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ORIGINAL PAPER

Concurrent administration of liposomal doxorubicin improves the survival of patients with invasive bladder cancer undergoing hypofractionated accelerated radiotherapy (HypoARC)

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Abstract Cisplatin-based radio-chemotherapy is an effective alternative to cystectomy. The position of cisplatin has been challenged by novel drugs, while altered radiotherapy fractionation is also tested against conventional radiotherapy (RT). This study focuses on liposomal doxorubicin (LDox) in combination with an aggressive radiotherapy scheme (HypoARC). Eighty-two bladder cancer patients were treated with hypofractionated/accelerated RT (14×2.7 Gy to the pelvis and 15×3.4 Gy to the bladder, within 19 days), supported with amifostine (0–1,000 mg sc.). Forty-one out of 82 patients received concurrently LDox (20 mg/m2 for 3 bi-weekly cycles). LDox was free of haematological toxicity, erythordysestesia grade 1 being the only side effect noted in 5/41 patients. Although the incidence of early toxicities did not increase with LDox, delays of radiotherapy were increased ($P = 0.16$). Amifostine significantly protected patients against toxicities and delays. There were no severe late complications recorded. Complete response rate was similar in both groups (85.4 vs. 87.8%). The 3-year local relapse-free survival was better in patients receiving LDox, but at a non-statistical level (64 vs. 47%; $P = 0.59$). The 3-year survival rate was significantly improved in T2-4 stage patients receiving LDox (72.1 vs. 58.7%; $P = 0.04$). Multivariate analysis did not identify any independent prognostic variables of relapse or death events. LDox is a well-tolerated drug during pelvic radiotherapy. Although its efficacy in terms of bladder tumour control rates could not be substantiated due to the high efficacy of the HypoARC regimen applied, survival was improved suggesting either a spatial co-operation or a radio-sensitization of pelvic in-field subclinical disease.

Keywords Bladder cancer · Radiotherapy · Liposomal doxorubicin · Amifostine

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Introduction

Today, combined radiotherapy and chemotherapy is an alternative to cystectomy for patients with invasive bladder cancer, providing high control and survival rates with the advantage of retaining a functional bladder. Early studies on concurrent cisplatin administration with standard radiation showed encouraging complete response and survival rates, better than those provided by radiotherapy alone [1] or by transurethral resection and chemotherapy without irradiation [2]. The application of neoadjuvant chemotherapy before radiotherapy provided higher toxicity rates and no significant benefit in terms of survival [3, 4].

The position of cisplatin radio-chemotherapy as a standard non-surgical therapy has been recently challenged in two areas of clinical research, namely the assessment of novel drug-based radio-chemotherapy and the usage of altered radiotherapy fractionation. Several RTOG protocols with encouraging results have been accomplished [5] and others are on going [6], while the recently introduced targeted agents (e.g. anti-EGFR and anti-VEGF agents) have already opened a new chapter in the field of radio-chemotherapy for a variety of carcinomas including bladder cancer [http://www.rtog.org/members/protocols/0524/0524.pdf].

Following previous studies from our group showing a preferential accumulation of liposomal doxorubicin (LDox) in a variety of human tumours, such as lung, head-neck cancer and sarcomas and the excellent tolerance profile of the drug in conjunction with radiotherapy [7, 8], we incorporated LDox in a protocol of hypofractionated and accelerated radiotherapy for the treatment of bladder carcinoma [9]. In this study we present mature results from this trial focusing on the tolerance of LDox combination with this aggressive radiotherapy scheme and on its role on tumour control and survival.

Table 1 Patient and disease characteristics

	All	No LDox	With LDox	*P*-value
No pts.	82	41	41	
Male/female	78/4	38/3	41/0	0.11
Age (years)				
Median	75	77	71	0.001
Range	53–88	60–88	65–82	
WHO PS				
Median	0	0	0	0.99
Range	0–1	0–1	0–1	
T-stage (*)				
T1	10	6	4	0.39
T2	33	14	19	
T3	34	17	17	
T4	5	4	1	
N-stage (*)				
N0	75	37	38	0.69
N1	7	4	3	
Grade				
2	10	3	7	0.17
3–4	72	38	34	

(*) UICC stage based on histology report and CT/MRI imaging

Patients and methods

From January 2003 to September 2009, 82 patients with invasive transitional cell bladder cancer have been recruited in the current prospective phase II study at the Department of Radiotherapy and Oncology, University Hospital of Alexandroupolis, Greece. The median follow-up of patients alive at the time of analysis ranges from 2 to 61 months (median 19 months).

All patients had a performance status of 0–1 (median 0; WHO scale). Patients previously treated with radiotherapy or pregnant women or patients with major heart, lung, liver, renal, psychiatric disease or haematological malignancies were excluded from the protocol. Table 1 shows the patient and disease characteristics. Written informed consent was obtained from all patients. The study has been approved by the local Ethics and Scientific committees.

HypoARC details

Radiotherapy was given using an 18MV linear accelerator (ELECTA) endowed with a multi-leaf collimator, after CT-simulation and conformal radiotherapy planning (Plato, Nucletron). A daily fraction of 2.7 Gy through four fields (box), directed to the pelvic area, was used to deliver a total of 14 fractions. These fields comprised the bladder, the prostatic urethra and the external iliac nodes up to the level of the common iliac ones. Using a concomitant boost technique, lateral fields confined to the whole bladder delivered an additional daily dose of 0.7 Gy, so that the daily dose to the bladder, through the six fields used, was 3.4 Gy for 14 fractions (day 1–18). An additional 3.4 Gy fraction was delivered to the whole bladder through the lateral booster fields, on day 19. For 10 T1-stage cases included in the study, a four field conformal technique, comprising the bladder alone was applied, using the same fractionation.

For the radiobiological analysis of the above scheme, the normalized total dose (NTD) was calculated using the formula proposed by Maciejewski, $\mathrm{NTD} = D\ [(\alpha/\beta + d)/(\alpha/\beta + 2)]$, where '$D$' is the total physical dose, 'd' the dose per fraction and α/β is the tissue-specific ratio. The NTD corrected for overall treatment time was calculated using a previously proposed formula [9], $\mathrm{NTD}_{(T)} = D\ [(\alpha/\beta + d)/(a/b + 2)] + \lambda(Tc - To)$, where Tc is the number of days required for the delivery of the NTD using a conventionally fractionated scheme, To is the number of days required for the delivery of the current scheme, and 'λ' is the estimated daily dose consumed to compensate for rapid tumour repopulation. For cancer tissue an α/β ratio of 4–10 Gy was considered. We also assumed a median 'λ' value of 0.4 Gy for cancer cells and of 0.2 Gy for normal tissues.

Through the pelvic fields, a total physical dose of 37.8 Gy (equivalent to 42.2 Gy for $\alpha/\beta = 4$ Gy) was delivered to the whole pelvis and lymph nodes (up to the

lower boarder of the 5th lumbar vertebra). This dose was given within 18 days, thus with an acceleration of 11 days. The biological dose with time correction for normal tissues ($\lambda = 0.2$ Gy) gives an equivalent of 44.4 Gy. For tumour spread to the nodes ($\lambda = 0.4$–0.8 Gy), the time-corrected dose is 46.6–51 Gy.

To the bladder, a total of 51 Gy of physical dose, equivalent to 62.9 Gy for $\alpha/\beta = 4$ Gy, was delivered within 19 days (acceleration by 24 days). Assuming a λ-value of 0.2 Gy for normal bladder, the time-corrected dose to the bladder was 67.7 Gy. Assuming a tumour λ-value of 0.4 Gy, the estimated time-corrected biological dose to the bladder tumour was 72 Gy (for a tumour $\alpha/\beta = 4$ Gy) and 66 Gy (for a tumour $\alpha/\beta = 10$ Gy).

Radiotherapy delays

Any grade 2 or higher toxicity (diarrhoea, proctitis or cystitis) was followed by treatment interruption, supportive medication (loperamide, analgesics or antibiotics when necessary) and treatment was restarted once regression of symptoms to grade 1 was achieved.

Amifostine administration

Ondasetron 8 mg was administered per os, 30–60 min before amifostine injection as antiemetic policy. Amifostine 1,000 mg was diluted in 5-ml water for injection and was injected in two sites (usually at the right and left shoulder), the patient being at a sitting position. Blood pressure assessment was not performed, as this is not necessary when amifostine is given subcutaneously [10]. The higher dose of amifostine (1,000 mg instead of 350–500 mg used in other studies) applied in the protocol was chosen in order to better protect tissues against the large fractions of radiotherapy in the HypoARC scheme.

The dose of 1,000 mg was reached gradually (1st day 500 mg, 2nd day 750 mg and 3rd day 1,000 mg) using a previously published algorithm [10]. The tolerance of amifostine was recorded daily using a scoring system [10]. Fever/rash attributed to amifostine (or to any other drug) is followed by immediate and permanent interruption of amifostine and by oral administration of corticosteroids and antihistamines for 2–3 days [10].

Concurrent chemotherapy

LDox (Caelyx®) 20 mg/m2 every 2 weeks was administered in 41/82 patients, for a total of 3 cycles. The drug was diluted in 500 ml Dextran Water and infused within 1 h. Intravenous pre-medication with methylprednisolone, dimetindene, ondasetron and ranitidine preceded chemotherapy.

Chemotherapy administration was not randomized. The expected benefits and side effects were explained at the first consultation of the patient, and they were freely left to decide whether they wished or not to receive this adjunctive therapy. Complete blood counts were performed every 2 weeks, and G-CSF was administered once grade II neutropenia was documented. Erythropoietin was given in patients with Hb levels lower than 11 gr%.

Treatment evaluation

Complete blood cell count, serum urea, creatinine and liver enzymes were assessed once every 2 weeks during the radio-chemotherapy therapy period. Radiation toxicity was monitored daily during radiotherapy, weekly for 1 month following the end of radiotherapy, monthly for 4 months and once every 3 months thereafter. The NCI (National Cancer Institute) Common Toxicity Criteria Version 2 scale was used to assess chemotherapy and acute radiation toxicity. The LENT-SOMA toxicity scale was used to assess late radiation sequelae.

Response to treatment of measurable lesions was assessed with CT scan and bladder endoscopy 2 and 4 months after treatment completion. CR was defined as complete disappearance of the intravescical lesion and normalization of the CT scan. Residual tumour during cystoscopy 4 months after radiotherapy was considered as incomplete remission and failure of radiotherapy. Multi-agent chemotherapy was considered in these patients for palliation.

Statistical analysis

The statistical analysis and graph presentation of survival curves was performed using the GraphPad Prism 5.00 version and the GraphPad Instat packages. The Fisher's exact test or the unpaired two-tailed t-test was used to compare categorical variables, as appropriate. Survival curves were plotted using the Kaplan–Meier method, and the log-rank test was used to determine statistical differences between life tables. Patient- and treatment-related variables were analysed in a multivariate stepwise logistic regression model to determine which ones contain independently significant information. P values $< .05$ were considered to be statistically significant.

Results

Acceptance of chemotherapy

Forty-one out of 82 (50%) patients decided to receive LDox. Patient and disease characteristics according to patient decision are shown in Table 1. Analysis showed that

chemotherapy was more frequently accepted by younger patients (median age 70.2 years vs. 75.5 years, $P = 0.001$). There was no other difference between groups.

Chemotherapy toxicity

None of the 41 patients receiving Lox presented any haematological toxicity related to chemotherapy. Out of 41 patients receiving LDox, 5 developed grade 1 palmar-plantar erythrodysesthesia, following the third cycle. No other systemic toxicity was recorded. In 4/41 patients back pain, flash and dyspnea appeared during LDox infusion. Symptoms regressed within 15–30 min after infusion interruption and all patients received the drug with no problems thereafter.

Radiation toxicity

Table 2 reports the early toxicity in patients treated with hypoARC according to the administration of LDox. There was no statistical difference between groups in terms of frequency, dysuria, proctitis, diarrhoea or skin toxicities.

Delays of radiotherapy because of early toxicity are probably a more accurate index of acute toxicities as it does not only take into account the grade score but also the time for regression of toxicities to levels acceptable for radiotherapy continuation. Out of 41 patients receiving LDox, 18 (43.9%) had to interrupt radiotherapy for 1–2 weeks vs. 12/41 (29.2%) of patients treated without LDox. The difference, however, did not reach significance ($P = 0.16$; Table 3).

Further analysis of the radiotherapy delays, according to the amifostine dose administered, showed that by increasing the dose of amifostine to 1000 mg there was a statistically significant better protection of patients who received LDox and of those who did not ($P < 0.05$; Table 3).

Regarding late radiation sequelae, within a median follow-up of 19 months (2–61 months), there was a low incidence of severe complications. Bladder grade 1 and 2 toxicities were recorded in 3 (7.3%) and 3 (7.3%) cases, respectively, in the group receiving RT alone and in 2 (4.9%) and 2 (4.9%) cases, respectively, in patients receiving LDox. Colitis grade 1 was noted in 1 case (2.4%)

Table 2 Early pelvic toxicity assessed with the NCI (National Cancer Institute) Common Toxicity Criteria in patients treated with HypoARC with or without liposomal doxorubicin

	With LDox No pts 41 (%)	Without LDox No pt 41 (%)	*P*-value
Frequency			
0. None	20 (48.8)	22 (53.7)	
1. Up to 2 × normal	17 (41.5)	14 (34.1)	0.91
2. >2 × normal but < hourly	3 (7.3)	4 (9.8)	
3. >hourly, demands catheter	1 (2.4)	1 (2.4)	
Dysurea			
0. None	35 (85.3)	34 (82.9)	
1. Mild	6 (14.7)	6 (14.7)	0.60
2. Relieved with analgesics	0 (0.0)	1 (2.4)	
3. Persistent—demand catheter	0 (0.0)	0 (0)	
Proctitis			
0. None	26 (63.4)	23 (56.1)	
1. Mild rectal discomfort	9 (21.9)	12 (29.3)	0.70
2. Requires medication	6 (14.7)	5 (12.2)	
3. Pads—parenteral support—transfusion	0 (0.0)	1 (2.4)	
4. Necrosis—life threatening bleeding—colostomy			
Diarrhoea			
0. <4 Stools	31 (75.6)	26 (63.4)	
1. 4–6 Stools	7 (17.1)	11 (26.8)	0.47
2. >7Stools—incontinence	3 (7.3)	4 (9.8)	
3. Hospitalization—collapse	0 (0)	0 (0)	
Dermatitis			
0. None	38 (92.7)	40 (97.6)	
1. Faint erythema/dry desquamation	1 (2.4)	1 (2.4)	
2. Brisk erythema/patchy moist desquamation	2 (4.9)	0 (0.0)	0.35
3. Confluent moist desquamation	0 (0)	0 (0)	
4. Skin necrosis	0 (0)	0 (0)	

Table 3 Overall treatment time and radiotherapy delays according to the concurrent administration of LDox

LDox	Amifostine dose	Accomplishment of RT		
		19 days No pts (%)	22–26 days No pts (%)	29–33 days No pts (%)
No (**)	*All cases (*)*	*29 (70.8)*	*6 (14.6)*	*6 (14.6)*
	A. 0 mg (10 pts)	4 (40.0)	2 (20.0)	4 (40.0)
	B. 500–750 mg (13 pts)	10 (76.9)	1 (7.7)	2 (15.4)
	C. 1,000 mg (18 pt)	15 (8.3)	3 (16.7)	0 (0.0)
Yes (***)	*All cases (*)*	*23 (56.1%)*	*8 (19.5%)*	*10 (24.4%)*
	A. 0 mg (3 pts)	1 (33.3)	1 (33.3)	1 (33.3)
	B. 500–750 mg (10 pts)	3 (30.0)	2 (20.0)	5 (50.0)
	C. 1,000 mg (28 pt)	19 (67.9)	5 (17.9)	4 (14.2)
P-value		*(*) 0.16*		
		(**) A vs. B vs. C: 0.04, A vs. C: 0.01		
		(***) A,B vs. C: 0.04		

in each group. Analysis according to the dose of amifostine showed that patients who did not receive amifostine had significantly worse frequency ($P = 0.04$).

Response rates

Following HypoARC the complete response rate was 86.6%. This was higher in the T1 stage (100%) and dropped gradually to 90.9% in the T2 stage and to 79.5% in the T3, 4 stages. There was not, however, a statistically significant difference ($P > 0.18$).

There was no effect of liposomal doxorubicin on the response rates of the bladder tumour. The CR rate was 85.4% in patients receiving LDox vs. 87.8% in patients who did not ($P > 0.99$). Moreover, there was no significant effect of the dose of amifostine on the complete response rates (0 mg: 10/13, 500 mg: 6/7, 750 mg: 13/16 and 1000 mg: 42/46; $P = 0.50$).

Analysis of local relapse

The 1-, 2- and 3-year local relapse-free survival (LRFS) was 75, 64 and 64%, respectively, in patients receiving LDox. This was 71, 71 and 47% in patients treated with radiotherapy alone. There was no statistically significant difference between T-stages. Statistical analysis did not reveal any benefit from chemotherapy overall ($P = 0.71$) nor in T-stages ≥ 2 ($P = 0.59$; Fig. 1a). In multivariate analysis none of the available parameters was an independent prognostic variable of relapse.

Overall survival

There was a trend towards better outcome in patients receiving LDox ($P = 0.09$), which reached significance in patients with stages higher than T1 ($P = 0.04$; Fig. 1b). The 1-, 2- and 3-year survival rate was 90.5, 86.5 and 72.1% in patients receiving LDox vs. 70.6, 58.7 and 58.7% in patients who were treated with radiotherapy alone. In multivariate

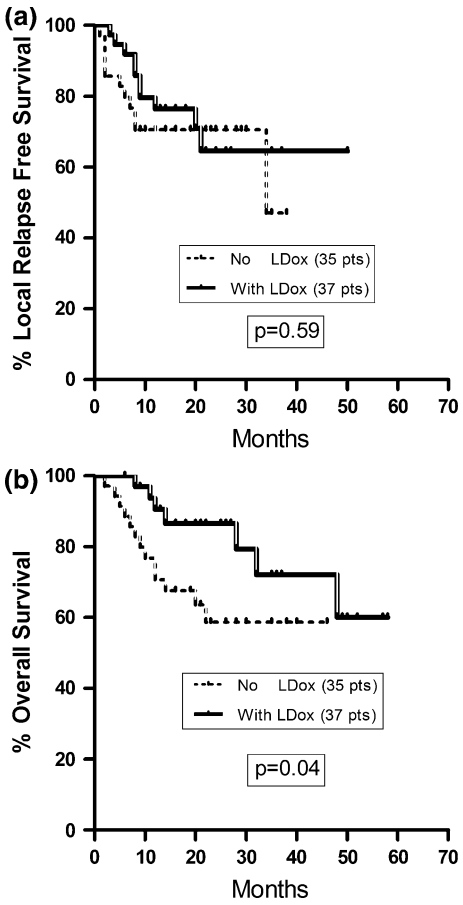

Fig. 1 Kaplan–Meier local relapse (**a**) and overall disease-specific (**b**) survival curves according to the administration of liposomal doxorubicin during HypoARC for stage T2-4 bladder cancer

analysis none of the available parameters was an independent prognostic variable of death events.

Discussion

Doxorubicin is a drug with established activity in a variety of human carcinomas including bladder cancer [11]. Its liposomal formulation allows the selective accumulation in the tumours, providing an increased exposure of cancer cells to the free drug form [7]. LDox has shown activity against urothelial tumours in clinical trials [12].

The concurrent administration of LDox with radiotherapy has been previously examined in head-neck, lung and breast cancer [7, 13], showing an excellent tolerance profile. Doxorubicin per se is a very toxic drug when combined with radiation [14], but its liposomal form did not increase radiation toxicities and, on the other hand, the efficacy of radiotherapy was improved. Moreover, the administration of LDox for three bi-weekly cycles to cover the radiotherapy period was free of haematological toxicities, and other systemic side effects were very low. In contrast to cisplatin, commonly used concurrently with radiotherapy in bladder and other carcinomas, LDox did not have any nausea/vomiting or asthenia side effects. Thus, it was postulated that LDox could be an effective substitute for cisplatin, with improved tolerance and at least as equal efficacy.

LDox was, therefore, incorporated in a highly accelerated and hypofractionated radiotherapy scheme (HypoARC) applied in our department for the treatment of bladder cancer. The protocol was not randomized, but patients were offered this complementary therapy and after explaining the potential benefits and side effect it was up to them to decide whether they wanted or not to receive LDox. Half of the patients decided to receive chemotherapy. Older patients and women were the ones that more often declined chemotherapy.

LDox showed an excellent tolerance profile, the only side effect being mild erythrodysestesia after the 3rd cycle in a minority of patients. Despite the aggressiveness of the HypoARC regimen, early radiation toxicity from pelvic tissues was low. LDox did not increase statistically the radiotherapy toxicities. Looking into the treatment delays, which is an index of severity but also of the time demanded for the toxicities to regress, there was a trend for increased delays in patients receiving LDox. However, the administration of amifostine was the only statistically significant factor contributing to the avoidance of treatment delays whether patients received LDox or not. It was concluded that, although LDox may increase slightly the early radiotherapy toxicities, the usage of amifostine, especially at high doses, reduces toxicities at levels lower than the expected from radiotherapy alone. Regarding the late radiation sequel, HypoARC with or without LDox was proved to be a safe regimen, at least in the range of the follow-up time available (median 19 months).

The local response rate and local progression-free intervals were not affected by the drug. Similarly, the delays of radiotherapy did not have any impact on local disease control. As the maximum delays of radiotherapy were 2 weeks, the regimen was highly accelerated for all patients. It seems that HypoARC by delivering more than 70 Gy of biological dose within 3–5 weeks is a highly effective regimen per se resulting in 86% complete responses and long-term control rates, regardless of the administration of LDox.

On the contrary, the overall survival of patients was significantly better in patients receiving LDox. This suggests an important role of the drug in the reduction of micro-metastatic cancer cell burden to distant organs, which results to prolonged survival and delayed appearance of metastasis. Moreover, as pelvic nodes receive a lower dose of radiation (48 Gy) compared to the bladder (>70 Gy), increased efficacy in eradicating the subclinical nodal disease by the concurrent radio-chemotherapy may also account for the improved overall survival.

It is concluded that LDox, the liposomal formulation of a well established drug in the treatment of bladder cancer, is a well-tolerated drug during pelvic radiotherapy. Although its efficacy in terms of bladder tumour control rates could not be substantiated due to the high efficacy of the HypoARC regimen applied in the current study, its efficacy in terms of survival is documented suggesting either a spatial co-operation with radiotherapy or a radiosensitization of pelvic in-field subclinical disease.

References

1. Coppin CM, Gospodarowicz MK, James K, Tannock IF, Zee B, Carson J, Pater J, Sullivan LD. Improved local control of invasive bladder cancer by concurrent cisplatin and preoperative or definitive radiation. The National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol. 1996;14:2901–7.
2. Herr HW, Bajorin DF, Scher HI. Neoadjuvant chemotherapy and bladder-sparing surgery for invasive bladder cancer: ten-year outcome. J Clin Oncol. 1998;16:1298–301.
3. Shipley WU, Winter KA, Kaufman DS, Lee WR, Heney NM, Tester WR, Donnelly BJ, Venner PM, Perez CA, Murray KJ, Doggett RS, True LD. Phase III trial of neoadjuvant chemotherapy in patients with invasive bladder cancer treated with selective bladder preservation by combined radiation therapy and chemotherapy: initial results of Radiation Therapy Oncology Group 89–03. J Clin Oncol. 1998;16:3576–83.
4. Advanced Bladder Cancer (ABC). Meta-analysis collaboration. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data

advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol. 2005;48:202–5.
5. Efstathiou JA, Bae K, Shipley WU, Kaufman DS, Hagan MP, Heney NM, Sandler HM. Late pelvic toxicity after bladder-sparing therapy in patients with invasive bladder cancer: RTOG 89–03, 95–06, 97–06, 99–06. J Clin Oncol. 2009;27:4055–61.
6. Mak RH, Zietman AL, Heney NM, Kaufman DS, Shipley WU. Bladder preservation: optimizing radiotherapy and integrated treatment strategies. BJU Int. 2008;102:1345–53.
7. Koukourakis MI, Koukouraki S, Giatromanolaki A, Archimandritis SC, Skarlatos J, Beroukas K, Bizakis JG, Retalis G, Karkavitsas N, Helidonis ES. Liposomal doxorubicin and conventionally fractionated radiotherapy in the treatment of locally advanced non-small-cell lung cancer and head and neck cancer. J Clin Oncol. 1999;17:3512–21.
8. Koukourakis MI, Koukouraki S, Giatromanolaki A, Kakolyris S, Georgoulias V, Velidaki A, Archimandritis S, Karkavitsas NN. High intratumoral accumulation of stealth liposomal doxorubicin in sarcomas-rationale for combination with radiotherapy. Acta Oncol. 2000;39:207–11.
9. Koukourakis MI, Tsolos C, Touloupidis S. Radical hypofractionated accelerated radiotherapy with cytoprotection for invasive bladder cancer. Urology. 2007;69:245–50.
10. Koukourakis MI, Abatzoglou I, Sivridis L, Tsarkatsi M, Delidou H. Individualization of the subcutaneous amifostine dose during hypofractionated/accelerated radiotherapy. Anticancer Res. 2006; 26:2437–43.
11. Grossman HB, Natale RB, Tangen CM, Speights VO, Vogelzang NJ, Trump DL, deVere White RW, Sarosdy MF, Wood DP Jr, Raghavan D, Crawford ED. Neoadjuvant chemotherapy plus cystectomy compared with cystectomy alone for locally advanced bladder cancer. N Engl J Med. 2003;349:859–66.
12. Winquist E, Ernst DS, Jonker D, Moore MJ, Segal R, Lockwood G, Rodgers A. Phase II trial of pegylated-liposomal doxorubicin in the treatment of locally advanced unresectable or metastatic transitional cell carcinoma of the urothelial tract. Eur J Cancer. 2003;39:1866–71.
13. Koukourakis MI, Manavis J, Simopoulos C, Liberis V, Giatromanolaki A, Sivridis E. Hypofractionated accelerated radiotherapy with cytoprotection combined with trastuzumab, liposomal doxorubicine, and docetaxel in c-erbB-2-positive breast cancer. Am J Clin Oncol. 2005;28:495–500.
14. Brooks BJ Jr, Seifter EJ, Walsh TE, Lichter AS, Bunn PA, Zabell A, Johnston-Early A, Edison M, Makuch RW, Cohen MH. Pulmonary toxicity with combined modality therapy for limited stage small-cell lung cancer. J Clin Oncol. 1986;4:200–9.