Divergent effects of taurolidine as potential anti-neoplastic agent: Inhibition of bladder carcinoma cells *in vitro* and promotion of bladder tumor *in vivo*

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Received January 19, 2009; Accepted March 24, 2009

DOI: 10.3892/or_00000452

Abstract. We investigated taurolidine (TRD) against various human bladder cell lines and the AY-27 rat bladder carcinoma cells. *In vitro* we tested the effect of TRD in ascending concentrations depending on different incubation times on cell proliferation by the XTT-test. Taurolidine had an inhibitory effect on all tested cell lines. Increasing concentrations and longer incubation times decreased the proliferation depending on the primary quantities of cells. For *in vivo* studies, an orthotopic rat bladder carcinoma was used. The animals were treated intravenously or intravesically and the tumors were harvested and weighted after the study. In contrast to other authors we could not find any anti-proliferative effect, we actually showed that instillation into the rat urinary bladder enhanced tumor growth.

Introduction

Bladder cancer is the fourth most frequently diagnosed cancer in men. Approximately 9,950 men and 4,150 women are estimated to die from this tumor entity in the United States and ~51,230 new cases of urinary bladder carcinoma in men and 17,580 new cases in women are predicted in 2008 (1).

The current standard therapy for non-muscle invasive bladder cancer (Ta, T1) is the transurethral resection of the bladder (TURB). Carcinoma *in situ* (Cis) and multi-localized bladder cancer cannot be eradicated by transurethral resection. Since there is a considerable risk for recurrence and tumor progression after TURB an adjuvant intravesical therapy for Ta, T1 and Cis bladder tumor is recommended (2). For low risk bladder tumors instillation therapies with the chemotherapeutic drugs mitomycin C, epirubicin, or doxorubicine are available. For high risk, multi-localized TCC of the bladder the intravesical immunotherapy with the attenuated anti-tuberculosis vaccine Bacille Calmette-Guérin (BCG) is recommended. BCG is superior to the chemotherapy in reducing recurrences and progression, but, however, more toxic.

At this time there is still no effective therapeutic drug available to cure muscle-invasive and metastatic TCC systemically with only moderate side effects. Therefore, more efforts need to be done on testing potential chemotherapeutic substances for their efficacy in treating bladder carinoma. Taurolidine [bis-(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)-methane] (TRD) is a new promising chemotherapeutic drug. *In vitro* and experimental *in vivo* studies have proved that TRD inhibits the growth of prostate (3), brain (4), colon (5), pancreatic, liver (6,7), melanoma (8), malignant mesothelioma (9) and ovarian tumor cells (10). Among these studies, TRD demonstrated its inhibitory effect on peritoneal tumor cells in a rat model (11-13) as well on a colorectal tumor cell line (14) and malignant melanoma cells in a mouse model (15). Preliminary clinical results in treating patients with TRD suffering from gastric cancer and glioblastoma also pointed out a tumor reducing effect (16,17).

TRD was synthesized by Geistlich Pharma AG (Wolhusen, Switzerland) about 30 years ago and was first used as a desinfectant, antibiotic and anti-mycotic agent. Methylol-containing fragments are responsible for its antibiotic activities through direct adherence to the cell wall of microorganisms. This effect could be responsible for the reduction of peritoneal infections and adhesions post-operatively (18,19). Additionally, TRD has been reported to reduce tumor necrosis factor α (TNF-α) and interleukin-1 ß (IL-1ß) synthesis and activity (20-22). The reduction of tumor angiogenesis, supposedly by preventing the activation of VEGF production in tumor cells (23,24) and the induction of cell apoptosis (10,25,26), might be an explanation for the anti-neoplastic properties of TRD.

The goals of our investigations are to determine the impact of TRD as an anti-neoplastic agent in different human bladder cell lines *in vitro* and also on the AY-27 rat bladder

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Key words: bladder cancer, tumor growth, anti-neoplastic agent, taurolidine, rat tumor model

carcinoma model *in vivo*. To our knowledge this is the first study on the effect of TRD on human and rat bladder carcinoma cells.

Materials and methods

Reagents. The ready-to-use solution taurolidine 2% was obtained from Geistlich Pharma (Geistlich Pharma AG) and used for the intravenous (i.v.) and intravesical (i.ves.) therapy. To obtain lower concentrations for the *in vitro* studies TRD was diluted with RPMI (0, 2, 4, 8, 16, 32, 64 and 128 μmol/l).

Cell lines. Four different human cell lines were obtained for the *in vitro* study: a normal differentiated (HCV-29), a well differentiated (RT-4), a moderate differentiated (RT-112) and an undifferentiated human bladder cell line (J-82, ATCC). Additionally, the rat urothelial carcinoma cell line AY-27 (generous gift from Professor Notter, Marseille, France) was used.

The cells were cultured in 90% RPMI-medium supplemented with 10% FBS (HCV-29 with 5%) and penicillin-streptomycin (PAA Laboratories GmbH, Pasching, Austria) and incubated at 37˚C in 5% CO_2 for ~7 days until confluence was reached.

To generate the rat bladder carcinoma for the *in vivo* study we used the AY-27 cells. After reaching confluency AY-27 rat bladder cancer cells were removed from the tissue culture flasks with trypsin/EDTA and 4 ml RPMI-1640 was added. The tumor cells were centrifuged, washed in PBS, counted, and resuspended in RPMI-1640 medium. The viability of the cells was controlled by trypan blue staining and counted in a Neubauer chamber.

Animals. For all experiments 26 female, 8-week-old Fischer rats (F344) were used. The rats were purchased from Charles River, Sulzfeld, Germany. The animals were housed in the Charité Laboratory Animal Resource Center under a 12 h day/night cycle at 20-22˚C and were fed standard laboratory food and water *ad libitum*. The performance of this study was in accordance to the German animal protection requirements and approved by the responsible local authority (Landesamt für Gesundheit und Soziales, Berlin, Germany).

In vitro studies. The effects of various TRD concentrations (0, 2, 4, 8, 16, 32, 64 and 128 μmol/l) on the bladder cell lines with three incubation times (24, 48 and 72 h) were analyzed. For every cell line three 96-well plates were used, each for one incubation time. Each six wells of a plate were inoculated with 100 μl of one concentration of TRD, the following six wells were charged with the next higher concentration. At the beginning of the study the quantity of cells were 2,000 cells/well. Since we hypothesized an inhibiting effect of TRD on the human bladder cancer cell lines we also evaluated individually the primary quantity of each cell line (2,000, 4,000, 6,000 and 8,000).

The different cell lines were plated in their exponential growth stage in 0.1 ml medium on 96-well micro-titer plates. After cell adhesion and removal of the medium the different concentrations of TRD were added. The proliferation was measured with the standard XTT assay (Roche Diagnostics GmbH, Germany). After an incubation time of 2-6 h at 37˚C the formazan absorbance could be directly quantified by photometry (Anthos HT3, Anthos Labtec Instruments, Salzburg, Austria). The proliferation of the cells without any addition of TRD was set at 100%.

In vivo study. Twenty-six female Fischer rats (control group n=8, i.v. group n=9, and i.ves. group n=9) were used to generate the bladder carcinoma by injection of $2x10^6$ AY-27 cells/0.05 ml PBS solution. The animals were anesthetized with 2% isoflurane for ~15 min. After laparotomy and exposure of the bladder, the AY-27 cells were injected into the bladder muscle of each animal with a 26G needle. Subsequently, the bladder was relocated into the abdomen, the abdominal wall sutured and a post-operative analgesia was provided to the animals.

The rats were treated according to clinical practice dose in humans (27) and other animal studies with comparable total doses (28,29) with i.v. TRD injection three times/week with 15 ml/kg. In order to reach a TRD plasma level the treatment with TRD was initiated 2 days before tumor cell injection. In the i.v. therapy group the animals were treated by TRD injection through the lateral caudal vein during a short isoflurane anesthesia. The animals in the control group were treated in accordance to the intravesical and intravenous treatment groups. In the control group one half of each of the animals was treated i.v. and one half i.ves. For the i.ves. treatment polyethylene catheters (0.86 mm ID, 1.52 mm OD, SIMS Portex, Kent, UK) were set into the rat bladder, using a short isoflurane anesthesia. TRD was instilled into the bladder through a urethral catheter to an extent that a physiological filling of the bladder was palpable from the abdomen. This i.ves. TRD instillation was performed once per week. The study ended 5 weeks after the cell injections by sacrifice of the animals and immediate resection and measurement of the tumors. During the following autopsy each animal was examined macroscopically for metastasis and the tumors were extracted and weighed.

Statistical analysis. The software GraphPadPrism for Windows, version 4.0a (GraphPad, San Diego, CA) was used to perform the statistical analyses. For the *in vitro* studies ANOVA with the Dunnett's multiple comparison test and post test for linear trend was performed. The Mann-Whitney test was used for independent non-normal distribution of samples for the *in vivo* studies. Differences of $P<0.05$ were considered statistically significant.

Results

In vitro studies. Fig. 1a-e shows the influence of various TRD concentrations (0, 2, 4, 8, 16, 32, 64, 128 μmol/l) on the cell proliferation of the HCV-29, RT-4, RT-112, J-82 and AY-27 cell lines after incubation times of 24, 48 and 72 h. TRD inhibited the growth of all tested cell lines. An increase of TRD concentration resulted in decreasing cell proliferation, whereas longer incubation times of 48 and 72 h resulted in a quantitative higher loss of cell proliferation than the equivalent concentration with the incubation time of 24 h.

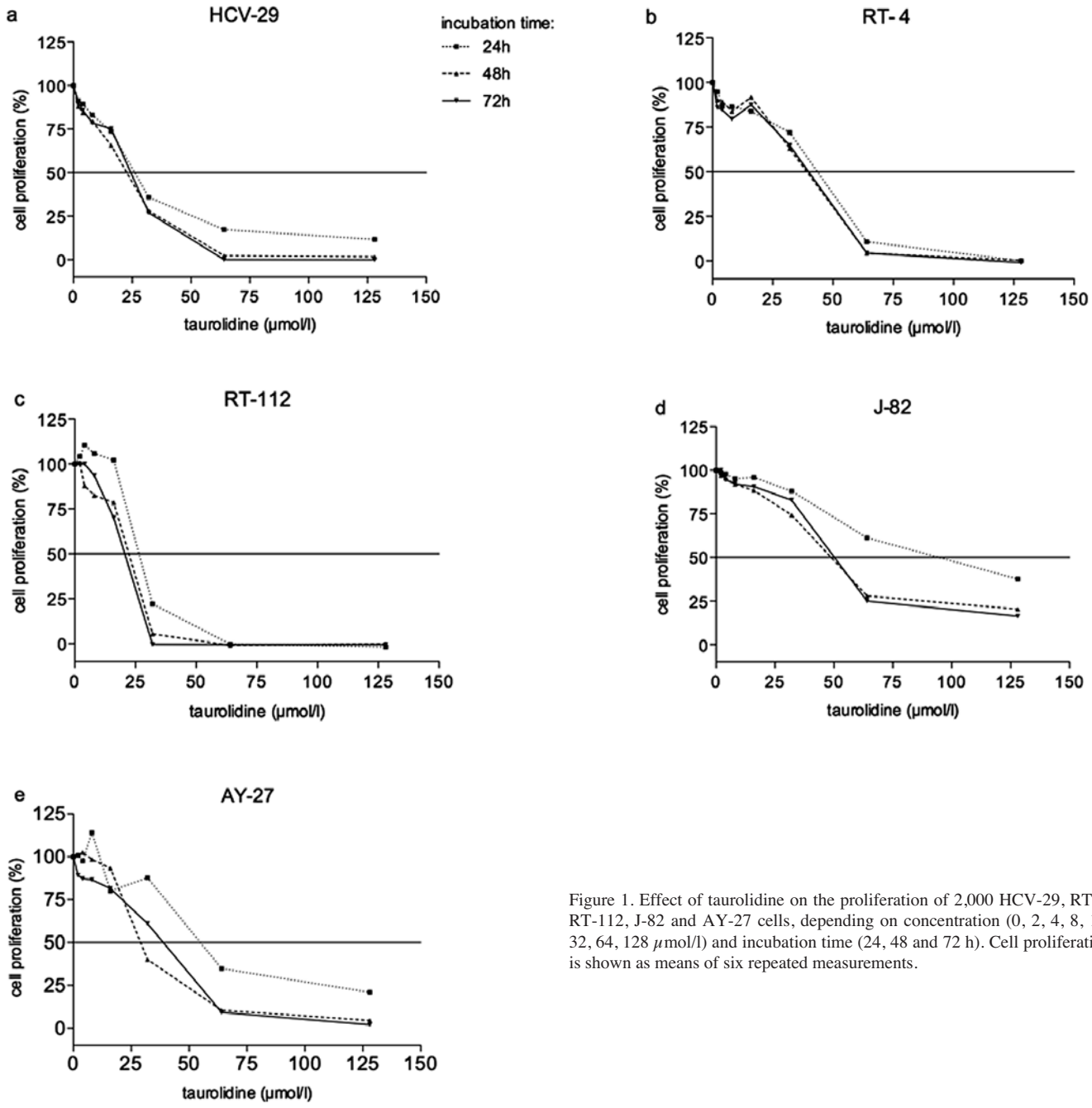

Figure 1. Effect of taurolidine on the proliferation of 2,000 HCV-29, RT-4, RT-112, J-82 and AY-27 cells, depending on concentration (0, 2, 4, 8, 16, 32, 64, 128 μmol/l) and incubation time (24, 48 and 72 h). Cell proliferation is shown as means of six repeated measurements.

At the TRD concentration of 32 μmol/l there was already a 50% inhibition of cell proliferation noticeable in the HCV-29 and RT-112 cell lines. The following concentration of 64 μmol/l showed a >90% up to 100% reduction of cell proliferation in the HCV-29, RT-4, RT-112 and AY-27 cell lines at 48 and 72 h of incubation. An additional doubling of the TRD concentration up to 128 μmol/l resulted in no further measurable effects in these tested cell lines. In comparison to the inhibitory effect with a relatively shorter (24 h) or longer incubation time (72 h), we observed that during longer incubation times less concentrations of TRD were needed to result in the same inhibitory effect of cell proliferation.

The undifferentiated J-82 human bladder cell line showed exclusively only a 20% reduction in cell proliferation with the maximal TRD concentration of 128 μmol/l after an incubation time of 48 and 72 h, respectively a 37% reduction after 24 h of incubation. This findings indicate a lower sensitivity of the J-82 cells to TRD in comparison for all other tested cell lines.

Fig. 2a-d presents the influence of different concentrations of TRD regarding the primary quantity of cells (2,000, 4,000, 6,000 and 8,000/well) with an incubation time of 48 h. Between the tested primary amount of cells, a statistic significant difference of each concentration of taurolidine was shown in all cell lines (Dunnett's multiple comparison test, with the cell amount of lowest cell proliferation as controls was for all cell lines $P<0.01$). A definite concentration of taurolidine led to a lower cell proliferation when the primary quantity of cells was low. For higher quantities of cells more taurolidine was needed to inhibit cell growth (post test for linear trend was for all cell lines $P<0.0001$). We confirmed that an increase of the concentration of TRD

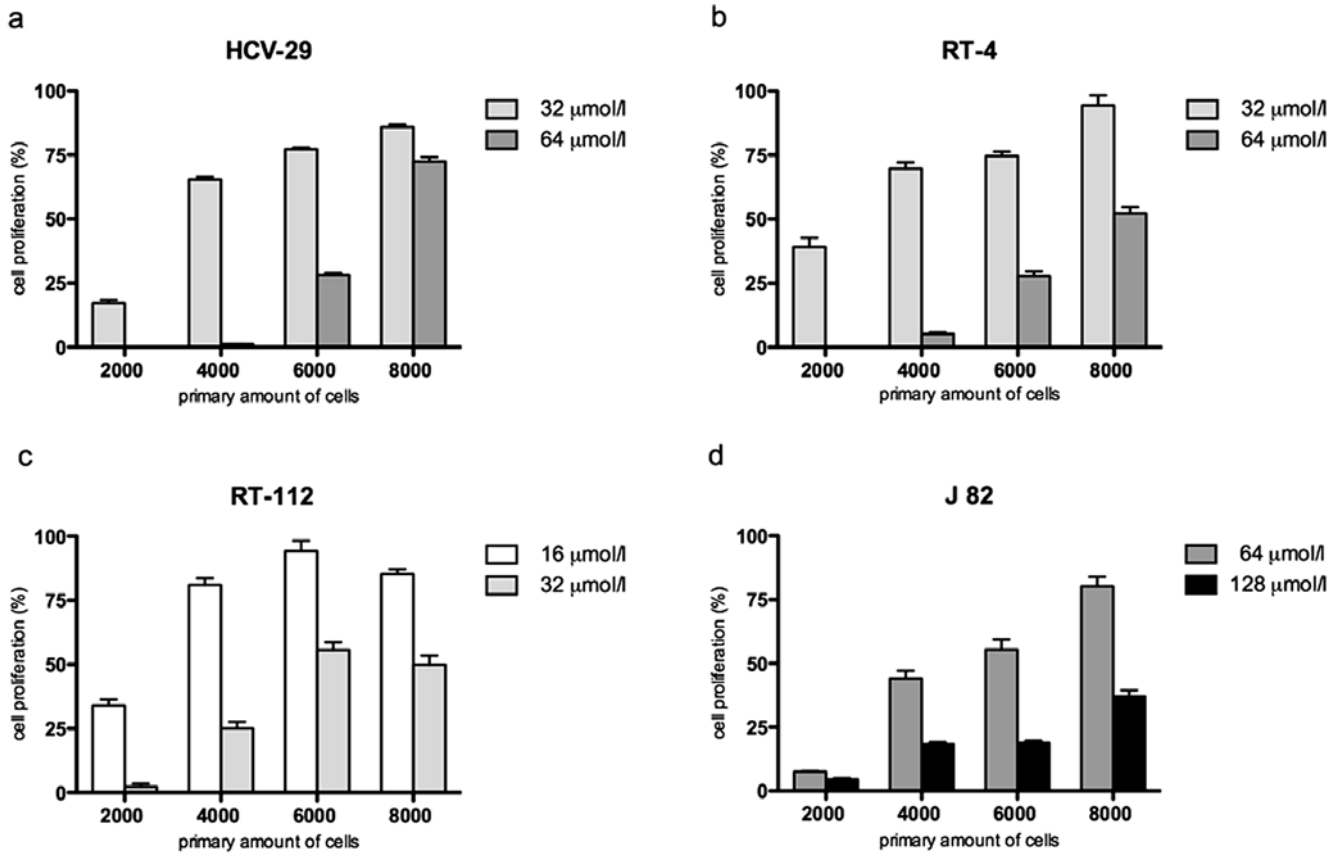

Figure 2. Effects of 48 h incubation of taurolidine on the proliferation on HCV-29, RT-4, RT-112 and J-82 cells, depending on concentration (16, 32, 64 and 128 μmol/l) and primary quantity of cells (2,000, 4,000, 6,000 and 8,000/well). Cell proliferation is shown as means of six repeated measurements.

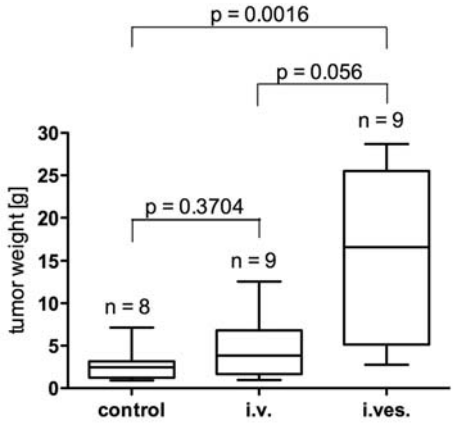

Figure 3. Tumor weights 5 weeks after $2x10^6$ AY-27 cell injection. Animals in the i.v. group received taurolidine 2% three times/week with 15 ml/kg, started already 2 days before cell injection. Animals in the i.ves. group were treated once per week with taurolidine 2% instillation into the urinary bladder.

resulted in a decrease of cell proliferation. The extent of cell proliferation reduction against different concentrations of TRD depended on the primary quantity of cells in our *in vitro* study. More cells yielded in higher concentrations of TRD in order to gain comparable inhibitory effects of cell proliferation.

In vivo study. In all rats, bladder tumors were successfully implanted by the tumor cell injection. From the initial 26 rats 4 rats (one in the control group, 3 in the i.ves. group) died prior to the end of the study due to the tumor size and/or associated complications during the therapeutic procedures under anesthesia. Fig. 3 shows the tumor weights of all animals after the end of the study. The tumor weights at death of the animals that were lost before the end of the study, were also included. Animals, which were treated systemically with TRD via intravenous injection (median: 3.8 g, min: 1.0 g, max: 12.6 g) showed no statistically significant difference of tumor weight in comparison to the animals in the control group (median 2.5 g, min: 0.9 g, max: 7.1 g), whereas in contrast, the animals treated i.ves. presented statistically significant higher tumor weights compared to the animals in the control group (median 16.6 g, min: 2.7 g, max: 28.7 g).

Discussion

Taurolidine [bis-(1,1-dioxoperhydro-1,2,4-thiadiazinyl-4)-methane] (TRD), a product derived from the aminosulfoacid taurin, was first described as an anti-bacterial substance (19,30). The agent was originally used in the local treatment for peritonitis as well as an anti-endotoxic agent in patients with a systematical inflammatory response syndrome (31), it has been shown to be effective in the prevention of catheter-related bloodstream infections (32,33). Moreover, it was demonstrated that TRD affects tumor growth in animals and humans due to induction of apoptosis (34-36) in addition to the influence in inflammatory diseases due to a destruction of the bacterial cell membrane (26,37).

In this study, we investigated the probable anti-neoplastic effect of TRD on different urothelial cell lines. To our knowledge this is the first analysis of TRD to investigate the inhibitory effect on the normal human urinary bladder cell line HCV-29, the human bladder carcinoma cell lines RT-4, RT-112 and the rat bladder carcinoma cell line AY-27. We demonstrated in our studies *in vitro* the inhibitory effect of TRD for the cell proliferation in a dose-dependent manner. An increase of TRD concentration resulted in a decrease or a nearly complete inhibition of cell proliferation. Higher quantities of cells needed higher concentrations of TRD to offer a comparable inhibition of cell proliferation. These results were demonstrated in all tested cell lines. We therefore suggest that the inhibitory effect of TRD is not tumor-specific. Only the undifferentiated human bladder carcinoma cell line J-82 resisted in longer incubation times with a residual cell proliferation. A maximum inhibiting effect could be shown with low primary quantities of cells, high concentrations and incubation times of TRD.

After the promising *in vitro* results of cell proliferation inhibition by TRD, an *in vivo* study with systemic vs. local treatment followed on the base of TRD treatment in clinical routine as shown in the literature (27).

In terms of choosing the right treatment concentration of TRD for the rats we faced a compromise. The concentration of TRD needed to be high enough to see an *in vitro* effect but also sufficiently low to prevent respiratory suppression in the animals as described in other studies (13). In this study, we decided to use the concentration as described in human standard therapy and suitable for intravenous (i.v.) injections and other animal studies with comparable total doses (28,29). We decided to use the commercially available ready-to-use TRD 2% solution, which has been already used in human i.v. therapeutic studies (27). In order to limit the respiratory depression caused by the injection of TRD we made very slow i.v. injections, which were better tolerated by the rats. Except for this side effect we did not observe any other toxicity.

The literature presents various techniques to generate a bladder carcinoma in the rat. After preliminary studies with different tumor induction (data not shown) we decided on the technique of the AY-27 cell injection into the urinary bladder muscle as described by Bachor *et al* (38). This model is succesful with a tumor incidence of 100% and a solitary tumor formation after a given period of growth. Using that model, TRD 2% was not able to prevent the growth of the tumor and did not demonstrate an inhibitory effect in the i.v. treated animal group nor in the intravesically (i.ves.) treated animal group. In contrast, the animals treated with TRD i.ves. showed statistical significant higher tumor weights in comparison to the systemically treated animals or control animals. Additionally, our study showed a tendency of increased tumor weights in the i.v.-treated group in comparison to the control group. Furthermore, we faced a loss of three animals in the i.ves. group, partly under anesthesia before the end of our study. Those animals suffered from very large tumor masses, which resulted in a reduced general condition and consequently a lower tolerance to anesthesia. These tumors were also weighted and included in the analysis.

This study revealed an unexpected effect of boosting tumor growth by the local, i.ves. therapy with TRD. Due to our findings it cannot be excluded that a weekly bladder instillation with TRD at a concentration of 2% could have some harmful effects on the urothelium, which could facilitate tumor growth. Braumann *et al* demonstrated, not as statistically significant but as a tendency, that bolus injection of TRD resulted in higher tumor weights when used in higher concentrations (13). In our study, the animals treated i.ves. presented the largest tumors from all study groups.

In the literature many of the *in vivo* studies of TRD describe a reduction of tumor growth induced by intraperitoneally injection of tumor cells. In this context a direct cytotoxic effect caused by an interaction with the tumor cell membrane and a subsequently intracellular alteration may explain the suppression of tumor growth (11). Bedrosian *et al* demonstrated that the effect of TRD depends on direct cell contact (20). By direct application TRD is able to induce apoptosis of tumor cells (11,14,34,35). The apoptotic mechanisms of TRD include activation of the mitochondrial cytochrome c-dependent pathway (3,26) as well as inhibition of protein synthesis (36,39). As stated in the literature the AY-27 tumors form a layer of normal or hyperplastic cells covering the carcinoma (38,40). It might be possible that TRD could not have been able to penetrate into the tumor when instilled into the bladder or did not get in sufficient close contact. As well it is possible that TRD did not have a sufficient high concentration after blood stream dilution when treated systemically to the newly generated tumor with the AY-27 cell line to expose any effect to the tumor cells. Furthermore, the concentration of TRD to treat the bladder carcinoma effectively was too low when injected intravenously. Above all, we additionally suppose unknown factors of the urothelial and tumoral microenvironment with TRD that encouraged tumor growth. We did not discuss the use of higher concentrations of TRD because of the standard concentration of 2% in human therapy and the fact described by Braumann *et al* that higher concentrations of TRD did not show superior effects in a rat tumor model (13). Because of the failure of the anti-tumoral effect of TRD we did not add further examinations.

We summarize that TRD confirmed its anti-proliferative effect on human bladder carcinoma cells *in vitro* but has no reducing or inhibiting potential on the AY-27 bladder carcinoma model in the rat. In contrast, it seems to advance tumor growth when applied intravesically. In opposition to the tumor reducing effects of TRD described in the literature for other tumor entities, we cannot recommend TRD as a local alternative treatment in bladder cancer given the results from our study.

Acknowledgements

The authors thank Sabine Becker and Ines Baumert for their valuable technical assistance.

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