

Scientific rationale for the use of P-MAPA immunotherapy in the treatment of bladder cancer



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2018

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1. Overview

Bladder cancer treatment is still a challenge. More than 500,000 people suffer from bladder cancer and nearly 70,000 new cases are diagnosed each year in the U.S. In addition, urinary bladder cancer ranks ninth in worldwide cancer incidence. It is the seventh most common malignancy in men and seventeenth in women. Bladder cancer is the most costly cancer among the elderly in US, with values estimated at nearly \$4 billion per year ([41](#)).

The standard of care for bladder cancer has presented few changes over the last decades, and treatment options remain limited. Some treatments, such as cystectomy, imply drastic lifestyle changes that diminish the patients' quality of life while falling far short of achieving cure.

The standard conservative treatments – Transurethral Resection of Bladder Tumors (TURBT) followed by intravesical Bacillus Calmette-Guèrin (BCG) immunotherapy – avoid the progression of high-grade non-muscle invasive bladder cancer (NMIBC) to advanced disease, but often the efficacy is weakened by the emergence of refractory or relapsing disease, and toxicity causes the discontinuation of the treatment.

Radical or partial cystectomy is the option for non-responsive patients to the current bladder-sparing therapies. Patients who refuse or are not eligible for bladder removal face a dismal prognosis, due to the increased risk of progression to advanced disease. Despite conservative treatments, a large number of NMIBC patients at the time of diagnosis will develop invasive or metastatic disease.

Around half of patients with locally advanced or metastatic bladder cancer do not respond satisfactorily to first-line platinum-based chemotherapies, that is, methotrexate, vinblastine, doxorubicin (adriamycin) and cisplatin (MVAC), and gemcitabine and cisplatin (GC). Due to cisplatin's high toxicity, many patients will receive doses lower than those typically recommended or even no treatment. The alternative would be a carboplatin-based chemotherapy, as second-line treatment (gemcitabine plus carboplatin or gemcitabine plus paclitaxel), which provides a median survival of 9-10 months ([39](#), [23](#)).

Despite the first-line platinum-based therapy, options are quite few for those patients whose malignant lesions progress. Only 10% to 15% of them respond to second-line single-agent chemotherapy ([39](#), [23](#)). The recently approved immune checkpoint inhibitors seem to be a promising alternative to treat patients with advanced and metastatic bladder cancer who fail or are ineligible for first-line platinum-based chemotherapies, but the treatment has presented limitations due to toxicity and lack of effectivity for some patients ([28](#)).

In summary, conservative treatments provide a far from ideal solution for large groups of NMIBC patients and there is a huge need for bladder cancer therapies that really work.

P-MAPA – an antitumor compound in late-stage development, led by the research network Farmabrasilis – could be one of them. As argued in the next topics, P-MAPA can help to reach the best therapeutic strategy in the treatment of bladder cancer blocking the cancer process still in the urinary bladder with a bladder preservative approach, so avoiding the progression of the disease.

Based on preclinical studies carried out over the last years, intravesical P-MAPA immunotherapy represents a novel approach to fight high-grade malignant lesions still in the urinary bladder, before they spread to adjacent tissues and organs. Experimentally, P-MAPA has shown an impressive antitumor activity and a clear superiority over BCG, in comparative studies of efficacy and safety. As evidenced in animal models for study of bladder cancer, P-MAPA can help to overcome the BCG's lack of effectivity and high toxicity for large groups of patients. The toxicity of P-MAPA in the urothelium at therapeutic dosage is close to zero.

Under a bladder-sparing approach, intravesical P-MAPA could be used to treat NMIBC patients who are BCG-refractory, BCG relapsing and BCG-intolerant, as well as the refractory ones to approved second-line intravesical therapy, eliminating malignant lesions before they spread to other tissues and organs. Notably, as preclinical studies have evidenced, P-MAPA could also be used in the treatment of the advanced and metastatic forms of the disease, in association with other drugs, without additional toxicity.

2. Chemical characteristics of P-MAPA

P-MAPA is a non-linear, high-molecular weight biopolymer (~320 kDa), defined as a **protein magnesium ammonium phospholipoleate-palmitoleate-anhydride** polymer aggregated. The empirical formula is $(C_{18}H_{35}Mg_2NO_{21}P_5)_{391} (C_{326}H_{614}O_{163}N_{204}S_2)_{0.16}$

P-MAPA results from a fermentation process with of the fungus *Aspergillus oryzae* as a fermentation agent in an appropriate medium. The result from the fermentation is a pure compound in the form of crystals, which remains stable for two years after bottled in vials for end use ([42](#)).

P-MAPA has been used by intravesical or systemic via of application. For not being a biohazardous agent like BCG, P-MAPA and the devices used for its administration can be handled, used and disposed off easily and safely.

3. The immune-mediated mechanism of action of P-MAPA in urothelial bladder cancer

Experimental data have revealed the multiple ways by which P-MAPA, after its deployment inside the urinary bladder, can block tumor cell growth. In summary, P-MAPA activates pattern recognition receptors (PRRs) – specifically, Toll-Like Receptors 2 and 4 (TLR-2 and TLR-4) *in vitro* and *in vivo* – and induces a cascade of immune-mediated effects, responsible for the bladder cancer regression observed in animal models ([7](#), [11](#)).

P-MAPA also decreases androgen receptors (AR) protein levels and increases expression of estrogen receptors ([10](#), [12](#)).

4. Similarities and differences between the mechanisms of action of P-MAPA and BCG

Only minor similarities between the immune-mediated effects of P-MAPA and BCG were observed. Their mechanisms of action differ substantially ([11](#), [41](#)).

Evaluated in the same animal model for the study of bladder cancer, BCG also bound to TLR-2 and TLR-4 and induced immune-mediated effects, mainly a strong activation of the inflammatory cytokines signaling (canonical) pathway. P-MAPA induced a slight activation of the inflammatory cytokines signaling (canonical) pathway. However, this was not its main effect. Unlike BCG, P-MAPA caused a strong activation of the interferon-signaling (non-canonical) pathway and simultaneously induced a modulation of steroid hormone receptors and their co-activators and corepressors ([11](#), [10](#)).

5. The five conditions in which P-MAPA could be used

Taken together, the preclinical findings strongly suggest that P-MAPA could be used to treat bladder cancer patients who fit in five conditions arising in the course of the disease and treatments. The five conditions and the correspondent uses of P-MAPA are as follow:

- **Condition 1: Patients with high-grade non-muscle invasive bladder cancer (NMIBC) at high risk of recurrence and disease progression who are BCG-refractory or BCG-relapsing**

The elimination of malignant lesions still in the urinary bladder to avoid or retard the progression of disease is the ultimate goal of the bladder-sparing treatments. BCG is the drug of choice for conservative treatment of high-grade lesions after Transurethral Resection of Bladder Tumors (TURBT), but intravesical BCG therapy presents high rates of failures, known as BCG-refractory and BCG-relapsing disease.

Patients with high-grade NMIBC who are BCG-refractory and those BCG-relapsing ones present higher risk of progression to deadly invasive and/or metastatic disease. To date, no available drug has shown better efficacy than intravesical BCG to avoid or retard the disease progression ([33](#), [40](#)).

The P-MAPA distinct mechanism of action could be very beneficial to BCG-refractory and BCG-relapsing patients. Acting on distinct immune pathways, P-MAPA may eliminate urothelial cancer cells that survived or are resistant to BCG therapy possibly because of the escape and/or resistance mechanisms.

Three mechanisms features of P-MAPA action, compared to the BCG one, should be highlighted in this condition, as follows:

- Experimentally, P-MAPA activates distinct immune pathways more effectively than those ones induced by BCG to kill malignant cells into the urinary bladder. In a series of independent comparative experiments, intravesical P-MAPA presented a success rate from **80% to 100%**. The highest success rate of intravesical BCG, used as a positive control, was **40%** ([6](#), [7](#), [10](#), [11](#)).

- The immune-mediated downstream cascade induced by P-MAPA after binding to TLRs leads to a restoration of p53 protein levels, induces tumor arrest and apoptosis, and blocks angiogenesis. Clearly, the interferon signaling pathway induction and an increased p53 protein levels by P-MAPA led to remarkable antitumor effects, suppressing abnormal cell proliferation, and notably to an antiangiogenic effect by a strong inhibitory action of the vascular endothelial growth factor (VEGF) (11). Accordingly, strategies aiming the pharmacological reactivation of p53 are being seen as a promising approach for cancer therapy (37, 8).
- P-MAPA decreases androgen receptors (AR) and increases expression of estrogen receptors (ER), which help to eliminate bladder tumors (10). Considering the role of androgens and AR on bladder cancer tumorigenesis, drugs able to target these pathways in different stages of bladder cancer represent a new therapeutic approach for bladder cancer treatment (13, 15, 25). The modulation of activities of androgen receptors (AR) and expression of estrogen receptors (ER) by P-MAPA as intravesical monotherapy or associated with systemic androgen deprivation therapy (Flutamide) favored the recovery in the treated animals (10). Accordingly, clinical trials are investigating the effect of androgen deprivation therapy to prevent bladder cancer recurrences in NMIBC patients even in BCG use (47).

The P-MAPA use provides other beneficial features for NMIBC patients who failed BCG treatments, including those ones refractory to second-line intravesical therapies. The experimental results have suggested that P-MAPA could be used immediately after TURBT or in presence of macroscopic hematuria.

P-MAPA showed impressive therapeutic effects in high-grade NMIBC in animal models, even when used in presence of macroscopic hematuria induced by carcinogenic process. Of note, no sign of subsequent hematuria was observed in P-MAPA-treated animals, in sharp contrast with non-treated and BCG-treated animals (7, 10, 6).

BCG, though it represents the standard of care for high-grade NMIBC, is not an option to be used immediately after TURBT, in the following 14 days or in presence of macroscopic hematuria, due to the risk of systemic infection. Therefore, the best adjuvant treatment against high-grade tumors (BCG) has no role in the immediate postoperative setting or in presence of macroscopic hematuria, an event resulting of the surgical procedure itself or emerging as undesirable side event during the course of BCG therapy due to its inflammatory effects (35, 9, 3).

Delays or stoppages in the treatment due to BCG contraindications are a loss of opportunity to eliminate floating tumor cells or undetected high-grade tumors. The possibility of using P-MAPA immediately after TURBT even in presence of hematuria could help to eliminate free-floating cancer cells before adhering to the bladder wall, so contributing to a complete elimination of the lesions.

The experimental studies have also evidenced that:

- **P-MAPA is a curative drug.** Impressive therapeutic results of intravesical P-MAPA therapy were observed in experiments with animal models for bladder cancer studies without previous surgical procedures aiming to eradicate malignant lesions inside the bladder. Therefore, P-MAPA should be considered as a curative drug (7, 10, 11, 6). The finding is auspicious, considering the possible use of P-MAPA to treat NMIBC patients after TURBT; that could result in complete elimination of lesions.
- **P-MAPA blocks disease progression.** The compound helped to prevent hydronephrosis and hydronephrosis, in contrast with non-treated animals (6, 7, 10). Hydronephrosis was not observed also in the BCG-treated control group, confirming the BCG properties against disease progression (6, 7, 10). That feature of P-MAPA is relevant, as hydronephrosis is frequently associated to advanced stage bladder cancer and/or extravesical disease (2, 31).
- **P-MAPA is superior to BCG and second-line intravesical therapies for bladder cancer.** Cystectomy, the treatment of choice for BCG-refractory patients, is considered as overtreatment for one third of patients (18). The National Comprehensive Cancer Network clinical guidelines suggest that intravesical therapy with a different drug may offer an alternative to cystectomy for patients receiving a second course of BCG still presenting tumors. In comparative studies in the same animal model, intravesical P-MAPA showed a higher efficacy than BCG and doxorubicin (6). Doxorubicin is a drug of the same class of Valrubicin, the only FDA-approved second-line intravesical therapy for BCG-refractory patients, despite low effectivity (36, 5). Therefore, P-MAPA may help to treat high-grade NMIBC patients who are refractory or relapsing to intravesical BCG therapy and unfit the criteria for an early cystectomy.

To conclude, considering an organ-preservation approach to reduce surgical morbidity and maintain the patients' quality of life, the intravesical P-MAPA may provide a valuable option to eliminate malignant lesions still in the urinary bladder, avoiding an early cystectomy, in BCG-refractory and BCG-relapsing patients.

- **Condition 2: Patients with high-grade NMIBC at high risk of recurrence and disease progression who are BCG-intolerant**

Patients in this condition receive the BCG-based conservative treatments, but even so are at high risk of tumor recurrence and disease progression. The condition is clearly related to insufficient amounts of BCG received, as the treatment was interrupted due to BCG toxicity (34, 1, 20, 32, 29).

Most episodes of local and systemic BCG toxicity emerge during induction phase or in the first half year of maintenance therapy, resulting in delays and interruptions of BCG instillations. The consequences are deleterious, as BCG can prevent disease recurrence and progression only when maintenance therapy is carried out ([35](#), [14](#), [9](#), [3](#)).

Beyond noteworthy antitumor effects, the intravesical P-MAPA immunotherapy has presented a lower toxicity than BCG in the urothelium when both drugs were evaluated in the same animal model at equivalent therapeutic dosages. Experimentally, the toxicity of P-MAPA in the urothelium at therapeutic dosage is close to zero. Experiments in three animal species showed that a tenfold dose over the therapeutic dosage of intravesical P-MAPA does not cause significant toxicity in the urothelium.

Several experiments have shown that intravesical P-MAPA is able to revert macroscopic hematuria induced by NMIBC, in sharp contrast with BCG-treated animals ([7](#), [10](#), [6](#)). The interruption of macroscopic hematuria in P-MAPA-treated animals also suggests that the compound does not have potential to cause drug-induced cystitis, an event frequently related to hematuria and responsible for the most of treatment stoppages in the setting of BCG-intolerance ([35](#), [9](#), [3](#)).

P-MAPA represents an option to maintain the treatment in patients who had to stop their BCG courses due to clinical signs of local or systemic infection. Since P-MAPA is a molecule, not a live organism like BCG, it does not have potential to cause or aggravate infections. In addition, its use could be associated to antimicrobial drugs already used to treat local or systemic infections caused by BCG ([7](#)).

Because of its high molecular weight, intravesical P-MAPA probably does not reach the systemic circulation. In case of accidental introduction into systemic circulation during intravesical instillations, the potential for drug-induced damage is low, as P-MAPA did not show signs of toxicity when used by intraperitoneal and intramuscular administration in other animal models, as well as in clinical trials Phase I ([26](#), [27](#), [48](#)).

To conclude, the intravesical P-MAPA therapy could clearly benefit BCG-intolerant patients who had to stop the treatment on account of local or systemic BCG toxicity, eliminating malignant lesions before they spread to other organs.

- **Condition 3: Patients with high-grade NMIBC who are BCG-refractory or BCG-relapsing, for whom cystectomy would be associated with high morbidity or mortality**

Radical cystectomy is a complex surgery associated with up to 45% surgical complications and up to 8% mortality ([4](#), [22](#)). Patients who refuse or are unfit to undergo bladder removal face an increased risk of progression to muscle-invasive or metastatic disease, likely leading to death.

An intravesical anthracycline-drug (Valrubicin) is the only FDA-approved intravesical drug for BCG-refractory (Tis) patients and those who refuse or are medically unfit for cystectomy. Its success rate is around 20% in BCG-refractory patients ineligible for cystectomy ([21](#), [36](#), [5](#)).

An improvement in the clinical outcomes is clearly much needed, but no chemotherapy agent or immunotherapy has presented an activity equivalent to BCG in naïve patients with high-risk NMIBC, and none, including Valrubicin, has been fully successful to avoid disease progression in patients who do not respond to BCG ([30](#), [21](#)).

P-MAPA could be very beneficial to patients in this condition, replacing Valrubicin. Experimentally, the intravesical P-MAPA therapy presented an 80% to 100% success rate ([7](#), [10](#), [11](#), [6](#)). In the same experiments, the highest success rate of BCG, used as a positive control, was 40%.

Importantly, in another comparative experiment using an anthracycline (doxorubicin) as a positive control in the same animal model, 80% of animals treated with intravesical P-MAPA were tumor-free, while, inversely, 100% of animals treated with the intravesical anthracycline presented no regression, meaning 100% tumors ([6](#)).

The experimental data strongly suggest a reasonable expectation of success in using P-MAPA immunotherapy as an option also for patients in this condition. P-MAPA could replace anthracyclines, including Valrubicin, in the treatment of NMIBC patients at high risk of disease progression, for whom cystectomy would not be recommendable.

• Condition 4: Patients with high-grade NMIBC, BCG-refractory and BCG-relapsing, at high risk of recurrence and progression, for whom cystectomy would be associated with high morbidity or mortality, and who are refractory to Valrubicin as second-line therapy

Patients in this condition have a very poor prognosis because remain unfit for cystectomy. Valrubicin has failed to treat them – response rates in heavily pretreated patients are approximately 20%, leading to 80% of Valrubicin-refractory patients – and none of the available alternative salvage treatments have prevented the progression to invasive or metastatic disease. No new option in evaluation – e.g. interferon-alpha, gemcitabine, docetaxel, electromotive drug administration, thermochemotherapy, radiotherapy and sequential association of these techniques with intravesical agents – has proven to be equivalent to BCG to avoid the disease progression ([33](#), [40](#)).

As described, P-MAPA presented a higher efficacy over BCG and anthracyclines (doxorubicin), both used by intravesical administration in the same animal model. Therefore, the experimental data and the minimal intravesical toxicity at therapeutic dosages observed in animal models have suggested that P-MAPA could be a rewarding therapeutic option for patients also in this condition

• Condition 5: Patients with locally advanced and metastatic bladder cancer

The standard of care for locally advanced and metastatic bladder cancer is surgery and chemotherapy, mainly platinum-based therapy. Androgen deprivation therapy is commonly used with radiotherapy for patients with clinically localized and advanced prostate cancer.

The association of drugs, and new drugs, such as the immune checkpoint inhibitors, have presented limitations due to toxicity and lack of effectivity for some patients, though represent a very welcome therapeutic approach (28).

P-MAPA has great potential to be used in association with other drugs in the treatment of locally advanced and metastatic bladder cancer, as preclinical studies evidenced. In animal model, the association of intravesical P-MAPA with systemic cisplatin (CIS) resulted in an 80% tumor regression without signs of antagonistic effects between the two drugs. On the contrary, analysis of VEGF protein and NF-kB levels has indicated a synergistic, apoptotic and antiangiogenic effect between the two drugs, leading to a better histopathological recovery in the treated animals (6).

Intravesical P-MAPA also showed potential to be synergistically used with androgen deprivation therapy to kill malignant lesions in the bladder (10). Androgen deprivation therapy has been proposed to treat NMIBC patients with or without BCG and is under investigation in clinical trials (47).

Therefore, the association of intravesical P-MAPA with systemic cisplatin, cisplatin-based chemotherapies and androgen deprivation therapy could also be beneficial to patients presenting advanced disease and unfit for cystectomy, offering the possibility to fight localized bladder tumors and micrometastases or locally invasive bladder cancer at the same time. Accordingly, systemic chemotherapy, including cisplatin and cisplatin-based chemotherapies, has been proposed in association with TURBT and radiotherapy for conservative treatment of NMIBC (T1) patients and those ones with invasive or metastatic disease (19, 34).

Beyond intravesical use, systemic P-MAPA can be proposed to treat patients with advanced and metastatic bladder cancer. Experimentally, systemic P-MAPA monotherapy showed therapeutic effects against other tumors, such as Walker 256 tumor (43), renal carcinoma (46a), Ehrlich ascites tumor (17), pancreatic cancer (47a) and ovarian carcinoma (46b).

In addition, systemic P-MAPA in association with Gemcitabine showed synergistic effect and an impressive histopathological recovery of pancreatic cancer in animal model (47a, 47b) and systemic P-MAPA associated with systemic cisplatin (CIS) showed a greater survival rate than CIS alone in studies carried out in animal model for the study of ovarian carcinoma (46b).

Importantly, systemic P-MAPA was also effective against tumors in prostate and lungs, common targets of locally advanced and metastatic bladder cancer, respectively.

In the first case, P-MAPA was used by systemic via alone and in association with the angiogenesis inhibitor TNP-470 in animal model for study of prostate cancer (45). Systemic P-MAPA monotherapy showed a very significant antitumor activity against intermediate grade and high-grade adenocarcinomas and the association of P-MAPA with TNP-470 was the best therapeutic approach against premalignant lesions (45).

Systemic P-MAPA monotherapy also showed therapeutic effect in Lewis lung carcinoma, a murine model of lung cancer. P-MAPA suppressed tumors, and the P-MAPA-treated animals presented a 60% survival rate at 100 days (44).

Taken together, the experimental data suggest that P-MAPA could be used in three different ways:

- The first is by **intravesical via**, in association with **systemic** platinum-based chemotherapy, to manage lesions on the surface of the inside lining of the urinary bladder and also invasive lesions in patients with locally advanced bladder cancer who are ineligible for cystectomy.
- The second is by **intravesical and systemic via** to manage lesions on the surface of the inside lining of the bladder and invasive ones in patients with locally advanced bladder cancer, who **are not eligible** for cystectomy and for platinum-based therapies at the same time.
- The third is by **systemic via** to treat metastatic bladder cancer in patients who fail or stop their treatments with platinum-based chemotherapy or immune checkpoint inhibitors.

6. Conclusions

This scientific rationale has exposed the efficacy and limits of standard and new therapies to treat bladder cancer patients, discussed the urgent need of more efficient approaches, and presented the results of preclinical studies of P-MAPA to pave the way to its clinical evaluations as a novel therapy to treat bladder cancer patients in five conditions arising during the course of disease or treatment.

Based on this scientific rationale, Farmabrazilis teams will be happy to discuss the possibilities of use of P-MAPA immunotherapy with patient advocates, bladder cancer advocacy networks, research groups, institutions and pharmaceutical companies interested in establishing collaborations to move forward this novel therapy for treatment of bladder cancer.

Our action can make the difference in the life of bladder cancer patients.

Send your questions, comments and/or proposal to alliances@farmabrazilis.org; please write P-MAPA in the subject line. You will receive a reply as soon as possible.

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Farmabrasilis is a non-profit research network based in Brazil who runs the development of P-MAPA in collaboration with research centers and universities in Brazil, the U.S. and Europe.

For more information about Farmabrasilis and P-MAPA, visit the website www.farmabrasilis.org and the PubMed database, <https://www.ncbi.nlm.nih.gov/pubmed/?term=p-mapa>.

7. References

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