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SESSION IV

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Superficial bladder cancer: state of the art

Key words Superficial bladder cancer · State of the art

Natural history

Tumors that are limited to the inner layers of the bladder, i.e., the mucosa and submucosa, are classified as "superficial." The term includes carcinoma in situ (Cais), tumors that are limited to the mucosa (Ta), and the more invasive forms that penetrate into the lamina propria (T1). These tumors vary in their degree of cellular differentiation (from G1 to G3). Therefore, within the group of superficial bladder tumors there is a wide spectrum of tumors with different biological behaviors. Currently, it is assumed that every superficial tumor has the potential to progress to invade the muscle coat, but the majority of invasive tumors involve the muscle at first diagnosis, and only 40% of invasive tumors are true progressions from lower-stage tumors [37].

Grading is related to invasiveness: grade 1 tumors are usually papillary and confined to the mucosa (Ta), although lamina propria invasion can be observed in some cases [27]. Grade 2 tumors have a somewhat unpredictable behavior: lamina propria invasion at first diagnosis is more frequent (about 40%) and is related to high recurrence and progression rates. Grade 3 cancers display cellular pleomorphism, mytosis, and atypia, and muscle invasion can be expected in about 30%–50% of patients within 3 years.

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Carcinoma in situ (Cais) is a flat tumor occurring in association with papillary forms (concurrent Cais) or alone. In the latter case it may be primary or associated with papillary recurrences. The tumor foci are typically multiple and, in the pure form, are frequently dispersed throughout the entire mucosal surface. In about 60% of specimens from cystectomies performed for Cais, neoplastic foci can be found in the terminal ureters and prostatic urethra [26]. In the bladder bearing primary Cais, the development of invasive forms was highly probable (60%–70%) before the advent of bacillus Calmette-Guérin (BCG) treatment. The latter has changed the natural history of this disease, and complete and durable remissions may presently be achieved in about 65%–70% of cases by repeated intravesical instillations with BCG [29].

Superficial bladder carcinoma shows a high tendency to recur. For G1 and G2 tumors treated only be transurethral resection (TUR) the recurrence rate is about 30%–38%, whereas for grade 3 tumors it is greater than 70% [27]. Lamina propria invasion leads to a recurrence rate of more than 70%, regardless of grade.

Progression is defined as an increase in the grade or stage of the tumor at recurrence or the appearance of lymph-node or distant metastases. Distant metastases usually follow or occur concomitantly with local recurrence and progression, but in rare cases they may occur without apparent bladder recurrence. The accepted rates of progression as stratified for grade at first observation are 2%–5% for grade 1 (G1), 10% for G2, and 40%–50% for G3. Upgrading in recurrent papillary tumors is another form of progression. About 20% of G1 or G2 tumors show an increase in grade at recurrence. This type of progression is more frequent in G1 disease (13%) than in G2 tumors, which infrequently show an increase in grading at recurrence (only 3%) [61]. Progression rates are also quite obviously related to stage: Ta tumors have a progression rate of about 4% as compared with 30% for T1 disease.

Prognostic factors

One of the most important steps achieved in recent years has been the identification of the most significant risk factors in superficial bladder cancer.

In 1985 in Antwerp, Belgium, at the first Consensus Conference on bladder cancer, a committee for prognostic factors was set up and a consensus document indicating the most important prognostic factors was prepared [4].

Recurrence rates and survival correlate mostly with stage and grade and with the number of tumors seen at first observation [42]. Furthermore, five additional risk factors for recurrence can be indicated for primary tumors, including the number of tumors, the tumor size, the morphology of tumoral masses, positive cytology, mucosal dysplasia, and recurrence.

Tumor stage is a quite obvious prognostic factor, but the grade at first observation is also a rather reliable factor for predicting the disease-free interval was well as the recurrence and progression rates. The free interval is longer for G1 tumors and the progression rate is higher in G2 than in G1 tumors [40]. The association of stage and grade is a very important covariable in predicting the biological behavior of superficial bladder tumors [2].

The number of tumors at first observation has been seen to influence recurrence rates [47]. The European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary (GU) Group [14] has found in a controlled study that the recurrence rate significantly increases with the number of tumors present at first cystoscopy, and this finding has been confirmed in a personal series of 128 patients with primary T1G3 tumors treated conservatively. Some studies have even found a correlation between the number of tumors and recurrence rates [27]. In contrast, Cutler et al. [12] did not find any relationship between the number of tumors and the progression rate.

The impact of tumor size on the natural history of superficial bladder tumors is controversial due to the objective difficulty in performing accurate measurements and the influence of parameters such as the presence and size of a tumoral stalk, among others. Tumor size is usually well correlated to stage [75], and recurrence rates are frequently significantly lower in patients bearing tumors with maximal diameters of 1 cm or less [59]. In most studies, statistical analysis is not performed or size does not appear to be significant with respect to the recurrence rate [46]. A recent study at our institution, however, has found that a size greater than 3 cm is a significant predictor of recurrence for T1G3 primary tumors (unpublished data).

The morphology of the tumor appears to be another important prognostic factor for recurrence. Solid masses are reported to show high recurrence rates [5], but usually solid morphology is considered more predictive for invasion than for recurrence.

Positive cytology is generally related to a high histological grade and is therefore considered a predictor of shorter disease-free intervals [26]. At present, it is well established that the ploidy of cells found in urine or in pathology material is rather well correlated with the biological aggressiveness of superficial bladder tumors. The sensitivity of this technique is about 85%–90% and increases with stage. Diploid cells are usually found in tumors of low stage and grade, whereas tetraploidy, aneuploidy, and hyperploidy are related to aggressiveness and high progression rates. DNA analysis is helpful mainly for identifying those G2 superficial tumors at risk for recurrence [25], since the majority of G3 tumors are tetra- or aneuploid and there is a frequent correlation between ploidy and grading [53]. Therefore, it is possible that in routine practice the assessment of the DNA content of tumor cells does not add much to the information obtained via optical cytology and histology.

Urothelial dysplasia in bladder mucosa is a well-known prognostic factor [77], and the recurrence rate is significantly higher in cases with dysplasia than in those without dysplasia [68]. The presence of Cais increases the risk of recurrence, but recently three categories of Cais have been identified: (a) Cais associated with papillary tumors, (b) total bladder (and upper tract) disease, and (c) relatively asymptomatic patchy disease. Whereas the former two forms carry a poor prognosis, the asymptomatic form seems to have a good outlook [62].

Our recent data (unpublished) indicate that positive cytology and the presence of epithelial dysplasia at entry are the most significant factors for the prediction of recurrence in stage 1, G3 tumors. They were also found to influence the free interval to first recurrence. The pathology of the first recurrence and the number of subsequent recurrences did not appear to be risk factors for further recurrence.

The number of recurrences seems to be another important prognostic factor: the difference in the recurrence rate between primary and recurring Ta is about 5%, and in T1 this differences becomes very significant (24% versus 56%) [13]. The EORTC studies have shown that the recurrence rate prior to observation is a very significant prognostic factor for further recurrence [74].

In examination of the progression rate in series of superficial bladder tumors carefully followed for a sufficient number of years, it appears again that the grade and stage are predictive factors. The National Bladder Cancer Group [27] and European studies [73] have found that stage T1, G3 tumors carry a very high risk of progression (43% for G3 and 30% for T1). Cais is G3 by definition and has long been recognized as a predictor of progression when associated with papillary tumors [69]. However, more recent observations seem to suggest that the presence of Cais with papillary forms does not always predict invasiveness [29]. Epithelial dysplasia or atypia, even without overt Cais, are other important risk factors associated with muscle invasion: in patients with such dysplasia, progression may be expected in about 30% of cases.

Small-vessel invasion in the lamina propria is also a reliable prognostic index: the majority of patients in whom T1 tumors show small-vessel invasion progress and the disease- specific mortality is very high (70%) [2].

When recurrence occurs, the pathology of recurring tumors may be indicative of the future outcome of the disease: a high percentage of cases with progression in grade or stage and/or with Cais ultimately develop muscle-invasive disease. In contrast, the time to first recurrence and the number of recurrences do not appear to be significant.

Surgery in superficial bladder carcinoma

Presently, surgery for superficial bladder carcinoma is performed endoscopically, with rare exceptions being large tumors located in thin-wall diverticula or associated with huge prostatic hyperplasia.

Endoscopic surgery is preceded by examination of the entire distended urethra through a 0° lens and the taking of cold-up biopsies with appropriate forceps. The resection must extend into the muscle, but a separate specimen of the bladder wall underlying the tumors should be obtained. It is also preferable to perform multiple cold biopsies of the muscle with a forceps after the transurethral resection (TUR). When Cais is present or suspected, a biopsy of the prostate is recommended. Bimanual palpation of the bladder is mandatory, as is removal of a urine sample for exfoliative cytology just before the start of resection. Video endoscopy with recording, which allows complete documentation of the macroscopic situation in the bladder before and after surgery, is becoming routine.

During the last decade, laser photocoagulation has been increasingly adopted in the treatment of superficial bladder tumors. Experience has demonstrated the reliability of this technique and its relative safety. Laser surgery probably will not replace the usual electroresection, but it has some advantages that cannot be ignored. Some experimental data suggest that laser surgery can decrease the recurrence rate by avoiding the immediate implantation of floating vital cells after TUR [67], probably because there is no contact between the coagulating device and the tumor [47]. Another advantage could be the sealing of small lymph vessels during laser photocoagulation, which could be of benefit in terms of prevention of local tumor spread. Moreover, the Nd:YAG laser is very effective in coagulating blood vessels and, thus, reducing intraoperative and postoperative bleeding such that patients can resume their normal activities almost immediately. Other advantages are: the absence of obturator nerve stimulation; the use of the laser device with flexible cystoscopes; less pain during treatment, leading to shorter periods of anesthesia; and a reduced need for postoperative catheterization.

Problems arise with the pathological examination after laser use. Although the dissected tissue maintains its architecture, it may be difficult to examine, and the assessment of invasion in the basal tissue may be impossible.

Pure Cais, being multifocal, cannot be eradicated by TUR alone and represents a good clinical model for testing antineoplastic drugs. In recent years, another clinical model has been proposed. In multifocal papillary tumors, one well-defined lesion is left unresected (marker lesion) and the intravesical treatment is carried out subsequently. The visual endoscopic and pathological examination will assess objectively the response to the therapy.

Indications for intravesical therapy

The body of experience and the assessment of risk factors strongly indicate that adjuvant local therapy yields better results in terms of both recurrence and progression rates in comparison with TUR alone [42].

Intravesical therapy is usually classified as follows: (1) adjunctive, a single administration after a complete TUR; (2) prophylactic or adjuvant, repeated administrations; and (3) therapeutic, to treat an unresected part of the tumor [64].

Adjunctive treatment serves mainly to avoid the implantation of floating cells during or immediately after TUR [71]. Some workers have demonstrated that single instillations are as effective as multiple courses, at least in tumors with favorable prognostic factors [19]. For intermediate-risk tumors, prophylactic treatment usually lasts for 1 year; its efficacy over TUR alone might be higher in low-grade than in high-grade tumors, and the beneficial effect could decrease in time [60]. Intravesical treatment decreases the incidence of short-term recurrences by 20%–30% [56], but it is doubtful whether it has any effect on long-term recurrence rates, progressions, or disease-specific mortality [3]. In fact, some of the initial studies conducted during the early 1980s suggested that intravesical prophylaxis could decrease the rate of progression to muscle invasion [24, 30], but subsequent controlled studies failed to confirm those favorable data [43, 63].

There is general agreement among urologists that post-TUR bladder instillations are advantageous, but no uniform consensus has been reached on the basic indications, the treatment duration, the timing for the start, the choice of drug, or the schedule. Large, multiple, or high-grade tumors, previous recurrence, positive urinary cytology, and the presence of epithelial dysplasia are the main indications for intravesical prophylaxis, as the recurrence and progression rates achieved with TUR alone are very high (>70% and 30%–50%, respectively) [24].

Principles of intravesical therapy

The goals of intravesical therapy may be summarized as follows: (a) to prevent tumor recurrence, (b) to increase the disease-free interval, (c) to eradicate residual tumor, (d) to prevent tumor progression and consequently save bladders, and (e) to improve the disease-specific survival.

In clinical practice, superficial bladder cancer commonly exhibits three distinct behavior patterns: (1) monofocal lesions, with a low recurrence rate and long disease-free intervals and without any tendency to progress in grade

Table 1 Therapeutic intravesical administration of chemotherapeutic agents: schedules (*CR* Complete response)

Drug	Reference	Regimen	Number of pts	Rate of response
THT	Edsmyr and Boman [17]	50 mg q2d × 6	29	83%
THT	Nieh et al. [54]	60 mg/week × 2	27	56%
MIT	Mishina et al. [51]	40 mg/week × 7	50	44% CR
MIT	Issel et al. [32]	30 mg/week × 8	29	43% CR
EPD	Colleen et al. [11]	1.1 mg every week × 13, every 2 weeks × 6, every month × 3, every 3 months	39	69%
DXR	Matsumura et al. [49]	50 mg 3 X weekly × 2	261	60%
DXR	Ek et al. [18]	80 mg/month × (variable)	22	58%
DXR	Abraham et al. [1]	50 mg in 1 instillation	33	40%
EPR	Matsumura et al. [50]	50–80 mg daily × 3 × 2	33	55%
EPR	Calais da Silva et al. [10]	50 mg/week × 8	44	50%
EPR	Burk et al. [9]	80 mg/week × 6	22	50%

or stage; (2) tumors with frequent recurrences, often with small, multiple lesions; and (3) aggressive tumors, associated with epithelial dysplasia, high recurrence rates, frequent recurrence at first control cystoscopy, and a tendency to progress in stage. At first observation, rough criteria for foreseeing the future behavior of disease may be as follows: single tumor, stage Ta, G1 or G2, absence of dysplasia, diploidy, negative urinary cytology = favorable outcome; Multiple lesions or large tumors, stage T1, G3, dysplasia present, aneuploidy, positive cytology = unfavorable outcome.

Once the decision has been made to proceed with instillation, the choice of drug is often difficult. The ideal therapeutic agent to be given intravesically should be very active (such that few instillations should be required), should not be absorbed by the bladder wall, and should be nontoxic. Quite obviously, none of the available drugs has all the aforementioned characteristics, and no single drug can be considered the best since many clinical trials have failed to show a clear advantage for any drug over the others.

Intravesical therapy with antineoplastic drugs dates back to the mid-1950s, and a wide number of agents have been tested. Currently, six drugs have demonstrated their therapeutic activity with acceptable toxicity: thiothepa (THT), mitomycin-C (MIT), ethoglucid (EPD), doxorubicin (DXR), and epirubicin (EPR). Experience has also shown that an attenuated strain of *Mycobacterium bovis*, bacillus Calmette-Guérin (BCG), is active against superficial bladder carcinoma.

THT is an alkylating agent that produces cross-linking between DNA, RNA, nucleic acids, and protein, ending in inhibition of protein synthesis. EPD is a podophyllin derivative that acts on cellular division in a manner similar to that of alkylating agents. MIT is an intracellular agent that produces a bifunctional alkylating effect. DXR and EPR are anthracycline antibiotics that bind to base pairs of DNA. BCG is an immune modulator that enhances the immune response and production of lymphokines.

Intravesical treatment implies some important problems other than the choice of the drug. According to the EORTC they include the timing of the first administration, the frequency of instillations, and the duration of treatment.

Early instillation may induce cystitis as the drug comes into contact with flogistic tissues. In largely resected patients the bladder tends to become spastic for a few days and frequently contains clots and necrotic debris in the lumen, preventing good contact between the drug and the transitional epithelium. The probability of cystitis from early instillation may be high and no clear therapeutic advantage has been observed [66]. However, in the EORTC experience, early instillations are not associated with a high rate of complications (EORTC 30831).

Despite extensive clinical research, the optimal frequency of drug instillation remains undefined: when the treatment has ablative purposes against residual tumor, it is probable that the administration should be intensive on a weekly base. Various therapeutic schedules have been reported, and Table 1 summarizes some of the most common of these.

For prophylaxis, an induction period followed by maintenance seems advisable. In Japan it has also been proposed that the instillations be grouped daily for 2–3 days every month or less [72]. Table 2 reports some data on prophylaxis. For BCG the increasing experience indicates that a single 6-week cycle of intravesical instillations is often adequate as either prophylaxis or treatment. Further cycles may be given to nonresponders, after which the response rate is shown to increase (EORTC 30861).

The duration of treatment is another point of controversy. A single early instillation has not infrequently been claimed to be prophylactically effective, especially in monofocal, low-grade primary tumors [41], but this schedule may be insufficient to treat urothelial precancerous

Table 2 Chemoprophylaxis: schedules

Drug	Reference	Regimen	Number of patients	Rate of recurrence
THT	Koontz et al. [38]	30 mg/week × 6, every month × 11	93	40%
THT	Schulman [65] (EORTC 30751)	30 mg/week × 4, every month × 11	122	56%[a] 71%[b]
MIT	Bracken et al. [7]	30 mg/week × 4, every month × 11	21	29%
MIT	Devonec et al. [16]	40 mg daily × 10	26	88%
DXR	Niijima [55]	30 mg biweekly × 1 20 mg biweekly × 1	149 148	43% 48%
DXR	Zincke et al. [79]	50 mg/week × 4, every month × 11	16	33%
DXR	EORTC 30832	50 mg early/delay: triweekly × 4 trimonthly × 5	366	13%/14% (early) 30%/24% (delay)
EPR	Calais da Silva et al. [10]	50 mg/week × 6	44	34%

[a] Primary tumors
[b] Recurrent tumors

abnormalities present in a significant number of patients. These abnormalities are probably responsible for most of the new tumors ("new occurrences") and can be destroyed only by means of long-term prophylactic treatment [33]. Empirically it is suggested that maintenance treatment be continued for 1 year: if the patient does not show recurrence during this period, prophylaxis can be safely stopped. When the prognostic factors are unfavorable, prolongation of maintenance therapy has recently been suggested – for 2 years or more. The real efficacy of such long-lasting maintenance is a matter of debate. For instance, the prophylactic administration of weekly doxorubicin for 6 weeks yields results comparable with those obtained by long-term 2-year maintenance [20].

Finally, it must be pointed out that consensus on the single drug dose per instillation and the drug dilution is lacking. For each chemotherapeutic drug, experience has indicated a mean dose providing maximal activity with minimal side-effects (Table 3). Dose escalation does not usually lead to better therapeutic activity, whereas it does increase systemic absorption and side effects. For BCG the identification of the optimal dose is of paramount importance, as the side effects are never negligible, even with a limited dose. In one series, half of the currently employed BCG dose (75 mg) was shown to be as effective as the usual regimen with minimal side effects [58].

Results of intravesical treatment

THT was the first intravesical agent used. In prophylaxis, THT is associated with a 30% reduction in recurrence rate as compared with TUR alone (66% versus 44% of patients being tumor-free at 1 year) [8, 38]. In about 50% of patients with residual disease after TUR, the weekly administration of THT (6–12 weeks) eradicates the residual tumor. Cais responds poorly to THT (response rate not greater than 20%–30%); therefore, the drug is no longer used. EORTC study 30782 (THT versus DXR versus cisplatin) has shown that long-term disease-free survival and disease-specific survival are not modified by THT prophylaxis.

The prophylactic activity of epodyl is comparable with that of DXR (EORTC 30790), as it reduces tumor recurrence by 50%. When it is given as a therapeutic agent the response rates [complete (CR) and partial (PR)] are about 80% [70]. The drug has also shown some activity in Cais. Whether this drug may prevent progression, thus prolonging survival, is not known.

The response rates observed after mitomycin-C therapy range from 50% to 90%, with an objective CR rate of about 44% [51], and Cais responds fairly well to the drug [30]. It is noteworthy that MIT can be active in case of THT failure [15].

DXR has been studied extensively. On the whole, many controlled clinical trials have shown that DXR decreases recurrence rates by 35% as compared with TUR alone. Niijima [55] reported a response rate of 74% with 60-mg instillations, whereas Garnick et al. [21] registered a 53% response rate. When the data coming from current experience are taken into account, a CR rate of about 50% in residual tumors can be expected with this drug [31] (Table 4). DXR is clearly active against Cais; in a controlled study on 55 patients with primary, secondary, and concurrent Cais

Table 3 Current doses used in intravesical treatments

Drug	Min. dose (mg)	Max. dose (mg)	Mean dilution
THT	30	60	30–60 ml
EPD	1000	1300	100 ml
MIT	20	60	50 ml
DXR	30	200	30–100 ml
EPR	30	50	50 ml
BCG	75	150	50 ml

Table 4 Doxorubicin as definitive treatment

Reference	Number of patients	CR (%)	PR (%)	Failures (%)
Ozaki et al. [57]	80	27	44	29
Niijima [55]	194	20	37	43
Edsmyr and Boman [17]	53	70	9	21
Garnick et al. [21]	27	56	11	33

the response rate reached 80%, 67%, and 25%, respectively [22]. The EORTC Genito-Urinary (GU) Group has studied the activity of the drug in a phase II study with a marker lesion, the statistical analysis of which is ongoing (30869).

In prophylaxis, DXR has been tested in several controlled studies involving numerous patients treated with various doses (Table 4). The so-called BLINST study [6] evaluated the activity of the drug in 236 patients with primary tumors and 199 patients with recurrent tumors and found that the median time to recurrence was 27 months for primary lesions and 16 months for recurrent disease. The study carefully assessed the local side effects (25.4%) and systemic adverse reactions (6.5%); the treatment was discontinued in 6.5% of cases.

Another large study was performed in Japan by the Japanese Urological Cancer Research Group [39, 56]. DXR was tested at various doses and dilutions (30 mg/30 ml; 20 mg/40 ml) using short- and long-term treatments in 644 patients in comparison with mitomycin (314 patients) and no treatment (318 patients). For short-term therapy the recurrence rates were 34% (30 mg/30 ml) and 31% (20 mg/40 ml), and for long term treatment they were 27% and 24%, respectively (for MIT, 31.7% and 24.4%). In the United States, Burk et al. [9] tested DXR at the same dose with different instillation intervals (1–4 weeks): the recurrence rates at 36 months of follow-up were correlated to the frequency of instillations (from 1.6% to 29.4%). Clear prophylactic activity has also been shown for single instillations with a recurrence rate of only 25% [79]. The EORTC GU Group analyzed the efficacy of early versus delayed instillations in 448 patients (study 30832) and the preliminary results obtained at the present cut-off analysis seem to confirm equivalent activity for both schedules. Personal experience with DXR prophylaxis in high-risk tumors (T1G3, 128 primary cases with a mean follow-up of 6 years) has shown that the drug is effective in a high percentage of cases (56.2% recurrence rate and 23.4% progression rate).

EPR was tested through a marker-lesion clinical model in an early clinical trial; weekly administration proved to be very effective with a high proportion of pathological CRs (67% in primary lesions and 37% recurrent tumors) [10]. In Japan, Matsumura et al. [50] treated 33 patients and obtained a 55% therapeutic response rate. The EORTC GU Group has undertaken a study to compare the prophylactic activity of EPR versus controls in good-prognosis superficial tumors (30863), and more recently another trial analyzing the activity of single instillation has been activated.

In 1976, Morales et al. [52] reported that BCG was particularly active in the treatment of superficial bladder cancer. The mechanism of action is not yet completely known, but BCG stimulates a systemic immune response as evidenced by the granulomatous reaction that takes place locally in the regional lymph nodes and in the liver. The administration of BCG causes an increase in T-cells, B-cells and macrophages as well as in killer-cell and natural killer (NK)-cell activities. Lymphokines can be retrieved in the bladder lumen after instillation, and a lymphokine-activated killer (LAK)-cell activity has been seen experimentally in the spleen and lymph nodes. The attachment and internalization of BCG into the urothelium is mediated by fibronectin.

A great number of clinical trials have demonstrated that BCG significantly reduces short-term recurrences and that it is more active against Cais than conventional chemotherapeutic agents. In papillary tumors with poor prognostic factors the use of BCG is frequently advocated as the treatment of choice [64]. Martinez-Pineiro et al. [48] showed that BCG was more effective in the prophylaxis of Ta, T1 tumors as compared with THT and DXR (recurrence rate: THT, 35.7%; DXR, 43.4%; BCG, 13.4%), also improving the disease-free interval. Similar results were registered by Lamm et al. [45]. In contrast, an EORTC GU Group study (30845) comparing BCG (RIVM) and MIT, for which the final analysis is not yet available, seems to fail to demonstrate any superiority for immunotherapy. Another EORTC study comparing EPR and BCG (Connaught) is ongoing (30911).

EORTC GU Group study 30861 recruited 104 patients with Cais to be treated with 120 mg BCG Connaught and achieved a CR rate of 83% (76% after only one cycle of six instillations), thus demonstrating the high therapeutic activity [35]. In conclusion, although adjuvant intravesical treatment is surely active, whichever drug is imployed, only the disease-free interval and short-term recurrence rates seem to be favorably influenced (decreased by 30%–40%). With BCG, the recurrence rate may be further reduced (by more than 50%).

Intravesical chemotherapy probably does not decrease progression rates in high-risk tumors [3], but some activity in decreasing progressions cannot be completely excluded [31]. In fact, although MIT is not always capable of concentrating within the lamina propria [5], DXR and EPR have proved to be active on marker lesions and on Cais [10, 34, 44] and BCG seems to be effective in altering the natural history of the disease and, probably, in reducing progressions [28, 58].

Complications

The instilled drugs may induce adverse reactions within the bladder or systemically. It is quite obvious that the systemic side effects are correlated with transvesical absorption of the drug, which depends mostly on the molecular weight of the compound.

About 20% of THT is normally absorbed through the normal bladder wall. If inflammation is present, absorption may increase. The principal adverse systemic effect of THT is mylosuppression, which seems to be related to the monthly cumulative dose. When the delivered monthly dose exceeds 80–90 mg, the risk of myelosuppression increases. Systemic reactions have also been reported for EPD, but their frequency is difficult to determine. MIT absorption is low due to its high molecular weight, but allergic reactions are somewhat frequent (3%–20%). In rare cases, MIT has been associated with leukopenia and thrombocytopenia. Systemic absorption of DXR and EPR is negligible; therefore, the side effects of these drugs are mainly local.

BCG adverse effects may be severe, even though less than 5% of patients will manifest general reactions. A recent analysis has investigated the adverse systemic reactions and complications observed in 2400 patients. These include fever (3%), granulomatous prostatitis (1%), systemic infections (0.7%), sepsis (0.4%), allergic reactions and arthralgia (0.8%), localized infections such as epididymitis (0.4%), and contracted bladder (0.2%). When a serious BCG infection is clinically evident, the recommended treatment is a three-drug antitubercular regimen (Isoniazid, Rifampicin, Cycloserine). In case of improvement, Isoniazid and Rifampicin are continued for 2 weeks. In case of persistent symptoms or pneumonitis, the treatment must be continued for at least 3 months.

Future prospects

Interferons

Interferons (IFN) are induced proteins with antiviral, antiproliferative, and immunomodulatory properties. They have been used for therapeutic purposes through instillation or intralesional administration. A 1988 review stated that complete responses could be obtained in about 25% of cases after incomplete TUR. More recently, a beneficial effect has been confirmed in Cais and in papillary tumors with IFN-alpha [23, 76]. Personal experience with IFN-beta in a series of low-risk primary tumors has demonstrated an absence of toxicity for the drug and an activity comparable with that of common chemotherapeutic agents.

Interleukin

Interleukin (IL), or T-cell growth factor, is a polypeptide lymphokine acting similarly to hormones. It also activates LAK and NK cells, which respond by releasing IFN-gamma. The timing, dose, and activity of IL-2 remain to be defined. A pilot personal study with IL-2 in low-risk primary tumors failed to demonstrate reliable prophylactic activity.

Keyhole-limpet hemocyanin

Keyhole-limpet hemocyanin (KLH) is a high-molecular-weight protein extracted from this sea mollusk. It is a potent aspecific immunostimulant used in skin tests. The substance was used first in 1974 and sporadically in the following years. It has more recently been used subcutaneously and intravesically in a controlled study in comparison with Epodyl. The recurrence rate was lower in the KHL-treated group of patients [36].

Camptothecin

Camptothecin is a vegetal alkaloid having experimental activity against mouse leukemia, as it probably interferes with DNA synthesis. It has been used in 77 patients with superficial bladder cancer or papilloma through instillation of 20 mg and compared with BCG (49 patients). The major side effect was nausea and vomiting. The drug was comparable with BCG [78].

Brompirimine

Brompirimine (2-amino-5-bromo-6-phenyl-4H-pyrimidone) is a biological response modifier eliciting cellular and humoral responses in animals. It induces the production of IFNs and modulates other lymphokines, and it has antiviral and antitumoral properties synergistically with other chemotherapeutic agents. Its antitumoral effect approaches that of BCG. It is also active following oral administration, and a controlled phase II trial in superficial bladder cancer will be activated soon.

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