomy for transitional cell carcinoma of the bladder and the effect of chemotherapy. Cancer 1994; 73: 1926–1931.
3. Bassi P, Ferrante GD, Piazza N et al. Prognostic factors of outcome after radical cystectomy for bladder cancer: a retrospective study of a homogeneous patients cohort. J Urol 1999; 161: 1494–1497.
4. Stein JP, Lieskovsky G, Cote R et al. Radical cystectomy in the treatment of invasive bladder cancer: long-term results in 1054 patients. J Clin Oncol 2001; 19: 666–675.
5. Barnias A, Tiliakos I, Karali MD, Dimopoulos MA. Systemic chemotherapy in inoperable or metastatic bladder cancer. Ann Oncol 2006; 17: 553–561.
6. Black PC, Brown GA, Grossman HB, Dinney CP. Neoadjuvant chemotherapy for bladder cancer. World J Urol 2006; 24: 531–542.
7. International Collaboration of Trialists. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. Lancet 1999; 354: 533–540.
8. Hall RR. Updated results of a randomized controlled trial of neoadjuvant cisplatin, methotrexate and vinblastine chemotherapy for muscle-invasive bladder cancer. Proc Am Soc Clin Oncol 2002; 21: 178.

9. Grossman HB, Natale RB, Tangen CM et al. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med 2003; 349: 859–66.
10. Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet 2003; 361: 1927–1934.
11. Winquist E, Kirchner TS, Segal R et al. Neoadjuvant chemotherapy for transitional cell carcinoma of the bladder: a systematic review and meta-analysis. J Urol 2004; 171: 561–569.
12. Schrag D, Mitra N, Xu F et al. Cystectomy for muscle-invasive bladder cancer: patterns and outcomes of care in the Medicare population. Urology 2005; 65: 1118–1125.
13. David KA, Milowsky MI, Ritchey J et al. Low incidence of perioperative chemotherapy for stage III bladder cancer 1998 to 2003: a report from the National Cancer Data base. J Urol 2007; 178: 451–454.
14. Sánchez-Ortiz R, Huang WC, Mick R et al. An interval longer than 12 weeks between the diagnosis of muscle invasion and cystectomy is associated with worse outcome in bladder carcinoma. J Urol 2003; 169: 110–115.
15. Lee CT, Madii R, Daignault S et al. Cystectomy delay more than 3 months from initial bladder cancer diagnosis results in decreased disease specific and overall survival. J Urol 2006; 175: 1262–1267.
16. Wang Q, Zhang H, Fishel R, Greene MI. BRCA1 and cell signaling. Oncogene 2000; 19: 6152–6158.
17. Kennedy RD, Quinn JE, Mullan PB et al. The role of BRCA1 in the cellular response to chemotherapy. J Natl Cancer Inst 2004; 96: 1659–1668.
18. Lafarge S, Sylvain V, Ferrara M, Bygnon YJ. Inhibition of BRCA1 leads to increased chemoresistance to microtubule-interfering agents, an effect that involves the JNK pathway. Oncogene 2001; 20: 6597–6606.
19. Quinn JE, Kennedy RD, Mullan PB et al. BRCA1 functions as a differential modulator of chemotherapy-induced apoptosis. Cancer Res 2003; 63: 6221–6228.
20. Quinn JE, James CR, Stewart GE et al. BRCA1 mRNA expression levels predict for overall survival in ovarian cancer after chemotherapy. Clin Cancer Res 2007; 13: 7413–7420.
21. Taron M, Rosell R, Felip E et al. BRCA1 mRNA expression as an indicator of chemoresistance in lung cancer. Hum Mol Genet 2004; 13: 2443–2449.
22. Sarkis A, Bajorin D, Reuter V et al. Prognostic value of p53 nuclear overexpression in patients with invasive bladder cancer treated with neoadjuvant MVAC. J Clin Oncol 1995; 13: 1384–1390.
23. Als AB, Dyrskjot L, von der Maase et al. Emmprin and surviving predict response and survival following cisplatin-containing in patients with advanced bladder cancer. Clin Cancer Res 2007; 13: 44407–44414.
24. Esrig D, Elmajian D, Groshen S et al. Accumulation of nuclear p53 and tumor progression in bladder cancer. N Engl J Med 1994; 331: 1259–1264.
25. Malats N, Bustos A, Nascimineto CM et al. p53 as a prognostic marker for bladder cancer: a meta-analysis and review. Lancet Oncol 2005; 6: 678–686.
26. Stadler WM, Lerner SP, Groshen S et al. Randomized trial of p53 targeted adjuvant therapy for patients with organ-confined node-negative urothelial bladder cancer. Proc Am Soc Clin Oncol 2009; 27: 239 (Abstr 5017).
27. Maluf FC, Cordon-Cardo C, Verbel DA et al. Assessing interactions between mdm-2, p53, and bcl-2 as prognostic variables in muscle-invasive bladder cancer treated with neo-adjuvant chemotherapy followed by locoregional surgical treatment. Ann Oncol 2006; 17: 1677–1686.
28. Chakravarti A, Winter K, Wu CL et al. Expression of the epidermal growth factor receptor and Her-2 are predictors of favorable outcome and reduced complete response rates, respectively, in patients with muscle-invading bladder cancers treated by concurrent radiation and cisplatin-based chemotherapy: a report from the Radiation Therapy Oncology Group. Int J Radiation Biol Phys 2005; 62: 309–317.
29. Hoffman AC, Wild P, Gauler T et al. Correlation of multidrug-resistance gene (MDR1) expression levels and outcome to adjuvant chemotherapy in patients enrolled in the AUO-AB 05/95 phase III trial. Proc Am Soc Clin Oncol 2009; 27: 241 (Abstr 5026).
30. Takata R, Katagiri T, Kanehira M et al. Predicting response to methotrexate, vinblastine, doxorubicin, and cisplatin neoadjuvant chemotherapy for bladder cancer through genome-wide gene expression profiling. Clin Cancer Res 2005; 11: 2625–2636.
31. Williams PD, Cheon S, Havaleshko DM et al. Concordant gene expression signatures predict clinical outcomes of cancer patients undergoing systemic therapy. Cancer Res 2009; 69: 8302–8309.
32. Bellmunt J, Paz-Ares L, Cuello M et al. Gene expression of ERCC1 as a novel prognostic marker in advanced bladder cancer receiving cisplatin-based chemotherapy. Ann Oncol 2007; 18: 522–528.
33. Guix M, Lema L, Lloreta J et al. Excision repair cross-complementing 1 (ERCC1) and survival in advanced bladder cancer: confirmatory results using immunohistochemistry. Proc Am Soc Clin Oncol 2009; 27: 240 (Abstr 5025).
34. Rosell R, Skrzypski M, Jassem E et al. BRCA1: a novel prognostic factor in resected non-small-cell lung cancer. PLoS One 2007; 2: e1129.
35. Boukovinas I, Papadaki C, Mendez P et al. Tumor BRCA1, RRM1 and RRM2 mRNA expression levels and clinical response to first-line gemcitabine plus docetaxel in non-small-cell lung cancer patients. PLoS One 2008; 3: e3695.
36. Wang L, Wei J, Qian X et al. ERCC1 and BRCA1 mRNA expression levels in metastatic malignant effusions is associated with chemosensitivity to cisplatin and/or docetaxel. BMC Cancer 2008; 8: 97.