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Bone Metastases in Patients with Prostate Cancer: A Literature Review

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Abstract: Prostate cancer is a major threat to men's health around the world. Bone is the most common metastasis site in patients with prostate cancer, which may lead to bone pain, pathological fracture and spinal cord compression, and it is related to various physiological or pathological factors such as age, physical condition, and previous treatment. The occurrence of bone-related events will seriously affect the quality of life of patients. In recent years, more and more people are concerned about bone metastasis of prostate cancer. Some important international cancer organizations have issued guidelines for the diagnosis and treatment of prostate cancer with bone metastasis. However, Clinicians still have some misunderstandings about bone metastasis of prostate cancer, especially selection of therapeutic strategies and the screening of appropriate drugs. Nowadays, the therapeutic strategies of prostate cancer with bone metastases mainly include primary lesions and bone metastases lesions. The former include surgery, radiotherapy, endocrine therapy, chemotherapy, immunotherapy, radiofrequency ablation and so on. And the later is made up of bone modification drug, radiopharmaceutical, lifestyle adjustment, and symptomatic analgesic treatment. The purpose of this review is to summarize the status and progression of bone metastasis in prostate cancer and to explore the best diagnosis and therapeutic strategies.

Keywords: Prostate cancer; bone metastasis; therapeutic strategy

Introduction

Prostate cancer (PCa) is one of the most common genitourinary tumors in Caucasian and African Americans. In particular, the morbidity and mortality of the elderly were at the forefront of malignant tumors. China is a country with low incidence of prostate cancer, but recently changes in some factors have led to a significant increase in incidence such as diet, society, environmental factor and so on[1,2]. According to the latest statistics in 2017 by China National Cancer Center, studies have shown that the incidence of prostate cancer is significantly different in urban and rural areas. People in major cities, such as Beijing, Shanghai and Guangzhou, are more likely to develop prostate cancer and the incidence is 17.26 cases per 100,000. On the contrary, the incidence of prostate cancer in some people living in small

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cities or rural areas is less than 5 per 100,000[3]. Prostate cancer has the characteristics of occult and is apt to metastasis in clinical. Bone is the most common metastatic site and it has been reported that about 70% of prostate cancer patients in Europe or United States may have bone metastasis in the course of disease, and bone metastasis will seriously affect the quality of life of patients[4]. The incidence of prostate cancer with bone metastasis in Japan is approximately 75%, which is also increasing with the extension of the patient's survival[5]. Bone metastasis may lead to bone pain, pathological fracture and spinal cord compression, which is related to various factors such as age, physical condition, and previous treatment. At present, people around the world are more concerned about the bone metastasis of prostate cancer. Some important international cancer organizations have issued guidelines for the diagnosis and treatment of prostate cancer related bone metastasis[6-8]. The purpose of this review is to summarize the status and progression of bone metastasis in prostate cancer and to explore the best diagnosis and treatment strategies.

1. Clinical manifestations of prostate cancer with bone metastases

Axial skeleton is the most common site of bone metastasis, which mainly occurs in the thoracic, lumbar spine, ribs, pelvis and so on, and it usually manifests multifocal metastasis. Prostate cancer with bone metastasis mainly dominated osteoblastic changes, but there may be osteoblastic and osteolytic coexisting in metastatic bone lesions[9,10]. Patients with early stages of bone metastasis in prostate cancer may have no associated clinical symptoms. However, as the disease progresses, pain is the first symptom in about 90 percent of patients with advanced prostate cancer. In addition, there may be pathological fractures, dyskinesia, spinal cord compression, hypercalcemia, coma, muscle weakness and paralysis[11]. The first skeletal related events (SREs) may occur 10 months after the diagnosis of prostate cancer. SREs is defined as bone complications caused by tumor bone metastasis, mainly including pathological fractures, spinal compression, hypercalcemia, and bone complications requiring surgical or radiotherapy. Acute SREs can affect the quality of life and survival of patients[7]. Prostate cancer with bone metastasis is quite complicated and the mechanism has not yet completely clear. It has been clearly related to the transduction and activation of some signaling pathways until now, such as MET, VEGF, β2-epinephrine signaling pathway, AR signaling pathway and RANKL signaling pathway[12].

2. Diagnosis of prostate cancer with bone metastasis

Accurate diagnosis of bone metastasis plays an important role in the clinical staging and programming of prostate cancer. Prostate cancer is similar to other tumors, mainly based on the clinical stage of AJCC. However, due to the high heterogeneity of prostate cancer, clinicians found that AJCC staging alone could not develop accurate and effective treatment methods. Therefore, NCCN found that on the basis of AJCC stage, increasing serum PSA level before treatment and Gleason score could constitute the prognostic risk assessment model of prostate cancer by summarizing evidence-based medical data. This model may be important for guiding the diagnosis and treatment of prostate cancer[13]. Current studies have found that novel prostate cancer patients with any of the following indicators can be considered as a high-risk population for bone metastasis, including: A. Bone pain or pathological fracture; B. PSA≥10 ng/ml; C. Alkaline phosphatase elevated; D. Hypercalcemia; E. Gleason score≥8 points; F. TNM stage≥T3 period[14]. Appropriate screening for high-risk groups is the key to accurate diagnosis. Bone metastasis in prostate cancer is mainly caused by osteogenic changes. Osteoblasts can form bone matrix, which can lead to ray impenetrability. However, histological studies have confirmed that osteoclast activity and resorption cavities can occur at the site of osteogenic lesions, indicating that there is also an increase in osteolytic activity in all metastatic bone lesions[6]. The diagnosis of prostate cancer with bone metastasis needs to be combined with the patient's clinical symptoms and advanced examination equipments, including X-ray, CT, ECT, MRI and PET-CT[15]. In addition, some biochemical markers can be needed such as Prostate Specific Antigen (PSA), Alkaline Phosphatase (ALP), Bone Sialoprotein (BSP) and Collagen type I pyridine crosslinking peptide (ICTP). A clinical control study found that the sensitivity of SP, ALP, ICTP and PSA is 80.95%, 57.14%, 69.05% and 71.43%, and the specificity is 72.80%, 64.80%, 76.80% and 88.80%, respectively. Sensitivity of the combined detection of the above 4 serological markers can be increased to 97.62%, which may

effectively increase the positive predictive value of prostate cancer with bone metastasis[16].

3. Therapy for prostate cancer with bone metastasis

The treatment of prostate cancer with bone metastases mainly include primary lesions and bone metastases lesions. The former include surgery, radiotherapy, endocrine therapy, chemotherapy, immunotherapy, radiofrequency ablation and so on. And the later is made up of bone modification drug, radiopharmaceutical, lifestyle adjustment, and symptomatic analgesic treatment. This chapter focuses on systemic treatment of prostate cancer and local treatment of bone metastases lesions.

4. Systemic treatment of prostate cancer

4.1 Endocrine therapy

Endocrine therapy is one of the most common therapeutic methods of prostate cancer. It is also a first-line treatment for advanced prostate cancer and significantly prolonged the progression free survival and overall survival of patients. It includes androgen deprivation therapy , single anti-androgen therapy, complete androgen blockading, androgen biosynthesis inhibitor , neoadjuvant endocrine therapy before radiothreapy, intermittent endocrine therapy and adjuvant endocrine therapy after radiotherapy and etc[17,18]. Endocrine therapy can be divided into first-line and second-line endocrine therapy, and the first-line endocrine therapy mainly includes androgen deprivation therapy, anti-androgen drug therapy, and complete androgen blocking therapy.

4.1.1 Androgen deprivation therapy (ADT)

ADT can inhibit the productions of androgen, reduce estrogen in the body, and remove the stimulating effect of androgen on the growth of prostate cancer cells. The methods mainly include surgical emasculation (bilateral orchiectomy) and drug emasculation (LHRH analogues, estrogen). It apply to the following diseases: ①metastatic prostate cancer; ②localized early-stage or located progressive prostate cancer, no prostatectomy or radiotherapy; ③neoadjuvant endocrine therapy before radical prostatectomy or radical radiotherapy; ④adjuvant endocrine therapy cooperated with radiotherapy; ⑤localized recurrence and metastasis after curative treatment; ⑥continuous androgen suppression on the stage of androgen-independent. See table 1 basic characteristics of drug emasculation therapy.

Classification	Name	Mechanism	Usage and Dosage	Announcements	Notes
Gonadotropin releasing hormone analogues (GnRH-A)	Leuprorelin	GnRH acts on the pituitary gland to secret luteinizing hormone (LH) and follicle stimulating hormone (FSH). LH acts on the interstitium of testis to secrete testosterone and FSH acts on sertoli cells to produce	3.75mg, subcutaneous injection, every 4 weeks	Serum testosterone rising temporarily after the administration can lead to a worsening of the patient's condition in the short term, and return to its original level after 4 weeks, and then the testosterone gradually declines to the castration level.	GnRH-A is one of the standard treatments for advanced prostate cancer. For bone metastasis patients with with spinal cord compression, LHRH should be used with caution, and the surgical excision of rapidly decreasing testosterone level
	Goserelin		3.6mg, subcutaneous injection, every 4		

		androgen synthesis proteins.	weeks		can be selected.
	Triptorelin	GnRH-A has a strong affinity with the pituitary gland. The release of LH may temporarily increase 15-20 times after the first administration.	3.75mg, intramuscular injection, every 4 weeks,	It may present with an exacerbation of transient clinical symptoms (especially osteodynia) and should be closely monitored at the initial stage of treatment, especially in patients with urinary tract obstruction and vertebral bone metastasis.	
	Buserelin	Testosterone secreted by the testicles also increased, but soon LH was exhausted, and the LH level in the blood dropped to a very low level, resulting in the testicular secretion of testosterone reduced to the castration level.	500μg, subcutaneous injection, tid, use for 7 days maintenance treatment: 100-200μg, nasal spray,three times a day		
GnRH receptor blockers	Degarelix	It binds rapidly and reversible to the pituitary GnRH receptor, reducing the release of gonadotropin and testosterone	200mg or 240mg in the first month, subcutaneous injection, then 60mg or 80mg once a month		
Estrogen	Diethylstilbestrol	It can inhibit the secretion of pituitary gonadotropin through the feedback regulation of	initial dose: 1~3mg/day, maintenance dosel: 1mg/day, use for 2-3 months	It will increase the incidence of adverse reactions in the cardiovascular and cerebrovascular areas.	It is rarely used for first-line treatment and is often used for second-line treatment.

		hypothalamus level, and reduce the production of LHRH and LH, so as to reduce the secretion of testosterone in testicles			

Table 1. Basic characteristics of drug emasculation therapy

4.1.2 Antiandrogen monotherapy (AAM)

AAM can be competitively combined with endogenous androgen receptors in target organs, and it can inhibit the entry of dihydrotestosterone into the nucleus by binding to the dihydrotestosterone receptor in the cytoplasm, thereby blocking the effect of androgens on prostate cancer cells. It is mainly applicable to prostate cancer with local advanced stage and no distant metastasis (T3-4NxM0 stage). According to different chemical structure, it can be divided into steroid and non-steroid. Specific drugs and dosage are shown in table 2.

Classification	Name	Mechanism	Usage and Dosage	Announcements	Notes
Steroids	Cyproterone acetate	It can inhibit the release of luteinizing hormone, block androgen receptors, and block the 5 prun-reductase, thereby reducing the concentration of prostatic dihydrotestosterone.	100mg, po, bid or tid.	Adverse reactions include reduced sexual interest and erectile dysfunction.	Serum testosterone levels gradually rise after 6-12 months of treatment, but it can be prevented by low-dose ethylene-estradiol (0.1 mg/d).
	Megestrol acetate		40mg, po, bid or tid or qd; 160mg, po, once a day Changing to maintenance dose after 3 months: 40mg, po, bid.		
Non-steroid	Flutamide	It works by blocking the binding of testosterone and dihydrotestosterone to its intracellular receptors, and has the inhibitory effect of blocking testosterone on gonadotropin secretion.	250mg, po, tid.	It is commonly used in combination with GnRH-A, and is suitable for patients who wish to preserve their sexual ability.	
	Bicalutamide		Single drug application: 150mg, po, once a day; Combined:50mg,		

	po, once a day	
Nilutamide	Induction dose: 300mg, po, once a day, for 4 weeks; Maintenance dose: 150mg, once a day, or in divided doses	
Enzalutamide	160mg, po, once a day.	It is suitable for patients with metastatic castration resistant prostate cancer who have failed treatment with docetaxel.

Table 2. Basic characteristics of Anti-androgen therapy

4.1.3 Androgen biosynthesis inhibitor therapy

Abiraterone acetate (AA) belongs to a kind of androgen biosynthesis inhibitors and can inhibit androgen synthesis of testicular, adrenal and prostate cancer cells by inhibiting CYP17 which is a key enzyme in the androgen synthesis pathway. The commonly used dosage of AA is 1000mg, orally, once a day. And it is suitable for first-line treatment of asymptomatic or mild symptoms of metastatic castration resistant prostate cancer (mCRPC), or is not suitable for chemotherapy in patients with symptomatic mCRPC, or patients with advanced mCRPC after chemotherapy. In the COU-AA-301 study, the median survival of abiraterone acetate plus prednisone was 15.8 months in patients with mCRPC who recieved docetaxel after chemotherapy, which was 4.6 months longer than the control group. The risk of death was reduced by 26%[19]. In the final analysis of the COU- aa-302 study, for patients with mCRPC without symptoms or mild symptoms, the median survival of abiraterone acetate combined with prednisone is 34.7 months and the control group is 30.3 months. The median survival extended by 4.4 months and the risk of death reduced by 19%[20].

4.1.4 Complete androgen blocking therapy (CAB)

CAB is also called maximal androgen blockade (MAB). The combination of castration and anti-androgen may remove testis-derived and adrenal-derived androgen. A combination of castration and anti-androgen therapy can simultaneously remove androgens from both the source of testis and the source of adrenal gland. Previous studies have shown that compared with LHRHa alone, CAB composing of LHRHa and bicalutamide can reduce the risk of death in patients with advanced prostate cancer and prolong their disease-free survival[21]. In recent years, the NCCN and EAU guidelines have shown that CAB can improve the overall survival of patients by 5-20%.

4.1.5 Neoadjuvant hormone therapy (NHT)

NHT is suitable for advanced prostate cancer patients with T2 and T3a stages. Recommended options include CAB, LHRH alone or anti-androgen drugs and treatment duration are 3 to 9 months.

4.1.6 Intermittent endocrine therapy (IHT)

IHT can delay tumor progression to hormone-independent period. It apply to localized prostate cancer that cannot undergo radical surgery or radiotherapy, or local advanced prostate cancer (T3-T4 stage), or metastatic prostate cancer with positive pathological margin and recurrence after radical resection. IHT usually adopts CAB, and can also be used for drug emasculation. The recommended discontinuation rate is 3 to 6 months after PSA is less than or equal to 2ng/ml.

4.1.7 Adjuvant endocrine therapy after radical treatment

The objective of adjuvant endocrine therapy after radical treatment is to treat the marginal residual lesion, residual positive lymph nodes, small metastatic lesion, etc. Its indications include positive pathologic margin after radical surgery, positive lymph nodes of postoperative pathological, T3 or T2 stage with high risk factors (Gleason > 7, PSA > 20ng/ml), and local advanced prostate cancer after radical radiotherapy. The main treatment methods include CAB, drugs or surgical excision, and anti-androgen therapy. It is recommended to start immediately after surgery or radiotherapy, with a minimum time of 18 months.

4.1.8 Anti-androgen withdrawal therapy

Patients with androgen deprivation therapy, androgen receptor gene mutation may occur and results in the decrease of the receptor specificity, antiandrogen medicines instead as agonist activation of downstream, eventually lead to treatment failure. At this point, if the anti-hormone drugs are discontinued, approximately 1/4 of the patients may have a 3-5 month PSA decline and local symptom improvement[22].

4.2 Chemotherapy

Chemotherapy is an important treatment for metastatic castration-resistant prostate cancer (CRPC). Common drugs include Taxanes, Mitoxantrone, Adriamycin, Epirubicin, Estramustine, Cyclophosphamide, Orally administered vinorelbine, cisplatin, and fluorouracil. Taxus drugs has become the standard first-line chemotherapy for endocrine failure in metastatic prostate cancer. However, single drug chemotherapy for advanced prostate cancer has a poor effect. Currently, the combined drug regimen is recommended, and specific chemotherapy drugs and regimens are shown in table 3.

Regimens	Drugs and Dosage	Notes
DP	Docetaxel 60-75mg/m^2, intravenous injection, d1; Prednisone 5mg, po, bid, day 1-21; Every 21 days.	TAX327 study demonstrated that compared with mitoxantrone, the median survival was significantly delayed in patients who received docetaxel 3-week regimen (18.9 vs. 16.5 months, P=0.009), and PSA response rates (45% vs. 32%, P<0.001), and remission rate of bone pain were significantly increased (35% vs. 22%, P=0.02)[23].
MP	Mitoxantrone10-12mg/m^2, intravenous injection, d1; Prednisone 5mg, po, bid, day 1-21; Every 21 days.	For symptomatic hormone-resistant prostate cancer, compared with monotherapy prednisone, mitoxantrone combined with prednisone significantly relieved bone pain (29% vs. 12%, P=0.01), but the overall survival did not extend significantly[24].
EMP	Estramustine 600mg/(m^2 • d), po, bid; A total of 3-4 months.	With the dual role of alkylating agent and estrogen.

CFP	Cisplatin 50mg/m^2, intravenous injection, d1; Cyclophosphamide 500mg/m^2, intravenous injection, d1; Fluorouracil500mg/m^2; intravenous injection; d1; Every 21 days.	
EEM	VP-16 50mg/(m^2 • d), po, d1-14; EM 15mg/(kg • d), po, d 1-21; Every 4 weeks, continuously to disease progression.	
NE	Norvinvinine 25mg/m^2, intravenous injection, d1 and d8; Estramustine 280mg, tid, d1-14; Every 21 days.	
FAM	Adriamycin 50mg/m^2, intravenous injection, d1; Mitomycin 5mg/m^2, intravenous injection, d1-2; Fluorouracil 750mg/m^2, intravenous injection, d1-2; Every 21 days.	
CP	Cabaztaxe l25mg/m^2, intravenous injection, d1; Prednisone 5mg, po, bid, d1-21; Every 21 days.	TROPIC study showed that compared to mitoxantrone, cabazitaxel is more effective in failed CRPC patients with PSA response rate of 39.2%, median PFS of 2.8 months, and 15.1 months of OS[25]. FIRSTANA study showed that cabazitaxel was not superior to docetaxel in both OS and PFS in patients with metastatic CRPC who are not received chemotherapy[26].

Table 3. Chemotherapy for advanced prostate cancer

4.3 Immunotherapy

At present, Sipuleucel-T (Provenge) is the only self-tumor vaccine used for the clinical treatment of prostate cancer. It is mainly adapted to CRPC patients with no symptoms or mild symptoms, no liver metastasis, > life expectancy for 6 months, and generally in good condition. Preparation process was first isolated from patient's body antigen presented cells, in vitro amplification and incubation activation in the prostatic acid phosphatase (PAP), and then back to the patient's body, induction of the innate immune response to prostate cancer and achieve the goal of treatment of tumor[27]. In Phase III studies, Sipuleucel-T prolonged the survival of CRPC patients by approximately 4 months compared with placebo and the survival rate of three-year is 31.7%. However, it is not recommended for patients with rapid disease progression, liver metastases or patients who are expected to survive for less than 6 months.

5. Treatment of bone metastases in prostate cancer

Currently, the drugs targeted at bone metastases of prostate cancer in clinical practice are mainly bone-modifying agents (BMAs) and radioactive drugs, among which BMAs include bisphosphate drugs and dino-resistant drugs and radioactive drugs include Strontium-89 (^{89}Sr), Samarium-153 (^{153}Sm) and Radium-223.

5.1 Bone-modifying agents

5.1.1 Bisphosphate drugs

Bisphosphate drugs are one of the most commonly used drugs to prevent and treatment for bone metastases related complications. It can obviously reduce or delay the incidence of bone metastases and some experts recommend starting treatment as soon as possible when bone metastasis is diagnosed, even in asymptomatic patients. The specific classification and usage amount are shown in table 4.

Classification	Names	Usage and Dosage	Indications
First generation bisphosphates	Clodronate	Intravenous drip:3 ～ 5mg/（kg • d） Oral:1200mg, bid	Osteolytic bone metastasis, osteoporosis and hypercalcemia caused by cancer
	Etidronate	Oral:0.2g, bid, between meals	Postmenopausal osteoporosis and senile osteoporosis
New nitrogen-containing bisphosphonates	Alendronate	Recommended dose: 70mg, once a week or 10mg, once a day; Recommended dose for osteoporosis: 10mg, once a day or 70mg, once a week.	1. Prevention and treatment of osteoporosis, such as osteoporosis in postmenopausal women, osteoporosis caused by the use of corticosteroids and osteoporosis in men. 2. Prevent hip and spine fractures, such as spinal compressibility fractures. 3. Treatment of Paget's disease and hypercalcemia. 4. Curative effect on the treatment of malignant tumor related bone metastatic pain.
	Ibandronate	The medicine must be fully hydrated with saline before use, and the severity of hypercalcemia and tumor type should be considered. For most patients with severe hypercalcemia (serum calcium concentration of 3mmol/L or 12mg/dL corrected by albumin), a single dose of 4mg is sufficient. For moderate hypercalcemia (serum calcium concentration corrected by albumin is no more than 3mmol/L or no more than 12mg/dL), a single dose of 2mg is effective. The highest single dose in clinical trials was 6mg, but did not improve the efficacy.	The treatment of pathological hypercalcemia caused by tumor (hypercalcemia)

Pamidronate	Intravenous infusion is strictly prohibited. The infusion speed should not exceed 60mg/ h.The maximum concentration of infusion solution is 90mg/250ml. Under normal circumstances, 90mg diluted in 250ml injection should be injected for more than 2 hours. In the treatment of multiple myeloma and tumor-induced hypercalcemia, the recommended concentration of the drug should not exceed 90mg/500ml, and the infusion time should be more than 4 hours.	Tumor induced hypercalcemia, breast cancer osteolytic bone metastasis and multiple myeloma osteolysis
Zoledronic acid	4mg, iv drip, infusion time should not be less than 15 minutes. Every 3-4 weeks	Pain caused by osteolytic bone metastasis in malignant tumors. The first and only bisphosphonates approved for use in CRPC patients can reduce the incidence of SREs.

Table 4. Classification and features of Bisphosphate drugs

5.1.2 Denozomab (D-mab)

Denozomab is a fully human monoclonal antibody of aspecific receptor activator of NF-κB ligand (RANKL) which may inhibit osteoclast activation to reduce bone resorption and tumor-associated bone destruction. It may have the effect of breaking the vicious circle caused by bone metastasis and activation of osteoclasts, and is suitable for treating solid tumors with bone metastasis in adult patients, but not for blood tumors. Fizazi *et al*. demonstrated that Denozomab prevents SREs better than zolledronic acid in CRPC patients with bone metastasis, and they found that compared with zolledronic acid, Denozomab delayed the first SREs onset by 17.1 months and 20.7 months respectively (P=0.008)[28]. Another Ⅲ period studies have shown that Denozomab can by changing the bone microenvironment and delay the onset of prostate cancer bone metastasis, the results showed that compared with placebo, bone metastases free survival time (BMFS) is 4.3 months by Denozomab extending (25.2 months to 29.5 months, p = 0.028), but the two groups of patients' overall survival are similar (43.9 to 44.8 months, p = 0.91). However, the risk of mandibular osteonecrosis and hypocalcemia in Denozomab group was higher than that in the placebo group[29]. In addition, Smith MR *et al*. found non-metastatic CRPC patients with PSA doubling in a short period of time are at high risk for bone metastasis. Denozomab can improve the BMFS of PSA doubling patients, especially for high-risk patients with suspected disease progression[30].

5.2 Radioactive drugs

5.2.1 89Sr and 153Sm

Radionuclide therapy is an effective treatment for bone metastasis of prostate cancer. ^{89}Sr and ^{153}Sm are mainly

used in the treatment of osteogenic bone metastasis. Both of them have similar effects, which are about 60-80%, but they are slightly different in terms of pain relief time and toxicity. ^{89}Sr can accumulate in bone metastases with active osteoblasts, and is an effective internal radiation therapy agent for bone tumors. Its therapeutic effect is mainly to kill the cancer cells by means of β rays, so as to achieve the analgesic effect. The energy of β rays emitted by ^{89}Sr is 1.46MeV with a half-life of 50.5 days, and it can be rapidly absorbed by bone after injection, with a half-life of 14 days in normal bone and a half-life of more than 50 days in bone metastases. ^{153}Sm is a radionuclide, produced by neutron bombardment of concentrated samarium 152 oxides, which is used to develop osteogenic bone metastases. ^{153}Sm can simultaneously emit γ and β rays, which have a very low osteotactic character, while ^{153}Sm-EDTMP, a new compound formed after the chelation of ^{153}Sm and EDTMP, has a high osteotactic character. The concentration of 153Sm- EDTMP in bone metastases was 5 times that of normal bone tissue, and tumor cells can be continuously exposed to higher dose of β rays to achieve the purpose of local treatment.

5.2.2 Radium-223

Radium-223 is a α-particle radiation therapy agent, whose activity is partially simulated by calcium ions, and it can form complex with hydroxyapatite (HAP) in bone and selectively target bone, especially in the area of bone metastasis. The results on ALSYMPCA study showed that compared with placebo, the median OS of patients in the Radium-223 group was 3.6 months longer (14.9 months vs. 11.3 months, P=0.00007) and reduced the risk of death by 30.5%. The time to the first SREs was delayed to 5.8 months (15.6 months vs. 9.8 months, $P < 0.0001$). Subgroup stratification suggested that patients could benefit from Radium-223 regardless of whether they received paclitaxel chemotherapy or bisphosphonate[31].

5.3 Other approaches

At present, the treatment of prostate cancer with bone metastases is recommended to carry on the diagnosis and treatment of multidisciplinary collaboration (MDT). Specialists in oncology, radiotherapy, bone surgery, pathology, radiography and palliative care are required to participate in the MDT. The ultimate goal is to provide accurate guidance for the clinical diagnosis and treatment of prostate cancer patients with bone metastasis.

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