INTRODUCTION

Bladder tumor is considered one of the most common cancers in the world, about 20 percent of people diagnosed eventually die because of the disease ***(Brausi et al., 2011).***

The highest incidence of bladder cancer was observed in Europe, the United States, and Egypt, respectively ***(Chavan et al., 2014).***

Bladder cancer is 3 to 4 times more common in men than women. It's incidence increase in the sixth decade of life ***(Malats and Real, 2015).***

It is the 2nd common site of cancer in men as it represent 12.7% ***(Ibrahim et al., 2014).***

Transitional cell carcinoma (TCC) is the most common tumor of the bladder and, at initial diagnosis, it occurs as a superficial disease in approximately 75% of patients ***(Babjuk et al., 2013).***

Transurethral resection of bladder tumor(s) (TURBT), is considered the treatment of choice ***(Crawford, 2002).***

Despite visually complete resection, there is a high rate of recurrence possibly due to implantation of tumor cells after TURBT or residual non visible disease ***(Sima et al., 2015).***

The high rate of recurrence and stage progression represents an important challenge. So intravesical instillation of chemotherapeutic or immunotherapeutic drugs following TURBT play a role in reducing the incidence of recurrence and progression of the disease. Immunotherapeutic drugs as Bacillus Calmette-Guérin (BCG) may stimulate the body's immune system which act directly on the tumor cells ***(Jones et al., 2012).***

There is Local side effects in 90% of patients undergoing BCG treatment. More seriously, severe systemic complications as hemodynamic changes, persistent high-grade fever, allergic reactions (joint pain, rash) or solid organ involvement (epididymitis, liver, lung, kidney, osteomyelitis, prostate) leading to discontinuation of the treatment or even resulted in several deaths ***(Van der Meijden et al., 2003).***

Despite the serious morbidity of BCG, improvement in overall survival has never been demonstrated and only two-thirds of patients respond to BCG treatment ***(Dalbagni et al., 2002).***

So researches was focused on new drugs or new drug combinations for intravesical instillation. Gemcitabine (GEM) has proven to be effective with minimal bladder irritation, and generally described as rapidly self-resolving ***(Laufer et al., 2003).***

Gemcitabine is an active systemic chemotherapeutic agent in the management of advanced bladder cancer and it has also been evaluated in the management of superficial disease ***(Jones et al., 2012).***

Gemcitabine has a molecular weight of 299 D, lower than that of commonly-used intravesical chemotherapeutic agents. This may enable gemcitabine to penetrate the bladder mucosa with beneficial effects. At the same time the molecular weight is high enough to prevent significant systemic absorption. Its pharmacokinetic properties also make gemcitabine an ideal drug for regional therapy ***(Gontero and Frea, 2006).***

Intravesical gemcitabine is a promising drug that may be an option in treating patients with non muscle invasive bladder cancer ***(Shelley et al., 2012).***

Trials of comparing between intravesical gemcitabine and BCG were performed, showed comparable results as regards recurrence rate, disease progression yet with less side effects for gemcitabine arm ***(Jones et al., 2012).***

Aim of the Work

The aim of this work is to evaluate the efficacy and safety of Gemcetabine as a local intravesical adjuvant treatment of non muscle invasive TCC in reducing the risk of recurrence and progression after TURBT in comparison to BCG.

Chapter (1)
Non Muscle Invasive Bladder Cancer

Introduction and incidence

Bladder tumor is the 9th most commonly diagnosed tumor in the world and the 2nd most common malignancy of the urogenital tract ***(Moreira et al., 2010).*** It's causing more than 130,000 deaths annually ***(Sinem et al., 2018).***

Bladder tumor is more common in developed countries, and more in males than females with incidence 4:1 ***(Ferlay et al., 2015).***

The incidence and prevalence of bladder tumors are seen in the sixth decade of life, especially its peak in the seventh and eighth. So it is mainly disease of elderly ***(Malats & Real, 2015).***

The highest incidence of bladder cancer was observed in Europe, the United States, and Egypt, respectively. There was the lowest level in Sub-Saharan Africa, Asia, and South America, respectively ***(Chavan et al., 2014).***

About 75% of bladder tumors are non-muscle invasive at initial diagnosis ***(Babjuk et al., 2017),*** Sixty percent of these patients experience recurrence and ten percent experience progression in 5 years ***(Ferro et al., 2019).***

Risk factors of bladder cancer

- ***Smoking:***

The most important risk factor for bladder cancer is cigarette smoking, although the association is not as strong as that observed between smoking and respiratory tract cancers. The burden of disease is substantial with an estimated 50% of bladder cancers caused by tobacco smoke. Known carcinogenic urinary compounds from cigarette smoking include aromatic amines, inorganic compounds such as arsenic, polyaromatic hydrocarbons, and aldehydes. Electronic cigarette use may not be risk free, as the composition of electronic cigarette liquids is complex and may contain, or create by the process of vaporization, known bladder carcinogens including aromatic amines, aldehydes, and polyaromatic hydrocarbons ***(Thomas et al., 2018).***

- ***Occupation:***

Occupation is the second most important risk factor for bladder cancer. It has been estimated that occupational exposures may account for as much as 20% of all bladder cancer. Exposure to naphthylamine, 4-aminobiphenyl (ABP), and benzidine, principally among workers in the textile dye and rubber tyre industries, are the agents that have been associated with bladder cancer. Because of strict regulations, these specific chemicals are now banned from

the workplace and contribute minimally to the current incidence of bladder cancer in Western countries. However, many other strong candidates for bladder carcinogens still exist, such as orthotoluidine, which is used now in the manufacture of dyes, rubber chemicals, pharmaceuticals, and pesticides. However the new finding stemming from different studies revealed that occupational cumulative exposure to aromatic acids are associated with high risk of bladder cancer ***(Porru et al., 2014).***

- ***Bacterial infections:***

Several investigators have suggested that chronic bacterial infections may play a role in bladder cancer formation. Clinically, chronic catheter use, stones, and infections are associated with bladder carcinoma, but the mechanism of neoplastic formation is not well understood. The mechanism of action may be related to the immunological disorders, and chronic chemical, mechanical irritation and production of carcinogens such as nitrosamines. Chronic urinary tract infections are associated with bladder cancer, reporting a 1.4 to 1.6 relative risk of developing bladder cancer for any history of urinary tract infection ***(Sui et al., 2017).***

- ***Radiation and chemotherapy:***

Second malignant neoplasms are late complications arising after exposure to genotoxic therapies, which include radiotherapy and some chemotherapeutic agents. It is interesting to note that urothelial cancer formation after radiation is not age related, but the latency period is 15 to 30 years. Further support that radiation can cause bladder cancer is an increased risk of urothelial cancer in patients with prostate or cervical cancer who were treated with radiation therapy ***(Steve and Jean, 2013).***

Chemotherapy destroys malignant cells by causing significant DNA and cellular damage but can also have a profound effect on rapidly dividing normal epithelium such as in the bladder. The only chemotherapeutic agent that has been proven to cause bladder cancer is cyclophosphamide ***(Nilsson and Ullen, 2008).***

- ***Genetic factor:***

Genetic predisposition has an influence on the incidence of BC via its impact on susceptibility to other risk factors. Exposure to arsenic in drinking water increases the risk of BC (Bladder Cancer) and chlorination of drinking water and subsequent levels of trihalomethanes are potentially carcinogenic ***(Steinmaus et al., 2014).*** A link between dietary habits and BC risk has been suggested ***(Witlox et al., 2020).*** While family history seems to have little impact ***(Egbers et al., 2015).***

Staging and Classification Systems

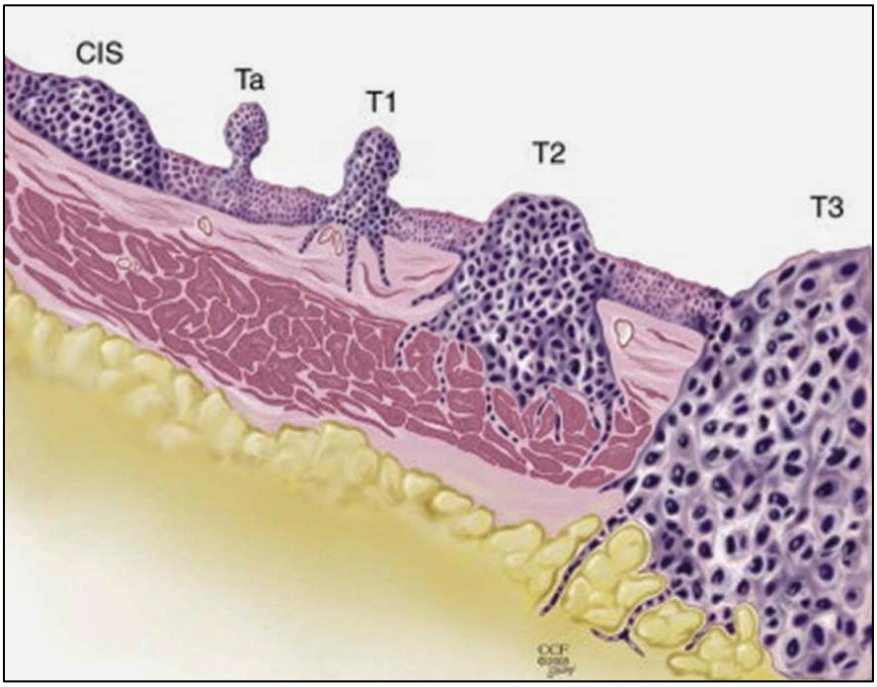

Figure (1): Histopathological classification of bladder cancer ***(Babjuk et al., 2021).***

Table (1): 2017 TNM classification of urinary bladder cancer ***(Babjuk et al., 2021)***

T: Primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Ta	Noninvasive papillary carcinoma
Tis	Carcinoma in situ: "flat tumor"
T1	Tumor invades subepithelial connective tissue
T2	Tumor invades muscle
T2a	Tumor invades superficial muscle (inner half)
T2b	Tumor invades deep muscle (outer half)
T3	Tumor invades perivesical tissue
T3a	Microscopic invasion
T3b	Macroscopic invasion (etravesical mass)
T4	Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
T4a	Tumor invades prostate stroma, seminal vesicles, uterus or vagina
T4b	Tumor invades pelvic wall or abdominal wall
N: Regional lymph nodes	
N	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral
N3	Metastasis in common iliac lymph node(s)
M: Distant metastasis	
M0	No distant metastasis
M1a	nonregional lymph nodes
M1b	Other distant metastases

Papillary tumors confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively (fig.1), according to the TNM classification system ***(Brierley et al., 2017).***

Flat, high- grade tumors confined to the mucosa are classified as CIS (carcinoma in situ) (Tis) (fig. 2). All of these tumors are grouped under the heading of NMIBC (non-muscle invasive bladder cancer).

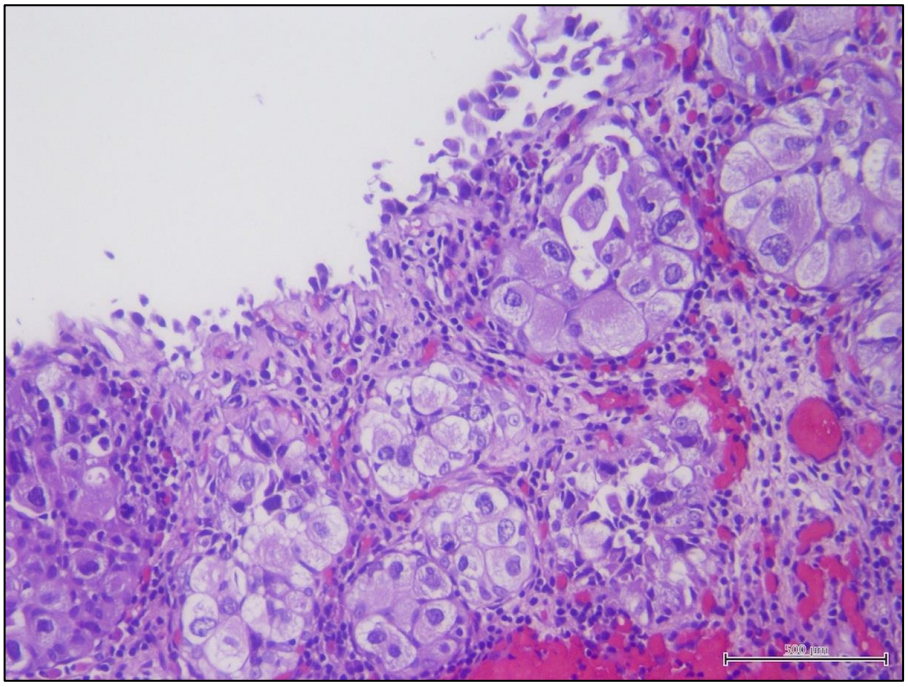

Figure (2): Carcinoma in situ ***(Magers et al., 2019).***

CIS and its classification:

CIS is a flat, high-grade, noninvasive urothelial carcinoma. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. CIS

is often multifocal and can occur in the bladder, as well as the upper urinary tract (UUT), prostatic ducts, and prostatic urethra ***(Babjuk et al., 2021).***

CIS can be classified as follows:

- Primary: isolated CIS with no previous or concurrent papillary tumors and no previous CIS.
- Secondary: CIS detected during follow-up of patients with a previous tumor that was not CIS.
- Concurrent: CIS in the presence of any other urothelial tumor in the bladder.

Histological grading of non–muscle-invasive bladder urothelial carcinomas

WHO and the International Society of Urological Pathology (ISUP) in 2016 updated a histological classification of urothelial carcinomas that provides a different patient stratification between individual categories compared to the older 1973 WHO classification ***(Moch et al., 2016)*** (Tables 2 and 3). In 2016, an update of the 2004 WHO grading classification without major changes ***(Moch et al., 2016).***

Table (2): WHO grading in 1973 and in 2004/2016 ***(Moch et al., 2016).***

1973 WHO grading
Grade 1: well differentiated
Grade 2: moderately differentiated
Grade 3: poorly differentiated
2004/2016 WHO grading system (papillary lesions)
Papillary urothelial neoplasm of low malignant potential (PUNLMP)
Low-grade (LG) papillary urothelial carcinoma
High-grade (HG) papillary urothelial carcinoma

Table (3): WHO 2004 histological classification for flat lesions ***(Babjuk et al., 2020).***

Non-malignant lesions
▪ Urothelial proliferation of uncertain malignant potential (flat lesion without atypia or papillary aspects ▪ Reactive atypia (flat lesion with atypia) ▪ Atypia of unknown significance ▪ Urothelial dysplasia
Malignant lesion
▪ Urothelial CIS is always high grade

Diagnosis of bladder tumors

- ***Signs and symptoms***

A- Gross painless hematuria is the most common finding in NMIBC. Visible hematuria was found to be associated with higher-stage disease compared to nonvisible (microscopic) hematuria ***(Ramirez et al., 2016).*** CIS might be suspected in patients with lower urinary tract symptoms, especially irritative voiding**.**

B- Voiding symptoms although most people with bladder cancer do not have symptoms, some have voiding symptoms, such frequency or urgency during the day or night and/or urge-incontence ***(Rais-Bahrami and Pietryga, 2016).***

- ***Imaging***

Ultrasonography (U/S) permits characterisation of renal masses, detection of hydronephrosis, and visualisation of intraluminal masses in the bladder. Ultrasound is able to differentiate between fluid-filled cysts and solid tumors as in (fig. 3), however, it cannot determine if a tumor is cancerous or not .U/S cannot rule out all potential causes of hematuria ***(Hilton & Jones, 2014).*** US cannot reliably exclude the presence of UTUC (upper tract urothelial carcinoma) and cannot replace CT urography.

Figure (3): Urinary bladder mass in U/S ***(Salmanoglu et al., 2018).***

Computed tomography (CT) (of the abdomen and pelvis) urography is used to detect papillary tumors in the urinary tract as mass lesion enhanced with cotrast, as showen in (fig. 4) and/or hydronephrosis. The CT scan can show the extent of a cancer, and determine if the cancer has spread outside the bladder ***(Trinh et al., 2018).*** The incidence of simultaneous upper tract urothelial carcinoma (UTUC) is low (1.8%), but increases to 7.5% for tumors located in the trigone ***(Lee & Chang, 2018).***

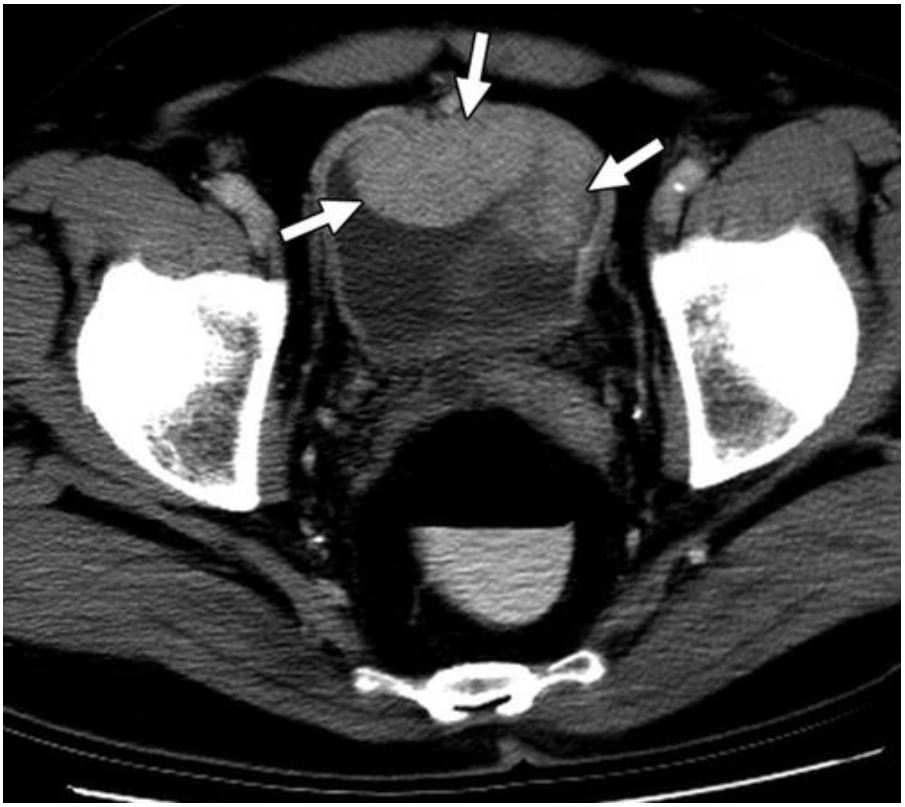

Figure (4): CT scan shows tumor as intraluminal enhancing mass (arrows) ***(Vikram et al., 2009)***

Magnetic resonance imaging (MRI) of the kidney, ureters, and bladder (fig.5) may provide additional information in staging bladder cancer and can be used in people with allergies to contrast dye ***(Rais-Bahrami and Pietryga 2016).***

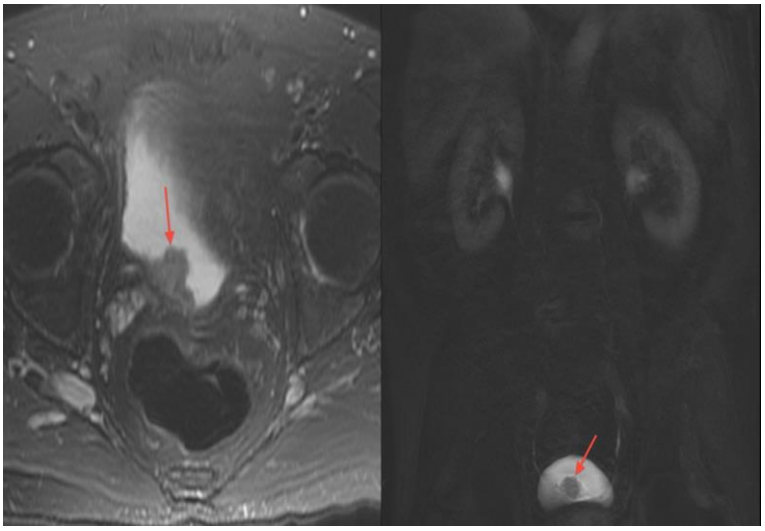

Figure (5): Bladder mass in MRI ***(Verma et al., 2012)***

- ***Urinary cytology.***

Examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in high-grade tumors (84%), but low sensitivity in low grade tumors (16%). The sensitivity for CIS detection is 28-100% ***(Liem et al., 2018)***.

Cytological interpretation is user-dependent. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations; however, in- experienced hands the specificity exceeds 90% ***(Goutas et al., 2021).***

- ***Urinary molecular marker tests.***

Numerous urinary tests have been developed as NMP22, Lewis X, FISH, CYFRA 21.1. None of these markers can replace cystoscopy in routine practice, but the

knowledge of positive test results can improve the quality of follow-up cystoscopy ***(Van Der Aa et al., 2010).***

- ***Endoscopic evaluation***

White light cystoscopy (WLC)

WLC is an endoscopic technique to visualize the urethra, bladder, and ureteric orifices. It is the gold standard for the examination and diagnosis of cancer of the lower urinary tract, using either flexible or rigid cystoscopy ***(Babjuk et al., 2017).***

WLC has a sensitivity of 85–90% for detecting papillary tumors and lower sensitivity (up to 67%) to detect CIS ***(Daneshmand et al., 2018).***

- *Advantages of semi-rigid WLC:-*

WLC has the advantage of being widely available and has lower cost than all the newer endoscopic techniques.

- *Disadvantages of semi-rigid WLC:-*

WLC has lower sensitivity to detect flat and CIS lesions, has limited ability to differentiate benign from malignant lesions, and is operator dependent ***(Tschirdewahn et al., 2020)***

Figure (6): Instruments of semi-rigid cystoscopy ***(Ku, 2019)***

Flexible cystoscopy

Flexible cystoscopy is often performed for initial diagnosis and surveillance.

- *Disadvantages of Flexible cystoscopy:-*

It can miss up to 10% of papillary tumors when compared to rigid cystoscopy ***(Daneshmand et al., 2018).***

The diagnostic yield of endoscopic removal of the tumor using flexible cystoscopy is limited, which can potentially compromise grading and staging of the tumor ***(Nargund et al., 2012).***

- *Advantages of flexible cystoscopy:-*

While flexible cystoscopy is more comfortable and convenient for the patient, and has higher cost than semi-rigid cystoscopy.

Flexible cystoscopy thus can be used in the primary evaluation or surveillance of BC patients, and (Trans-urethral resection of bladder tumor) (TURBT) can be then conducted using rigid cystoscopy when needed ***(Tschirdewahn et al., 2020).***

Fluorescent cystoscopy (FC).

FC, also known (photodynamic diagnosis) PDD, is a modification of WLC where an intravesical agent is instilled, and blue light (375-440 nm) is used for visualization. The instilled agents are photoactive porphyrin analogs, such as a 5-aminolevulinic acid (5-ALA) and hexaminolevulinate, which are taken up by epithelial cells and used in the formation of intermediate photoactive porphyrins. Intermediate porphyrins accumulate preferentially in neoplastic cells because of the accelerated enzymatic activity, and after excitation with blue light will return to lower energy levels and fluoresce. Tumor tissues will thus appear as well demarcated bright red lesions against a dark blue background (Fig. 7) ***(Soubra & Risk, 2015).***

PDD was found to have higher sensitivity 92% than WLC 71%, but lower specificity 57% vs. 72% ***(Liu et al., 2012).*** PDD has a higher sensitivity for CIS 92.4% compared to WLC 60.5% ***(Geavlete et al., 2010)*** and 10% more T1

lesions detected by PDD compared to WLC. No difference was detected for MIBC ***(Schumacher et al., 2010).***

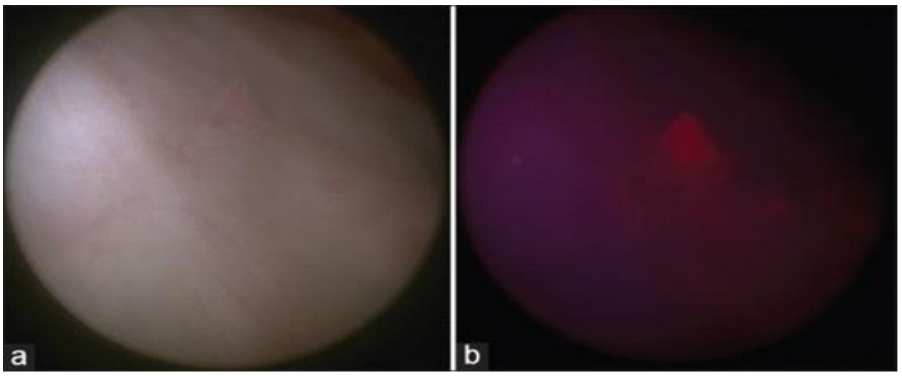

Figure (7): (a) White light cystoscopic image of a small bladder tumor. (b)Blue light cystoscopic image of the same small bladder tumor ***(Soubra & Risk, 2015).***

Narrow band imaging (NBI) (fig.8)

NBI is another modification to conventional WLC, where discrete blue (415 nm) and green (540 nm) light bands are used instead of the entire visible light spectrum ***(Lee et al., 2021).***

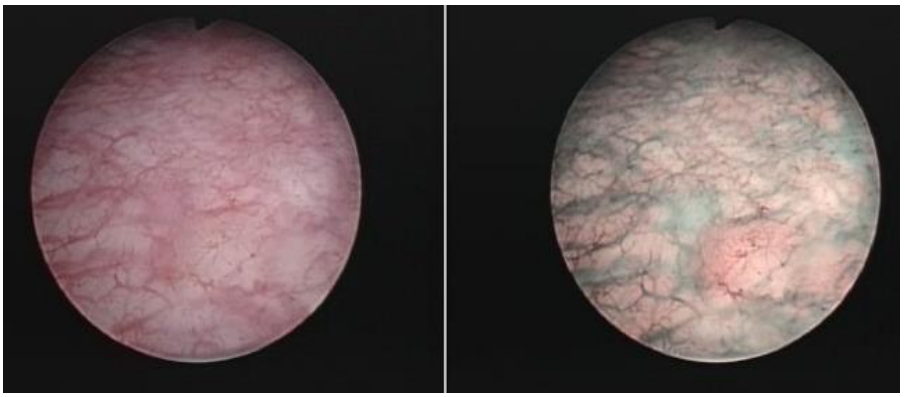

Figure (8): Carcinoma in situ lesion missed during standard cystoscopy and only visible in narrow-band imaging ***(Geavlete et al., 2012).***

Confocal laser endomicroscopy (CLE) (fig.9).

CLE is based on optical biopsy and high resolution in vivo subsurface imaging that enables the visualization of tissue microarchitecture and cellular features. It utilizes a 488 nm laser as the light source and fluorescein as an exogenous contrast agent. The fluorescein may be administered either intravenous or intravesical ***(Shkolyar et al., 2019).***

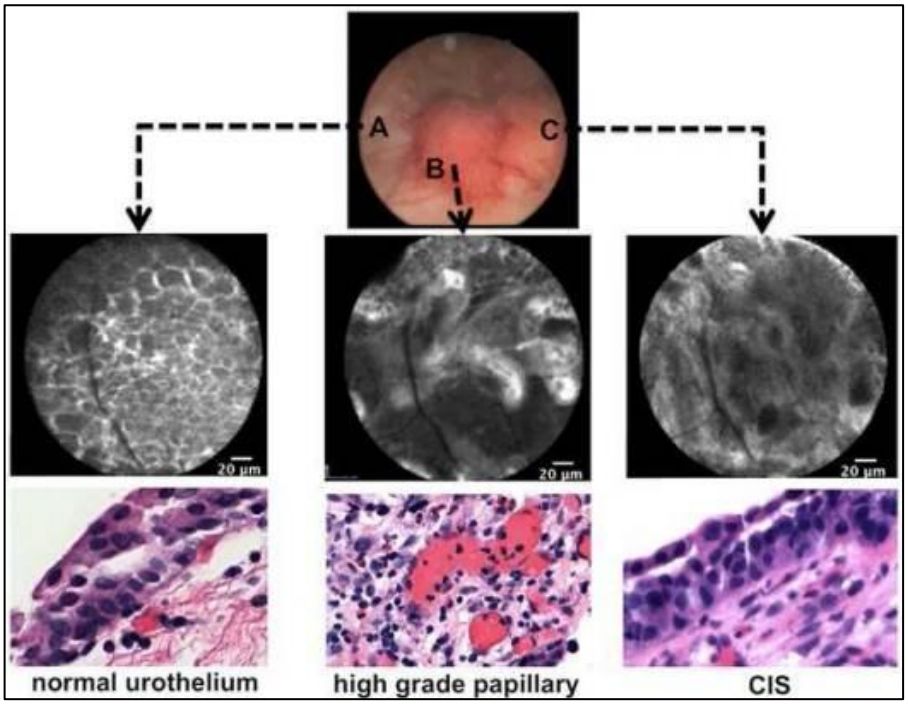

Figure (9): Intraoperative image guidance of a tumor seen under white light with corresponding confocal imaging and histology. A) Normal urothelium. B) High-grade, papillary tumor. C) CIS ***(Chen and Liao, 2014)***

Optical coherence tomography (OCT) (fig.10).

OCT is an optical equivalent of ultrasound that enables cross-sectional imaging of tissue, but different from ultrasound by using infrared light instead of sound waves, and having 10 times higher resolution ***(Xiong et al., 2019).***

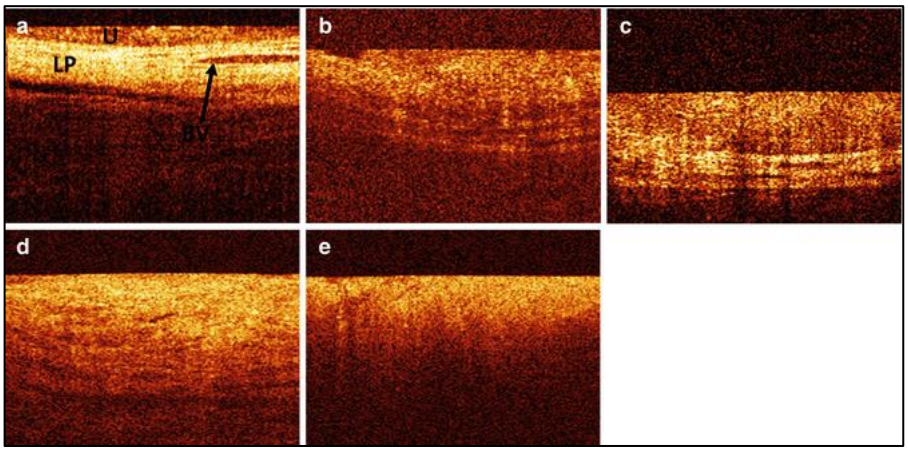

Figure (10): OCT bladder pathology. (a) Normal bladder lining (b) Carcinoma in situ (CIS), (c) Ta carcinoma of the bladder (d) T1 carcinoma of the bladder. (e) T2 carcinoma of the bladder ***(Bus et al., 2014).***

- ***Management of Non-muscle Invasive Bladder Cancer***

Counselling on smoking cessation:-

Smoking increases the risk of tumor recurrence and progression ***(Rink et al., 2012).*** While it is still controversial whether smoking cessation in BC will favourably influence the outcome of BC treatment, patients should be counseled to stop smoking because of the general risks connected to tobacco smoking ***(Crivelli et al., 2014).***

A. Transurethral resection of Ta/T1 bladder tumors:

The goal of TURBT in Ta/T1 BC is to make the correct diagnosis and completely remove all visible lesions. TURBT should be performed systematically in individual steps ***(Suarez-Ibarrola et al., 2019).***

A complete resection of the urinary bladder tumors, is essential to achieve good prognosis ***(Teoh et al., 2020).***

Bladder biopsies

CIS can present as a velvet-like, reddish area that is indistinguishable from inflammation, or it may not be visible at all. For this reason, biopsies from

1- Suspicious urothelium should be taken.

2- For patients with positive urine cytology.

3- With a history of HG (G3) NMIBC.

4- Tumors with a non-papillary appearance, mapping biopsies from normal-looking mucosa are recommended ***(Babjuk et al., 2021).***

Prostatic urethral biopsies

Involvement of the prostatic urethra and ducts in men with NMIBC has been reported ***(Palou et al., 2012).*** The

risk of prostatic urethra or duct involvement is higher if the:-

1- Tumor is located at the trigone or bladder neck.

2- Presence of bladder CIS, and in cases with

3- Multiple tumors.

On the basis of this observation, a biopsy from the prostatic urethra is necessary in some patients ***(Brant et al., 2019).***

B. Adjuvant treatment

Although TURBT by itself can eradicate a Ta/T1 tumor completely, these tumors commonly recur and can progress to MIBC. It is therefore necessary to consider adjuvant therapy for these patients ***(Babjuk et al., 2019).***

- ***Immediate intravesical chemotherapy***

A single, immediate, postoperative intravesical instillation of chemotherapy.

It has been shown that immediate single instillation (SI) acts by destroying circulating/floating tumor cells after TURBT, as well as via an ablative effect on residual tumor cells at the resection site and on small overlooked tumors ***(Girouard et al., 2020).***

Four large meta-analyses have consistently shown that after TURBT, SI significantly reduces the recurrence rate compared to TURBT alone**.** In a systematic review and meta-analysis, SI reduced the 5-yr recurrence rate by 14% ***(Sylvester et al., 2016).***

SIs with mitomycin C (MMC), epirubicin, or pirarubicin have all shown a beneficial effect ***(Sylvester et al., 2016).*** SI with gemcitabine was superior to a placebo control (saline) with remarkably low toxicity rates. The efficacy of continuous saline irrigation in the prevention of early recurrences has also been suggested. Prevention of tumor cell implantation should be initiated within the first few hours after TURBT ***(Roos et al., 2019).***

- ***Additional adjuvant intravesical immunotherapy and/or chemotherapy instillations.***

The need for further adjuvant intravesical therapy depends on prognosis. For patients with low-risk tumors, SI reduces the risk of recurrence and is considered to be the standard and complete treatment ***(Sylvester et al., 2016).***

For other patients, however, SIs remains an incomplete treatment because of the considerable likelihood of recurrence and/or progression**.** Treatment recommendations in Ta, T1 tumors and carcinoma in situ according to risk stratification as in table (4) ***(Babjuk et al., 2019).***

Table (4): Treatment recommendations in Ta, T1 tumors and carcinoma in situ according to risk stratification ***(Babjuk et al., 2019)***

Risk category	Definition	Treatment recommendation
Low-risk tumors	Primary, solitary, TaG1 (PUNLMP, LG), < 3 cm, no CIS.	One immediate instillation of intravesical chemotherapy after TURBT
Intermediate-risk tumors	All tumors not defined in the two adjacent categories (between the category of low and high risk)	In patients with previous low recurrence rate (less than or equal to one recurrence per year) and expected EORTC recurrence score <5, one immediate instillation of intravesical chemotherapy after TURBT. In all patients either one-year full-dose BCG treatment (induction plus 3weekly instillations at 3, 6 and 12 months), or instillations of chemotherapy (the optimal schedule is not known) for a maximum of one year.
High-risk tumors	Any of the following: • T1 tumors; • G3 tumor; • CIS; • Multiple, recurrent and large (>3 cm) TaG1G2 tumors (all features must be present).	Intravesical full-dose BCG instillations for one to three years or radical cystectomy (in highest-risk tumors – see below)
	Subgroup of highest-risk tumors	
	T1G3 associated with concurrent bladder CIS, multiple and/or large T1G3/ and/or recurrent T1G3, T1G3 with CIS in the prostatic urethra,some forms of variant histology of urothelial carcinoma, LVI.	Radical cystectomy should be considered. In those who refuse or are unfit for RC intravesical full-dose BCG instillations for one to three years

Intravesical BCG immunotherapy (discussed in next chapter)

Intravesical chemotherapeutic agents

Types of chemotherapeutic agents used intravesically

Many chemotherapeutic agents are used for induction and maintenance intravesical therapy.

I. **Thiotepa** is a nonspecific alkylating agent and was the first drug approved by the US Food and Drug Administration (FDA) at 1959 as intravesical therapy for NMIBC. Thiotepa is absorbed through the bladder mucosa and causes myelosuppression.

Its side effect are dose dependent. In a meta-analysis, patients who received thiotepa had a lower risk of bladder cancer recurrence than those who received only TURBT, but the difference was not significant, and the risks of progression and mortality also showed no differences ***(Chou et al., 2016).***

II. **MMC** is another alkylating agent but is rarely absorbed by the bladder mucosa and thus shows a lower risk of systemic side effects than thiotepa. MMC is the most widely used intravesical chemotherapeutic agent. MMC instillation has been reported to decrease the risk of recurrence in comparison with TURBT alone.

Both single instillation and maintenance therapy are effective. The effect on bladder cancer progression is significant ***(Chou et al., 2016).***

III. **Doxorubicin** is an anthracycline drug, with a high molecular weight. It is also rarely absorbed by the bladder mucosa; thus systemic side effects are not common. Intravesical instillation of doxorubicin has been shown to reduce the risk of recurrence but does not significantly reduce the risks of progression and mortality ***(Ku ,2019).***

IV. **Epirubicin** is another type of anthracycline drug; it is more effective and has fewer side effects than doxorubicin. Patients receiving epirubicin in addition to TURBT reportedly have a reduced risk of recurrence in comparison with TURBT alone ***(Chou et al., 2016).***

V. **Gemcitabine** is a nucleoside analog. Current evidence suggests that a single dose of gemcitabine is not as effective as multiple doses. The recurrence and progression rates have been reported to be lower with gemcitabine than with MMC ***(Shelley et al., 2012).***

- **Prognosis**

The cancer-specific survival in high-grade NMIBC is approximately 70-85% at 10 years. Low-grade Ta lesions demonstrates a progression rate of approximately 6%, whereas high-grade T1 lesions have an increased chance of progression of approximately 17% ***(Karaoglu et al., 2014)***.

Table (5): Probability of disease progression at 1, 5, and 10 yr for the new European Association of Urology non-muscle-invasive bladder cancer risk groups ***(Sylvester et al., 2021).***

New risk groups	Probability of progression. % (95% confidence interval)		
	1 yr	**5 yr**	**10 yr**
With WHO 2004/2016			
Low	006 (001-043)	0.93 (049-1.7)	3.7 (23-5.9)
Intermediate	10 (0.50-2.0)	4.9 (3.4-7.0)	8.5 (5.6-13)
High	3.5 (2.4-5.2)	9.6 (7.4-12)	14 (11-18)
Very high	16 (10-26)	40 (29-54)	53 (36-73)
With WHO 1973			
Low	0.12 (0.02-0.82)	0.57 (0.21-1.5)	3.0 (1.5-6.3)
Intermediate	0.65 (0.36-1.2)	3.6 (2.7-4.9)	7.4 (5.5-10)
High	3.8 (2.6-5.7)	11 (8.1-14)	14 (10-19)
Very high	20 (12-32)	44 (30-61)	59 (39-79)

Table (6 a, b and c): Probability of disease recurrence and progression at 1, 5 year, according to EORTC 2006 ***(Sylvester et al., 2006)***

Factor	Recurrence	Progression
Number of tumor		
Single	0	0
2-7	3	3
≥ 8	6	3
Tumor diameter		
< 3 cm	0	0
≥ 3	3	3
Prior recurrence rate		
Primary	0	0
≤ 1 recurrence/year	2	2
> 1 recurrence/year	4	2
Category		
Ta	0	0
T1	1	4

Table (6 . a): Continued

Factor	Recurrence	Progression
Concurrent CIS		
No	0	0
Yse	1	6
Grade		
G1	0	0
G2	1	0
G3	2	5
Total score	0-17	0-23

Table (6 . b):

Recurrence score	Probability of recurrence at 1 year		Probability of recurrence at 5 years	
	%	(95% CI)	%	(95% CI)
0	15	(10-19)	31	(24-37)
1-4	24	(21-26)	46	(42-49)
5-9	38	(35-41)	62	(58-65)
10-17	61	(55-67)	78	(73-84)

Table (6 . c):

Progression score	Probability of Progression at 1 year		Probability of Progression at 5years	
	%	(95% CI)	%	(95% CI)
0	0.2	(0-0.7)	0.8	(0-1.7)
2-6	1	(0.4-1.6)	6	(5-8)
7-13	5	(4-7)	17	(14-20)
14-23	17	(10-24)	45	(35-55)

Chapter (2)
Bacillus Calmette-Guérin (BCG) in Non-Muscle Invasive Transitional Cell Carcinoma of the Bladder

Introduction

BCG intravesical instillation therapy, which uses a live attenuated Mycobacterium bovis strain, is the most effective adjuvant treatment after TURBT in intermediate- to high-risk NMIBC patients. Several meta-analyses have shown favorable oncological outcomes of adjuvant intravesical BCG instillation compared with TURBT alone ***(Chou et al., 2016).***

History of BCG

Bacillus Calmette–Guérin (BCG, Mycobacterium bovis) was first discovered as a vaccine against tuberculosis by French scientists Albert Calmette and Camille Guerin in 1921 at the Pasteur Institute in Lille, France and it was named after them ***(Luca and Mihaescu, 2013).*** Pearl in 1929, hypothesis that clinical tuberculosis may cause lower frequency of tumors in autopsy materials, in the 1950s, Old, Clark and Benacerraf observed that BCG also prevented the growth of experimental tumors ***(Old et al., 1959).*** **Mathe et al., (1969)** showed that BCG has an effect against human leukaemia. **Morton et al., (1970)** demonstrated that intralesional BCG has an effect against human melanoma.

Bloomberg et al., (1975) showed that local BCG causes strong inflammatory reactions in the healthy bladder of dogs.

Morales in Canada was the first to use BCG vaccine in the bladder for the treatment of recurrent non-muscle invasive bladder cancer (NMIBC) ***(Morales et al., 1976)***.

Mechanism of action of BCG:

Intravesical BCG results in a massive local immune response characterized by induced expression of cytokines in the urine and in bladder tissue and by an influx of granulocytes as well as mononuclear and dendritic cells into the bladder wall ***(Shen et al., 2008)***.

The initial step is direct binding to fibronectin within the bladder wall leading to direct stimulation of cell-based immunologic response. Numerous cytokines involved in the initiation and maintenance of inflammatory processes including tumor necrosis factor-alpha, granulocyte macrophage-colony stimulating factor IFN-γ (interferon gamma)**,** interleukin (IL)-1, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12 and IL-18, has been detected in the urine of patients treated with intravesical BCG. The observed pattern of cytokine induction with preferential upregulation IFN, IL1 and IL2 reflect induction of T-helper type -1response. This activate cell mediated cytotoxic mechanism that are believed to underlie the efficacy of BCG in prevention of recurrence and progression of tumor ***(Bohle and Brandau, 2003).***

Immunological processes involved in BCG immunotherapy as described in (fig.11). During stimulation of human peripheral blood mononuclear cells with BCG cascade of events leads to generation of tumor cytotoxic NK BCG activated killer (BAK) cells. Accessory monocytes and dendritic cells take up BCG mycobacteria and become activated. IL-12 is crucial cytokine released by monocytes and DC (dendritic cell) in this process. CD4 cells also function as accessory cells by releasing cytokines. IFN-and IL-2 are essential for BCG induced cytotoxicity. Enhanced cytokine production results in NK cell activation. CD8/CD16dim NK cell subpopulation lyses tumor cells via perforin ***(Bohle and Brandau, 2003)***.

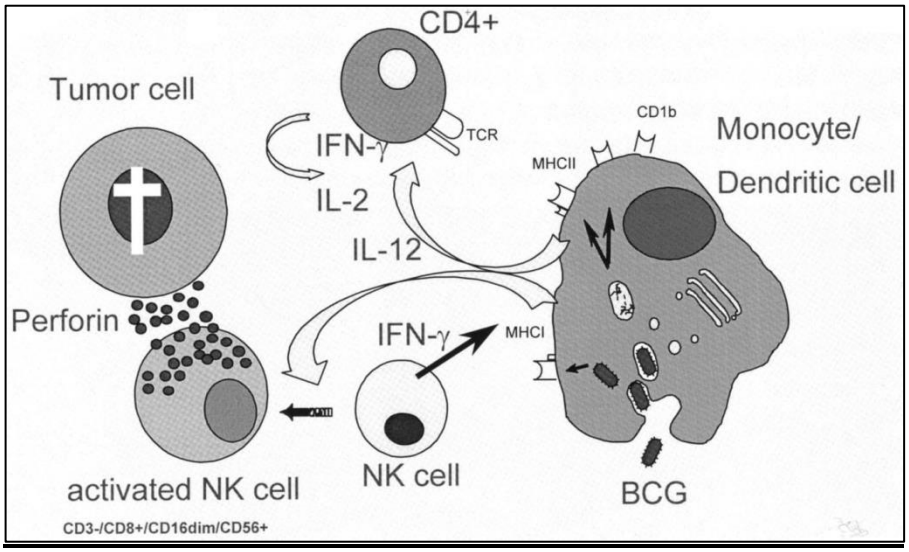

Figure (11): Immunological processes involved in BCG immunotherapy **(Bohle and Brandau, 2003)**

BCG Srains:-

One meta-analysis compared the therapeutic efficacy of five different BCG strains ***(Sylvester et al., 2002).***

1. **Tice** (Organon Inc., West Orange, NJ, USA).
2. **Connaught** (Connaught Laboratories, Toronto, ON, Canada).
3. **Pasteur** (Aventis Pasteur, Brussels، Belgium).
4. **RIVM** (National Institute for Public Health and the Environment, Bilthoven, the Netherlands).
5. **Frappier** (Institute Armand-Frappier, Laval, QC, Canada). The Tice strain was most frequently used in 38.9% of patients.

European Organization for Research and Treatment of Cancer (EORTC) meta-analysis suggested that there is no large difference between different strains ***(Sylvester et al., 2002).***

Intravesical BCG dose and schedule:-

Induction of a BCG instillation was first introduced by Morales in 1976, consisting of six weekly doses of 120 mg each ***(Morales et al., 1976).*** Induction therapy is associated with reductions in recurrence, progression, and mortality within 10 years. For optimal efficacy, maintenance BCG therapy should be given. Regardless of the induction

therapy, many different maintenance schedules are used ***(Lamm et al., 2000).*** The optimal protocol of maintenance BCG therapy has not yet been confirmed. Several studies have shown that 3-weekly BCG maintenance instillations after 6-week induction therapy reduce the risks of recurrence and progression of bladder cancer ***(Oddens et al., 2013).*** Another maintenance regimen designed by the Southwest Oncology Group (SWOG) consists of three once-weekly intravesical instillations of BCG at 3, 6, 12, 18, 24, 30, and 36 months after a 6-week induction phase ***(Lamm et al., 2000).***

To reduce BCG toxicity, instillation of a reduced dose has been proposed. However, it has been suggested that a full dose of BCG is more effective for multifocal tumors ***(Marcq & Kassouf, 2021).***

The EORTC Genito-urinary Cancers Group (EORTC-GU) compared the efficacy and toxicity of full-dose therapy and reduced-dose therapy using a one-third dose over 1-year and 3-year periods ***(Oddens et al., 2013).*** There was no significant dose-related difference in toxicity.

BCG side effects and toxicity

Intravesical BCG treatment carries more risk of complications than intravesical chemotherapy. Most of complications are local side effects. Which are easily treated ***(Sylvester et al., 2002).*** Fewer than 5% of patients experience severe systemic adverse events with a need to stop the instillation, and most of them are treated effectively ***(Van der Meijden et al., 2003).***

The incidence of local side effects is similar with or without maintenance therapy. For patient who receive or do not receive maintenance therapy respectively, include lower urinary tract symptoms (57-71%, 38-59%), hematuria (20%, 29%), and bladder contracture (3%, 1%) ***(Hall et al., 2007).***

Most of the systemic side effects occur within the first 6 months of treatment after that the incidence decreases. Maintenance treatment is not associated with an increase in adverse events local and systemic. So fear of increasing toxicity risks should not discourage use of maintenance BCG therapy ***(Van der Meijden et al., 2003).***

Systemic side effects can be divided into:-

1- Infectious (bacterial cystitis, epididymitis, prostatitis, urethral infections and systemic infection.

2- Noninfectious types as arthralgias, skin reactions and anaphylaxis ***(Hall et al., 2007).***

Treatment of BCG side effects and toxicity

A. Most BCG-associated cystitis symptoms can be effectively managed with aspirin, non-steroidal anti-inflammatory drugs (NSAIDs), urinary analgesics, and antispasmodics ***(O'Donnell and Bohle, 2006).*** In addition, ofloxacin can be given ***(Colombel et al., 2006).***

If symptoms of cystitis improve within a few days continue instillations, but if symptoms persist or worsen postpone the instillation and perform a urine culture and start empirical antibiotic.

If symptoms persist even with antibiotic treatment:

a) With positive culture: adjust antibiotic treatment according to sensitivity

b) With negative culture: quinolones and potentially analgesic anti-inflammatory once daily for 5 days (repeat cycle if necessary) ***(Palou et al., 2001).***

B. Hematuria Perform urine culture to exclude hemorrhagic cystitis. If hematuria persists, perform cystoscopy to evaluate presence of bladder tumor ***(Witjes et al., 2008)***.

C. Symptomatic granulomatous prostatitis is rare but if happened treated by quinolones. If quinolones are not effective: isoniazid (300 mg/day) and rifampicin (600 mg/day) for three months and stop BCG.

D. Epididymo-orchitis Perform urine culture and administrate quinolones. Cessation of intravesical therapy. Orchidectomy if abscess or no response to treatment ***(Alkensammer et al., 2005).***

E. General malaise, fever generally resolve within 48 hours, with or without antipyretics.

F. Arthritis and/or arthralgia are rare complication and considered autoimmune reaction.

   Arthralgia: treatment with NSAIDs. Arthritis: NSAIDs. If no/partial response, proceed to corticosteroids, high-dose quinolones or antituberculosis drugs ***(Tinazzi et al., 2006).***

G. Persistent high-grade fever >38.5°C for >48h permanent discontinuation of BCG instillations. And immediate evaluation by urine culture, blood tests, chest X-ray. Prompt treatment with more than two antimicrobial agents while diagnostic evaluation is conducted. Consultation with an infectious diseases specialist ***(Witjes et al., 2008).***

To prevent BCG sepsis initiate BCG at least 2 weeks after transurethral resection of the bladder tumors and if no signs and symptoms of hematuria. But if happened stop BCG instillation and in severe infection: High-dose quinolones or isoniazid, rifampicin and ethambutol 1.2 g daily should be started for 6 months. Early, high-dose corticosteroids as long as symptoms persist ***(Witjes et al., 2008).***

Consider an empirical non-specific antibiotic to cover Gram-negative bacteria and/or Enterococcus.

H. Allergic reactions:- delay therapy until reactions resolve and antihistamines and anti-inflammatory agents should be started and consider high-dose quinolones or isoniazid and rifampicin for persistent symptoms.

BCG failure

BCG intolerance:- means patients cannot continue to receive BCG instillation because of sever adverse effects ***(Witjes et al., 2008).***

High grade cancer BCG refractory: indicates the presence of persistent tumors within 6 months after induction therapy or progression of cancer within 3months after the start of induction therapy.

1. If T1G3 tumor is present at 3 months ***(Herr and Dalbagni ., 2003).*** Further conservative treatment with BCG is associated with an increased risk of progression ***(Lerner et al., 2009).***

2. If TaG3 tumor is present after 3 months and/or at 6 months, after either re-induction or first course of maintenance ***(Sylvester et al., 2005).***

3. If CIS (without concomitant papillary tumor) is present at 3 months and persists at 6 months after either re-induction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in >50% of cases ***(Jakse et al., 2001).***

4. If HG tumor appears during BCG maintenance therapy.

BCG relapse:- indicates cancer recurrence after achievement of a disease-free state within 6 months after treatment ***(Kamat et al., 2017).***

BCG unresponsive:- BCG refractory or T1Ta/HG BCG recurrence within 6 months of completion of adequate BCG exposure or development of CIS within 12 months of completion of adequate BCG exposure.

Chapter (3)

Gemcitabine for Non-Muscle-Invasive Bladder Cancer

Introduction

Gemcitabine (2′, 2′-difluorodeoxycytidine) is a well-known chemotherapeutic agent that inhibits DNA synthesis in dividing cells. Regimens containing gemcitabine are used systemically to treat MIBC and advanced urothelial bladder cancer ***(Scosyrev et al., 2012; Von der Maase et al., 2000).*** Sporadic evidence suggested that courses of intravesical gemcitabine could be safe and cost/effective for BCG unresponsive NMIBC, but most of those studies were limited by small number of patients and short-term follow-up ***(Addeo et al., 2010).***

Additionally, preliminary evidence suggests that courses of intravesical gemcitabine are safe and as effective or more effective than other chemotherapeutic agents for non-muscle-invasive urothelial cancer ***(Addeo et al., 2010).***

Gemcitabine was setted as first line intravesical therapy since 2010 in Australia. **Prasanna et al.** decided that intravesical gemcitabine had better efficacy and lower toxicity when compared with BCG ***(Prasanna, et al., 2017).***

Mechanism of action of gemcitabine intravesically

Gemcitabine (2, 2 -difluorodeoxycytidine, dFdC) is a deoxycytidine analogue with a broad spectrum of anti-tumor activity.

It is phosphorylated intracellularly by deoxycytidine kinase to gemcitabine monophosphate, which is further phosphorylated to active metabolites gemcitabine diphosphate and gemcitabine triphosphate **(*Spoerri et al., 2015)***

Gemcitabine diphosphate inhibits DNA synthesis by inhibiting ribonucleotide reductase.

Gemcitabine triphosphate is incorporated into DNA and inhibits DNA polymerase.

These metabolites are responsible for the cytotoxic action of gemcitabine by blocking DNA synthesis and this causes the inhibition of cell growth and triggers apoptosis ***(De Sousa Cavalcante & Monteiro, 2014).***

Gemcitabine transported out of the cell after deactivated by deamination into 2, 2-difluorodeoxyuridine (dFdU) ***(Bergman et al., 2002).***

Gemcitabine can penetrate the bladder mucosa with beneficial effects in the treatment of superficial urothelial

tumor of the bladder. Because of its lower molecular weight 299 D, than that of commonly-used intravesical chemotherapeutic agents such as mitomycin C (389 D) and doxorubicin (589 D). At the same time the molecular weight is high enough to prevent significant systemic absorption in an intact bladder. Gemcitabine an ideal agent for regional therapy due to its pharmacokinetic properties. It is rapidly deaminated into the inactive metabolite, thus resulting in a high total body clearance ***(Odonnel et al., 2003).***

Gemcitabine resulted in a more robust cytotoxic activity (90% lethality in all cell lines) than the other chemotherapeutic agents which was less than 60% ***(O'Donnell et al., 2003; Gontero and Frea, 2006).***

Gemcitabine hydrochloride (Gem-HCl) has a broad spectrum anti-tumor activity, and when given intravesically it has been shown to produce good response rates for the treatment of superficial bladder cancer ***(Witjes et al., 2004; Gontero and Tizzani, 2007).*** The success of intravesical chemotherapy with Gem-HCl depends on direct contact between the drug and the abnormal urothelium. Therefore, mechanisms that prolong exposure of the urothelium to the drug are expected to increase the efficacy of the treatment ***(Burjak et al., 2001; Şenyiğit et al., 2015).***

Intravesical gemcitabine dose and schedule

For intravesical drug instillation, usually a catheter is sterilely inserted into the bladder. When the bladder is completely drained, Gemcitabine 2 gm in 50 mL or 100 mL of saline are passed into the bladder through the catheter and the drug solution retained for 2 hours, once a week for six weeks (induction dose therapy). After that, the patient voids to remove the drug solution. Then maintenance treatment 2 gm gemcitabine in 50 mL or 100 mL of saline every month for 10 months during first year ***(Addeo et al., 2010).***

In the study of **Iannelli et al. (2004),** 21 patients received 2 gm gemcitabine in 50 mL saline for 1 h weekly 6 successive doses then monthly for 12 months (as a maintanence therapy).

Side effects:-

Pharmacokinetic data has clearly demonstrated that systemic absorption of intravesical gemcitabine, is minimal and transient, and thus unlikely to produce clinically significant adverse events ***(Gontero and Frea, 2006).***

Gemcitabine has several pharmacological properties that are conducive for its use as an intravesical agent in the management of NMIBC. The low molecular weight and the

high lipid solubility allow sufficient uptake into malignant urothelial cells for cytotoxicity in vivo. Many studies investigating the pharmacokinetics of intravesical gemcitabine. These studies have shown a high plasma clearance for gemcitabine, indicating that any drug distributed to the systemic circulation after intravesical administration, will be quickly eliminated, reducing the risk of systemic toxicity ***(Laufer et al., 2003).***

Minimal amounts of intravesical gemcitaine reach the systemic circulation with plasma levels ranging from undetectable to a maximum of 2.5 μ g/mL (0.83 μ M). As much as 100% of the instilled dose of gemcitabine has been reported to remain within the bladder, which is an ideal pharmacological characteristic for an intravesical agent. One study showed that the pH of the instilled gemcitabine, the urine concentration achieved and the dwell time are important for maximum tumor drug penetration ***(Gontero et al., 2010).***

Adverse events from intravesical anti-tumor agent instillation can be divided into local and systemic. The common local adverse events are urinary frequency, urinary urgency, dysuria, hematuria, bladder or pelvic pain, and prostatitis. However, most of these are usually self-limiting ***(Elsen, 2016).***

Systemic adverse events are rare and primarily result in myelosuppression. The most reported adverse events are voiding dysfunction, pain, hematuria, pyrexia, and alopecia ***(Packiam et al., 2018).***

Systemic toxicity was absent in the study of De Berardinis ***(De Berardinis et al., 2004).***

Local toxicity was minimal and described as rapidly self-resolving. With exception as urinary frequency reported by ***(Laufer et al., 2003)*** and ***(Dalbagni et al 2002).***

So far, gemcitabine seems to have fulfilled the requirements to be a promising new agent for standard intravesical therapy in superficial utothelial tumor of the bladder ***(Gontero and Frea, 2006).***