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REVIEW ARTICLE

Research progress in bladder cancer

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Abstract: Bladder cancer refers to malignant tumors that originate in the bladder mucosa. Globally, bladder cancer is the ninth most common malignant tumor and the second most common urinary tumor. Recently, the search for highly sensitive, specific, non-invasive, convenient, quick, and economical bladder cancer diagnosis and follow-up methods becomes a research challenge in the fields of basic medicine, oncology, and urology. This article covers the current status of national and international research on the diagnosis and treatment of bladder cancer, as well as the forefront achievement from our team and international peers in basic and translational medicine research on bladder cancer. As translational medicine is the only way to achieve precision medicine, there are unprecedented opportunities in the fields of bladder cancer research and translational medical research.

Keywords: bladder cancer; diagnosis; treatment; translational medicine; precision medicine

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1. Overview of Bladder Cancer

Bladder cancer refers to malignant tumors that originate in the bladder mucosa. The most common clinical manifestation is intermittent and painless gross hematuria. Globally, bladder cancer is the ninth most common malignant tumor and the second most common urinary tumor. The age-standardized incidence rate of bladder cancer for males is about 4.1 times that of females[1,2]. The mortality rate of bladder cancer in developed countries has a downward trend, ranking 13th malignant tumors[2]. In China, the overall incidence of bladder cancer rate ranks 6th in malignant tumors and 1st in urinary system tumors in males. Its incidence rate is 3.3 times higher in males than in females, and this increases with age, seriously jeopardizing the health of the Chinese people[3,4].

Histologically, urothelial carcinoma is the most common, accounting for more than 90% of all types of bladder cancer; squamous cell carcinoma accounts for about 5%; glandular carcinoma accounts for about 5% and is more common in patients with bladder valgus; while other types of bladder cancer are extremely rare[5,6]. Pathologically, bladder cancer is classified into non-muscle invasive bladder cancer (NMIBC) and MIBC. NMIBC is more common, accounting for about 75% of bladder cancer diagnosis (including Tis, Ta, T1, and carcinoma *in situ* [CIS]). About 50% of NMIBC is low-grade bladder cancer, and even though the prognosis is relatively good, the recurrence rate is high. Although CIS belongs to NMIBC, the degree of malignancy is high, the differentiation is poor, and the rate of progression is high. Another 25% of bladder cancers are MIBC (including T2, T3, and T4) or metastatic bladder cancer. The vast majority of MIBC are high-grade bladder cancer. The tumor is easy to infiltrate and metastasize and the prognosis is poor[7].

2. Current Status of National and International Research on the Diagnosis and Treatment of Bladder Cancer

2.1. Research status of bladder cancer diagnosis

Exfoliative cystoscopy combined with transurethral resection of bladder tumor (TURBT) biopsy is the most accurate diagnosis method for the clinical diagnosis and follow-up of bladder cancer. However, its drawback is the invasiveness of the examination and the chances of missing the diagnosis for CIS, microcarcinoma, and inflammatory cancer. Exfoliative cytology of the urine has a high specificity for bladder cancer, but it is not sensitive enough and is susceptible to trauma, inflammation, or other urinary benign lesions with false positive results. The search for highly sensitive, specific, non-invasive, convenient, quick, and economical bladder cancer diagnosis and follow-up methods has been a research challenge. In recent years, a large number of bladder cancer markers have been reported, all of which have certain auxiliary or potential clinical application value. Bladder cancer markers approved by the US FDA for clinical use include NMP22, BTAstat, BTAtrak, FDP, FISH, and ImmunoCyt.

2.2. Research status of NMIBC treatment

TURBT is the most important diagnosis and treatment method to confirm the diagnosis of NMIBC. Due to the high recurrence rate after NMIBC, a single TURBT is difficult to improve the prognosis of patients. Therefore, post-operative adjuvant intravesical chemotherapy (or immunotherapy) after TURBT has become the first-line program for clinical treatment of NMIBC. The latest guidelines from the European Association of Urology suggest that for patients with incomplete tumor resection of TURBT, no myometrial tissue in the tissue specimens and high-grade or T1 phase of the pathological report are recommended for the first time after the first electrotomy. Secondary resection within 2-6 weeks and immediate chemotherapy after TURBT are recommended for patients with low-risk NMIBC as well as intermediate-risk NMIBC with a low risk of recurrence. Patients with intermediate-risk NMIBC are recommended for a full-dose of Bacillus Calmette-Guerin (BCG) perfusion immunotherapy or post-operative intravesical chemotherapy after TURBT not exceeding 1 year. Patients with high-risk NMIBC are recommended for BCG perfusion after TURBT for 1-3 years, while patients with a higher risk of progression may be considered for radical cystectomy[8].

2.3. Research status of MIBC treatment

Radical cystectomy with pelvic lymphadenectomy is currently the first-line clinical treatment of MIBC, including open surgery and laparoscopic surgery. However, with the rapid development of minimally invasive urological surgery, open surgery has gradually been replaced by laparoscopic surgery. The need for extended lymph node dissection for MIBC remains a debatable issue. Most scholars believe that patients with suspected lymph node metastasis should undergo extended lymph node dissection. A meta-analysis indicated that extended lymph node dissection not only significantly prolonged the probability of recurrence-free survival for lymph node-positive patients with pT3~4 but also for lymph node-negative patients[9]. Chemotherapy is an important adjunct to MIBC, including neoadjuvant chemotherapy (pre-operative) and adjuvant chemotherapy (post-operative). Neoadjuvant chemotherapy has been a subject of debate in recent years through its efficacy is better than adjuvant chemotherapy. The most commonly used chemotherapy regimen is GC regimen (gemcitabine and cisplatin) and methotrexate, vinblastine, azithromycin, and cisplatin regimen (MVAC)[10]. Studies have shown that there is no significant difference in the pathologic complete response rates between GC and MVAC regimens in MIBC patients (31% vs. 29%, P=0.77)[11]. The current mainstream view is that neoadjuvant chemotherapy before radical cystectomy can improve the meticulousness of the surgical resection of tumor, significantly prolonging the overall survival rate and helping to improve the prognosis of patients[12].

3. The Important Value and Significance of Translational Medical Research

3.1. Translational medicine as the only way to achieve precision medicine

The original concept of translational medicine refers to the transformation of basic research results into products that can be applied in the clinic[13]. With the development of medical science and technology and precision medicine, the scope of translational medicine has been further expanded. The author believes that the more precise concept of translational medicine should be the comprehensive use of cutting-edge biomedical technology and scientific research methods through multi-faceted research, multi-angle verification, and multi-disciplinary and multi-agency collaborations with the aim to explore the mechanisms of disease occurrence and development to transform the research results in the basic field into products or technologies that can be applied in the clinic and ultimately achieve accurate prevention, diagnosis, and treatment of diseases.

3.2. Translational medicine as the basis for the research-based medical model

With the rapid development of China-based medical model and precision medicine, the scope of translational medicine has been further expanded. The author believes that the more precise concept of translation hospitals[14]. Clinical and scientific research is the basis for the

research-based medical model and translational medicine, with the capacity to improve the prevention, diagnosis, and treatment of diseases is the most reliable foundation for its construction.

3.3. Translational medicine as a means to improve the diagnosis and treatment of bladder cancer

Current methods for the clinical diagnosis and treatment of bladder cancer (such as cystoscopy, imaging technology, surgery and radiotherapy, and chemotherapy) have their respective limitations. Therefore, it is urgent and necessary to find a non-invasive, economical and efficient method for diagnosis and treatment of bladder cancer. Translational medicine provides such an opportunity. Genomics, proteomics, molecular biology, bioinformatics and the like that aid in studying and exploring the mechanism of bladder cancer development, bladder cancer-related genes, signaling pathways, key molecules or targets can be clearly used for the diagnosis and treatment of bladder cancer. Biomarkers have been developed as part of a new detection kit for the early screening, diagnosis, and recurrence monitoring of bladder cancer through translational medicine. In addition, targeted drugs and immunological preparations can be used for the treatment of bladder cancer and further improve its existing diagnosis, treatment, and prognosis.

4. Bladder Cancer as the Foundation for the Practice of Translational Medical Research

At present, China is still in the initial exploration of translational medicine and precision medicine, and therefore, a considerable amount of research is required, especially from basic to clinical research, before gaining international recognition. Nonetheless, there have been a few major original achievements and low conversion rates of scientific research results. In recent years, the research team of the Institute of Biophysics, Chinese Academy of Sciences, has made outstanding achievements in the fields of bladder cancer research and translational medical research, which has effectively promoted the development of translational medicine in bladder cancer in China.

4.1. *In vitro* diagnostic targeting the new bladder cancer tumor marker AG-α3β1

After more than 10 years of intensive research, we have discovered a bladder cancer-specific marker, AG-α3β1, and developed a highly specific and sensitive anti-bladder cancer monoclonal antibody known as BCMab1[15,16]. On this basis, the peripheral blood circulating tumor cell (CTC) kit and urine exfoliated cell (UTC) kit for the detection of bladder cancer were successfully developed. The BCMab1 monoclonal antibody was used as a probe to modify the magnetic nanoparticles (MNPs) to produce the BCMAb1-MNPs complex. The target cells were sorted and enriched by magnetic separation, which can be used for both qualitative and quantitative detection in clinical samples.

The CTC and UTC kits with BCMab1 as the core component can quickly and accurately detect tumor cells in blood and urine. Moreover, it not only can perform dynamic monitoring of tumor metastasis and real-time evaluation of therapeutic effects but also capture tumor cells that can be cultured *in vitro* and detected using genomic approaches. The kits have high scientific value and innovation as the original and innovative ideas underlying these kits have been turned into clinical applications involving the first urinary tumor markers that have been granted the independent intellectual property rights in China.

4.2. Targeted therapeutic drugs based on BCMab1 monoclonal antibody

Apart from diagnostic kits, we are proud to have successfully developed the BCMab1 monoclonal antibody-targeting drug with extremely high specificity and significant anti-tumor effect. The BCMab1-targeted drug for the infusion treatment of bladder cancer not only specifically kills tumor cells without damaging the bladder mucosa but it is also not absorbed by the bladder mucosa, preventing a series of difficulties encountered during intravenous use. In terms of safety and effectiveness, it is incomparable with other drugs. This is also the first project in China that has been completely developed independently and has successfully transformed the field of clinical precision medicine. This project will further progress the precision medicine of bladder cancer in China and across the globe.

4.3. Localization of NMP22 kit

Nuclear matrix protein (NMP22) acts as a scaffold for the nuclear structure and is involved in DNA replication and transcription. NMP22 level in the urine of healthy people is usually extremely low. When the cells are malignant, NMP22 is abnormally increased at the end of the division. After a long-term follow-up study on NMP22, we have successfully developed a domestic NMP22 test kit to fill the gap in bladder tumor detection in China. The sensitivity of the kit is significantly better than that of the Alere NMP22 test kit in the US. It has broad application prospects in the screening, early diagnosis, and recurrence monitoring of patients with a high risk of bladder cancer, making it another important achievement in bladder cancer translational medicine in China. The successful development of the domestic NMP22 kit has broken the technological monopoly of the foreign biomedical industry.

4.4. Important advances in genetics research on the origin of bladder cancer stem cells

Cancer stem cells play an important role in tumor cell self-renewal, tumorigenesis, drug resistance, and metastasis.

The origin and genetic basis of bladder cancer stem cells (BCSCs) are still unclear. We have published two consecutive articles in the journal European Urology, revealing the genetic basis of the origin of human bladder cancer stem cells and elucidating on how the driver mutations in cancerous cells regulate the self-renewal mechanism of BCSCs[17,18]. In these studies, we have found that BCSCs originate from the epithelial stem cells in bladder or bladder cancer non-stem cells. Of the 21 key genes that have been mutated in BCSCs, six have not been reported in bladder cancer (*ETS1*, *GPRC5A*, *MKL1*, *PAWR*, *PITX2,* and *RGS9BP*). The combination of *ARID1A*, *GPRC5A,* and *MLL2* mutations significantly enhance the ability of bladder cancer non-stem cells to convert into BCSCs. This is the first time that the genomics of BCSCs using single-cell all-exome sequencing technology has been described. It has experimentally confirmed that BCSCs originate from the scientific problem of the epithelial stem cells in bladder or bladder cancer non-stem cells. This is also the first attempt in the world to use single-cell sequencing technology to explore the genomics of cancer stem cells, which has been verified by functional experiments.

4.5. Multi-party collaboration in the launching of China bladder cancer precision medical plan

In 2016, the media reported that the Institute of Biophysics, Chinese Academy of Sciences, together with many top hospitals and universities in China, formed a research and innovation team and launched the "China Bladder Cancer Precision Medical Plan" to provide early screening and diagnosis, pre-operative risk assessment, prognosis, recurrence judgment, targeted therapy monitoring and other aspects for bladder cancer patients to provide them with comprehensive treatment and care.

In this comprehensive treatment for bladder cancer, the diagnostic system and targeted drugs based on the BCMab1 monoclonal antibody are the first in China to apply original scientific research results to precision medicine in clinical trials for bladder cancer. The series of research results have been published in international peer-reviewed journals such as Clinical Cancer Research, Cancer Research and European Urology, among others, and have won three Chinese patents and one US patent, which were evaluated by international peers as e patents and one US patent, which were evaluated by international pee."

5. Current Issues and Challenges in Bladder Cancer and Translational Medical Research

At present, the main challenges in bladder cancer research and translational medical research can be summarized in the following: (1) The realization of multi-disciplinary and multi-technology integration, the rational and effective use of clinically existing bladder cancer diagnosis and treatment procedures and their new research frontiers, the improvement of early diagnosis of bladder cancer, the reduction in post-operative recurrence rate and the attainment of an accurate diagnosis and treatment of bladder cancer; (2) the use of genomics, epigenetics and cancer stem cell research to further reveal the origin of bladder cancer and its molecular mechanism during its occurrence and development to establish a more accurate molecular classification of bladder cancer and to guide the diagnosis and treatment of bladder cancer; (3) the exploration of the regulation of non-coding RNA in the occurrence and development of bladder cancer so as to determine its application value in the diagnosis and treatment of bladder cancer; (4) the detection of bladder cancer markers with high sensitivity and specificity to develop early diagnosis kits, targeted therapeutic drugs and immunological preparations based on bladder cancer markers through translational medicine so as to improve the conversion rate of scientific research results; (5) the selection and establishment of the best animal model in bladder cancer, making full use of the similarities between animal and human bodies but additionally improving animal models for basic and clinical research; (6) the improvement of patients. Ment of the best neoadjuvant chemotherapy as well as screening their sensitivity to certain types of chemotherapy drugs; (7) the accurate prediction of the effectiveness of chemotherapy and immunotherapy so that a patientmotherapy drugs; etween animal and human band (8) new endoscopic techniques, imaging techniques, and a combination of multiple bladder cancer markers that are expected to improve the rate of early diagnosis of bladder cancer. However, the challenge lies in achieving the most accurate diagnosis with the lowest detection cost; and (9) the types of drugs combined with chemotherapy, chemotherapy combined with immunotherapy, chemotherapy-assisted surgery and other comprehensive treatment programs that are expected to improve the prognosis of patients with bladder cancer. However, the increase in efficacy may also be countered by the adverse reactions caused by the combination of multiple drugs which, in turn, increase and complicate problems.

6. Conclusion and Outlook

With the cross-integration of information technology, biological science and technology in recent years, as well as the rapid development of omics technology, second-generation sequencing technology, molecular biology technologies and minimally invasive urological surgery, modern medical models have gradually moved toward a multi-disciplinary, multi-centered direction of precision medicine. Translational medicine is the only way to achieve precision medicine. Thus, there are unprecedented opportunities in the fields of bladder cancer research and translational medical research.

Conflicts of Interest

The authors declare conflicts of interest.

References

1. Torre LA, Bray F, Siegel RL, *et al*., 2015, Global Cancer Statistics, 2012. *CA Cancer J Clin*, 65(2):87-108.
2. Antoni S, Ferlay J, Soerjomataram I, *et al*., 2016, Bladder Cancer Incidence and Mortality: A Global Overview and Recent Trends. *Eur Urol*, 71:96-108. DOI 10.1016/j.eururo.2016.06.010.
3. Sujun H, Sizhi Z, Wanqing C, *et al*., 2013, Analysis of the Current Status and Epidemic Trends of Bladder Cancer in China. *Cancer Prog*, 11(1):89-95.
4. Wanqing C, Rongshou Z, Sizhi Z, *et al*., 2016, Analysis of the Incidence and Mortality of Malignant Tumors in China in 2012. *Chin J Tumor*, 25(1):1-8.
5. Murta-Nascimento C, Schmitz-Drager BJ, Zeegers MP, *et al*., 2007, Epidemiology of Urinary Bladder Cancer: From Tumor Development to Patient's Death. *World J Urol*, 25(3):285-95. DOI 10.1007/s00345-007-0168-5.
6. Zhang H, Guo Y, Song Y, *et al*., 2016, Long Noncoding RNA GAS5 Inhibits Malignant Proliferation and Chemotherapy Resistance to Doxorubicin in Bladder Transitional Cell Carcinoma. *Cancer Chemother Pharmacol*, 79(1):49-55. DOI 10.1007/s00280-016-3194-4.
7. Kamat AM, Hahn NM, Efstathiou JA, *et al*., 2016, Bladder Cancer. *Lancet*, 388(10061):2796-810. DOI 10.1016/s0140-6736(16)30512-8.
8. Babjuk M, Bohle A, Burger M, *et al*., 2016, EAU Guidelines on Non-muscle-invasive Urothelial Carcinoma of the Bladder: Update 2016. *Eur Urol*, 71(3):447-61. DOI 10.1016/j.eururo.2016.11.030.
9. Bi L, Huang H, Fan X, *et al*., 2014, Extended vs Non-extended Pelvic Lymph Node Dissection and their Influence on Recurrence-free Survival in Patients Undergoing Radical Cystectomy for Bladder Cancer: A Systematic Review and Meta-analysis of Comparative Studies. *BJU Int*, 113(5b):E39-E48. DOI 10.1111/bju.12371.
10. Zargar H, Espiritu PN, Fairey AS, *et al*., 2015, Multicenter Assessment of Neoadjuvant Chemotherapy for Muscle-invasive Bladder Cancer. *Eur Urol*, 67(2):241-49.
11. Galsky MD, Pal SK, Chowdhury S, *et al*., 2015, Comparative Effectiveness of Gemcitabine Plus Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, Plus Cisplatin as Neoadjuvant Therapy for Muscle-invasive Bladder Cancer. *Cancer*, 121(15):2586-93. DOI 10.1002/cncr.29387.
12. Grossman HB, Natale RB, Tangen CM, *et al*., Neoadjuvant Chemotherapy Plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer. *N Engl J Med*, 349(9):859-66. DOI 10.1056/nejmoa022148.
13. Mankoff SP, Brander C, Ferrone S, *et al*., 2004, Lost in Translation: Obstacles to Translational Medicine. *J Transl Med*, 2(1):14.
14. Xia X, Jinming Z, Hong Z, *et al*., 2016, Practice and Thinking of Translational Medicine from the Perspective of Research-oriented Medicine. *Chin J Hosp Manag* 32(1):19-21.
15. Li C, Du Y, Yang Z, *et al*., 2016, GALNT1-Mediated Glycosylation and Activation of Sonic Hedgehog Signaling Maintains the Self-renewal and Tumor-initiating Capacity of Bladder Cancer Stem Cells. *Cancer Res*, 76(5):1273-83. DOI 10.1158/0008-5472.can-15-2309.
16. Li C, Yang Z, Du Y, *et al*., 2014, BCMab1, a Monoclonal Antibody Against Aberrantly Glycosylated Integrin alpha3beta1, has Potent Antitumor Activity of Bladder Cancer *in vivo*. *Clin Cancer Res*, 20(15):4001-13. DOI 10.1158/1078-0432.ccr-13-3397.
17. Yang Z, Li C, Liu H, *et al*., 2016, Single-cell Sequencing Reveals Variants in ARID1A, GPRC5A and MLL2 Driving Self-renewal of Human Bladder Cancer Stem Cells. *Eur Urol*, 71(1):8-12. DOI 10.1016/j.eururo.2016.06.025.
18. Yang Z, Wu S, Cai Z, *et al*., 2016, Reply from Authors Re: Xue-Ru Wu. Attention to Detail by Single-cell Sequencing. *Eur Urol*, 71(1):15-6. DOI 10.1016/j.eururo.2016.11.003.