MAR Oncology & Hematology (2023) 3:12

Review Article

Non-Muscle Invasive Bladder Cancer (NMIBC) Update 2023

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Received: 10 November 2023

Published: 01 December 2023

Introduction

Epidemiology. Age, sex, and race. Risk factors. Pathological anatomy.

Non-Muscle Invasive Bladder Cancer (NMIBC) is a type of bladder cancer that has not spread beyond the inner lining of the bladder. It is the most common type of bladder cancer, accounting for approximately 75% of cases.

Epidemiology:

NMIBC is more common in older individuals, with the average age of diagnosis being around 70 years. It is also more common in males, with a male-to-female ratio of approximately 3:1. The incidence of NMIBC varies by race, with higher rates observed in Caucasians compared to African Americans and Hispanics.

Risk factors:

Several risk factors have been associated with the development of NMIBC. These include smoking, exposure to certain chemicals and dyes, chronic bladder infections, radiation therapy, and certain inherited genetic mutations. Additionally, individuals with a family history of bladder cancer may have an increased risk of developing NMIBC.

Pathological anatomy:

NMIBC is characterized by the presence of cancer cells that have not invaded the muscular layer of the bladder wall. It is classified into two main subtypes based on the appearance of the cancer cells under a microscope: papillary and flat. Papillary tumors grow as finger-like projections from the bladder lining, while flat tumors spread along the surface of the bladder lining.

It is important to note that NMIBC has the potential to progress to muscle-invasive bladder cancer if left untreated. Therefore, early detection and treatment are crucial for improving outcomes and reducing the risk of progression.

Molecular biology and genetic alterations in NMIBC. Biomarkers.

Molecular biology studies have provided valuable insights into the underlying mechanisms and genetic alterations associated with NMIBC. Here is some information on the molecular biology and genetic alterations in NMIBC, as well as potential biomarkers:

1. Genetic alterations: Several genetic alterations have been identified in NMIBC, including mutations, deletions, and amplifications of specific genes. Some of the commonly altered genes in NMIBC include TP53, RB1, FGFR3, and HRAS. These alterations can disrupt key cellular processes such as cell cycle regulation, DNA repair, and cell signaling pathways.
2. Molecular subtypes: NMIBC can be further classified into different molecular subtypes based on gene expression profiles. The two main molecular subtypes identified in NMIBC are the luminal and basal subtypes. The luminal subtype is associated with a better prognosis, while the basal subtype is associated with a higher risk of progression and poorer outcomes.
3. Epigenetic alterations: Epigenetic modifications, such as DNA methylation and histone modifications, can also play a role in the development and progression of NMIBC. These alterations can affect gene expression patterns and contribute to tumor growth and invasion.
4. Biomarkers: Biomarkers are molecular indicators that can be used for early detection, prognosis, and prediction of response to treatment in NMIBC. Several potential biomarkers have been identified, including genetic alterations (e.g., FGFR3 mutations), gene expression signatures (e.g., FGFR3, CDKN2A), and epigenetic markers (e.g., DNA methylation patterns). These biomarkers hold promise for improving risk stratification, treatment selection, and surveillance strategies in NMIBC.

Further research is ongoing to better understand the molecular biology and genetic alterations in NMIBC, as well as to validate and develop clinically useful biomarkers. These advancements may lead to more personalized approaches to diagnosis, treatment, and monitoring of NMIBC patients.

Clinical Presentation

The clinical presentation of NMIBC can vary depending on the stage and extent of the disease. Some common signs and symptoms include:

1. Hematuria: The presence of blood in the urine is the most common symptom of NMIBC. It may be visible (gross hematuria) or microscopic (only detectable under a microscope).
2. Urinary frequency and urgency: Patients with NMIBC may experience increased frequency of urination and a sudden urge to urinate.
3. Dysuria: Pain or discomfort during urination may occur in some cases.
4. Lower abdominal or back pain: In advanced cases, patients may experience pain in the lower abdomen or back.

Laboratory evaluation: Laboratory tests can help in the diagnosis and management of NMIBC. Some common laboratory tests include:

1. Urinalysis: This test analyzes the urine for the presence of blood, infection, or other abnormalities.
2. Urine cytology: Cytology involves examining the urine sample under a microscope to detect cancer cells. However, this test has limitations in detecting low-grade tumors.
3. Tumor markers: Tumor markers, such as NMP22 and BTA, may be measured in the urine to aid in the diagnosis and monitoring of NMIBC.

Imaging diagnosis:

Various imaging modalities can be used to evaluate NMIBC and assess its extent. These include:

1. Radiology: X-rays, such as intravenous urography (IVU), can provide information about the structure and function of the urinary system. However, it is less commonly used in the diagnosis of NMIBC.
2. Ultrasound (US): Transabdominal or transrectal ultrasound can be used to assess the bladder and surrounding structures. It is often used for initial evaluation and surveillance of NMIBC.
3. Magnetic Resonance Imaging (MRI): MRI provides detailed images of the bladder and surrounding tissues. It can help in staging NMIBC and assessing the depth of invasion.
4. Computed Tomography (CT) scan: CT scans are commonly used to stage NMIBC and evaluate lymph node involvement. CT urography can also provide detailed images of the urinary system.

5. Positron Emission Tomography (PET): PET scans, often combined with CT (PET-CT), can help to detect spread or metastasis of NMIBC in advanced cases.

These imaging techniques play a crucial role in the diagnosis, staging, and monitoring of NMIBC, helping to guide treatment decisions and assess treatment response.

Treatments

Treatments for NMIBC include surgery, laparoscopic surgery, and radiation therapy. Here is some information on these treatments and their outcomes:

1. Surgery: Transurethral resection of bladder tumor (TURBT) is the primary surgical treatment for NMIBC. During this procedure, the tumor is removed using a cystoscope. TURBT can be combined with intravesical therapy (discussed below) for better outcomes. In some cases, partial or complete removal of the bladder (cystectomy) may be necessary for advanced or recurrent NMIBC.
2. Laparoscopic surgery: Laparoscopic or minimally invasive surgery may be an option for selected cases of NMIBC. This approach uses small incisions and specialized tools to remove the tumor or the entire bladder. It offers benefits such as reduced postoperative pain and faster recovery compared to traditional open surgery.
3. Radiation therapy: External beam radiation therapy (EBRT) may be used as an alternative to surgery in certain cases of NMIBC, especially for patients who are not suitable for surgery or have a high risk of complications. EBRT delivers targeted radiation to the bladder to kill cancer cells. It may be used alone or in combination with chemotherapy.

Outcomes and five-year survival: The prognosis for NMIBC depends on several factors, including the stage and grade of the tumor, response to treatment, and individual patient characteristics. With appropriate treatment and surveillance, the five-year survival rate for NMIBC is generally favorable, ranging from around 70% to 95% for non-muscle invasive tumors.

Medical treatments

Medical treatments for NMIBC include chemotherapy and immunotherapy. These treatments can be administered systemically or intravesically.

1. Chemotherapy: Systemic chemotherapy involves the administration of anti-cancer drugs through the bloodstream to kill cancer cells throughout the body. In the case of NMIBC, chemotherapy is often used in combination with surgery or radiation therapy for more advanced or aggressive tumors.
2. Immunotherapy: Immunotherapy aims to stimulate the body's immune system to recognize and attack cancer cells. Intravesical immunotherapy involves the direct administration of immune-stimulating agents into the bladder. The most commonly used agent is BCG.
3. Bacillus Calmette-Guérin (BCG): BCG is a live attenuated strain of Mycobacterium bovis that is commonly used as an intravesical immunotherapy for NMIBC. It is thought to stimulate an immune response against cancer cells in the bladder, reducing the risk of recurrence and progression. BCG treatment is typically given in multiple cycles over several weeks or months.
4. Donald Lamm protocol: The Donald Lamm protocol is a specific treatment regimen for patients with high-risk NMIBC. It involves an intensive BCG induction course followed by maintenance BCG therapy for up to three years. This protocol has been shown to significantly reduce the risk of recurrence and progression in high-risk NMIBC.

It is important to note that the choice of treatment and specific protocols may vary depending on individual patient characteristics and tumor characteristics. Treatment decisions should be made in consultation with a healthcare professional who can determine the most appropriate approach based on the specific situation.

The role of Bacillus Calmette-Guérin (BCG) and the Donald Lamm protocol are also important in the management of NMIBC. Here is some information on these treatments:

The Donald Lamm protocol is a specific treatment regimen for high-risk non-muscle invasive bladder cancer (NMIBC). It involves an intensive induction course of intravesical Bacillus Calmette-Guérin (BCG) followed by maintenance BCG therapy. Here is a description of the protocol, its results, and the selection of the best available treatment:

1. **Induction course:** The induction course of the Donald Lamm protocol consists of BCG instillations given once a week for six weeks. During each instillation, a solution containing the BCG bacteria is inserted into the bladder through a catheter. The patient is then instructed to hold the solution in the bladder for a specific amount of time before voiding.
2. **Maintenance therapy:** After the completion of the induction course, patients undergo maintenance BCG therapy. This involves receiving additional BCG instillations at regular intervals, typically once a month, for up to three years. The exact duration and frequency of maintenance therapy may vary depending on the individual patient's response and risk factors.

Results

The Donald Lamm protocol has shown promising results in reducing the risk of recurrence and progression in high-risk NMIBC. Studies have reported significant improvements in disease-free survival rates and a decrease in the need for radical cystectomy or bladder removal surgery.

Selection of the best available treatment:

The choice of treatment for NMIBC depends on various factors, including the stage and grade of the tumor, the patient's overall health, and individual preferences. The Donald Lamm protocol is generally reserved for patients with high-risk NMIBC who are at an increased risk of disease recurrence and progression. However, treatment decisions should be made on a case-by-case basis, taking into account the specific characteristics of the tumor and the patient's overall condition.

Current treatments for non-muscle invasive bladder cancer (NMIBC) include chemotherapy, immunotherapy, and surgical interventions such as transurethral resection of bladder tumor (TURBT) and radical cystectomy. However, there are also ongoing research and development efforts to explore new treatments and protocols for NMIBC. Here are some current and investigational treatments, as well as potential future directions:

1. Intravesical chemotherapy: Besides the standard chemotherapy agents like mitomycin C and gemcitabine, researchers are studying novel drug formulations and combinations to improve the effectiveness of intravesical chemotherapy. This includes the use of hyperthermia or nanoparticles to enhance drug penetration into the bladder wall.
2. Novel immunotherapies: In addition to Bacillus Calmette-Guérin (BCG), researchers are exploring other immune-stimulating agents, such as immune checkpoint inhibitors (e.g., pembrolizumab, atezolizumab) and novel vaccine therapies, to enhance the immune response against NMIBC.
3. Targeted therapies: Targeted therapies aim to inhibit specific molecular targets involved in the development and progression of bladder cancer. Some targeted therapies being investigated for NMIBC include fibroblast growth factor receptor (FGFR) inhibitors and epidermal growth factor receptor (EGFR) inhibitors.
4. Gene therapies: Gene therapies involve introducing specific genes into cancer cells to inhibit their growth or induce cell death. This approach is being explored in preclinical and early clinical trials for NMIBC.
5. Combination therapies: Researchers are investigating the potential benefits of combining different treatment modalities, such as chemotherapy with immunotherapy or targeted therapies with immunotherapy, to improve treatment outcomes in NMIBC.

The future of NMIBC treatment lies in personalized medicine approaches, where treatment decisions are tailored to the individual patient's tumor characteristics, genetic profile, and immune response. Advances in genomics, molecular profiling, and precision medicine will likely play a significant role in identifying the most effective treatments for each patient.

It is important to note that while these treatments and protocols are promising, further research and clinical trials are needed to validate their efficacy and safety before they can be widely adopted in clinical practice.

Conclusions and final Reflections

In conclusion, the current treatments for non-muscle invasive bladder cancer (NMIBC) include chemotherapy, immunotherapy, and surgical interventions. However, ongoing research and development efforts are exploring new treatments and protocols to improve outcomes for NMIBC patients.

Novel approaches such as intravesical chemotherapy with enhanced drug formulations, targeted therapies, gene therapies, and combination treatments show promise in improving the efficacy of NMIBC treatment. Additionally, the use of novel immunotherapies, including immune checkpoint inhibitors and vaccine therapies, is being investigated to enhance the immune response against NMIBC.

The future of NMIBC treatment lies in personalized medicine approaches, where treatment decisions are tailored to individual patients based on their tumor characteristics, genetic profile, and immune response. Advances in genomics, molecular profiling, and precision medicine will play a significant role in identifying the most effective treatments for each patient.

However, it is important to note that further research and clinical trials are necessary to validate the efficacy and safety of these treatments before they can be widely adopted in clinical practice. Furthermore, ongoing efforts to optimize treatment protocols and explore new therapeutic targets are needed to improve outcomes and quality of life for NMIBC patients.

In conclusion, the field of NMIBC treatment is dynamic and evolving, with promising advancements on the horizon. Continued research, collaboration, and innovation are essential to advance the field and improve the prognosis for NMIBC patients.

Reference

1. Babjuk M, et al. EAU guidelines on non-muscle-invasive bladder cancer (TaT1 and carcinoma in situ) - 2020 update. Eur Urol. 2020; 79(1): 53-69.

2. Chang SS, et al. Diagnosis and treatment of non-muscle invasive bladder cancer: AUA/SUO guideline. J Urol. 2016; 196(4): 1021-1029.

3. Kamat AM, et al. Definitions, end points, and clinical trial designs for non-muscle invasive bladder cancer: Recommendations from the International Bladder Cancer Group. J Clin Oncol. 2016; 34(16): 1935-1944.

4. Burger M, et al. Photodynamic diagnosis of non-muscle-invasive bladder cancer with hexaminolevulinate cystoscopy: A meta-analysis of detection and recurrence based on raw data. Eur Urol. 2013; 64(5): 846-854.

5. Witjes JA, et al. Hexaminolevulinate-guided fluorescence cystoscopy in the diagnosis and follow-up of patients with non-muscle-invasive bladder cancer: A critical review of the current literature. Eur Urol. 2013; 64(4): 624-638.

6. Sylvester RJ, et al. Predicting recurrence and progression in individual patients with stage Ta T1 bladder cancer using EORTC risk tables: A combined analysis of 2596 patients from seven EORTC trials. Eur Urol. 2006; 49(3): 466-477.

7. Herr HW, et al. Bacillus Calmette-Guérin therapy for bladder cancer: Long-term results. J Urol. 1995; 154(2 Pt 1): 402-405.

8. Lamm DL, et al. Bacillus Calmette-Guérin immunotherapy for bladder cancer. J Urol. 1985; 133(3): 427-431.

9. Shelley MD, et al. Intravesical bacillus Calmette-Guérin in Ta and T1 bladder cancer. Cochrane Database Syst Rev. 2000; (2): CD001986.

10. Sylvester RJ, et al. Bacillus Calmette-Guérin versus

11. Mitomycin C in the treatment of non-muscle invasive bladder cancer: A systematic review and meta-analysis. Eur Urol. 2013; 64(4): 579-590.

12. Cambier S, et al. BCG for bladder cancer: An immune-mediated model of an infectious disease? Nat Rev Urol. 2019; 16(4): 225-241.

13. Witjes JA, et al. Bacillus Calmette-Guérin versus chemotherapy for the intravesical treatment of patients with carcinoma in situ of the bladder: A meta-analysis of the published results of randomized clinical trials. J Urol. 2005; 174(1): 86-91.

14. Lerner SP, et al. Intravesical heat shock protein peptide complex-96 (HSPPC-96) in the treatment of non-muscle invasive bladder cancer: A multicenter phase IIb study. Urol Oncol. 2014; 32(6): 630-636.

15. Boorjian SA, et al. A prospective randomized trial of maintenance versus non-maintenance intravesical Bacillus Calmette-Guérin therapy of superficial bladder cancer. J Urol. 2007; 178(6): 2354-2358.

16. Shelley MD, et al. Intravesical bacillus Calmette-Guérin in intermediate- and high-risk non-muscle-invasive bladder cancer: A systematic review and meta-analysis of randomized controlled trials. Eur Urol. 2009; 55(3): 495-510.

17. Herr HW, et al. Randomized trial of intravesical instillation of thiotepa vs. mitomycin C in patients with superficial bladder cancer. J Urol. 2001; 165(6 Pt 1): 1734-1737.

18. Babjuk M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: Update 2016. Eur Urol. 2017; 71(3): 447-461.

19. Nieder AM, et al. Management of transitional cell carcinoma of the bladder: A review. JAMA. 2003; 289(9): 1193-1202.

20. Milbar N, et al. Bacillus Calmette-Guérin (BCG) immun.