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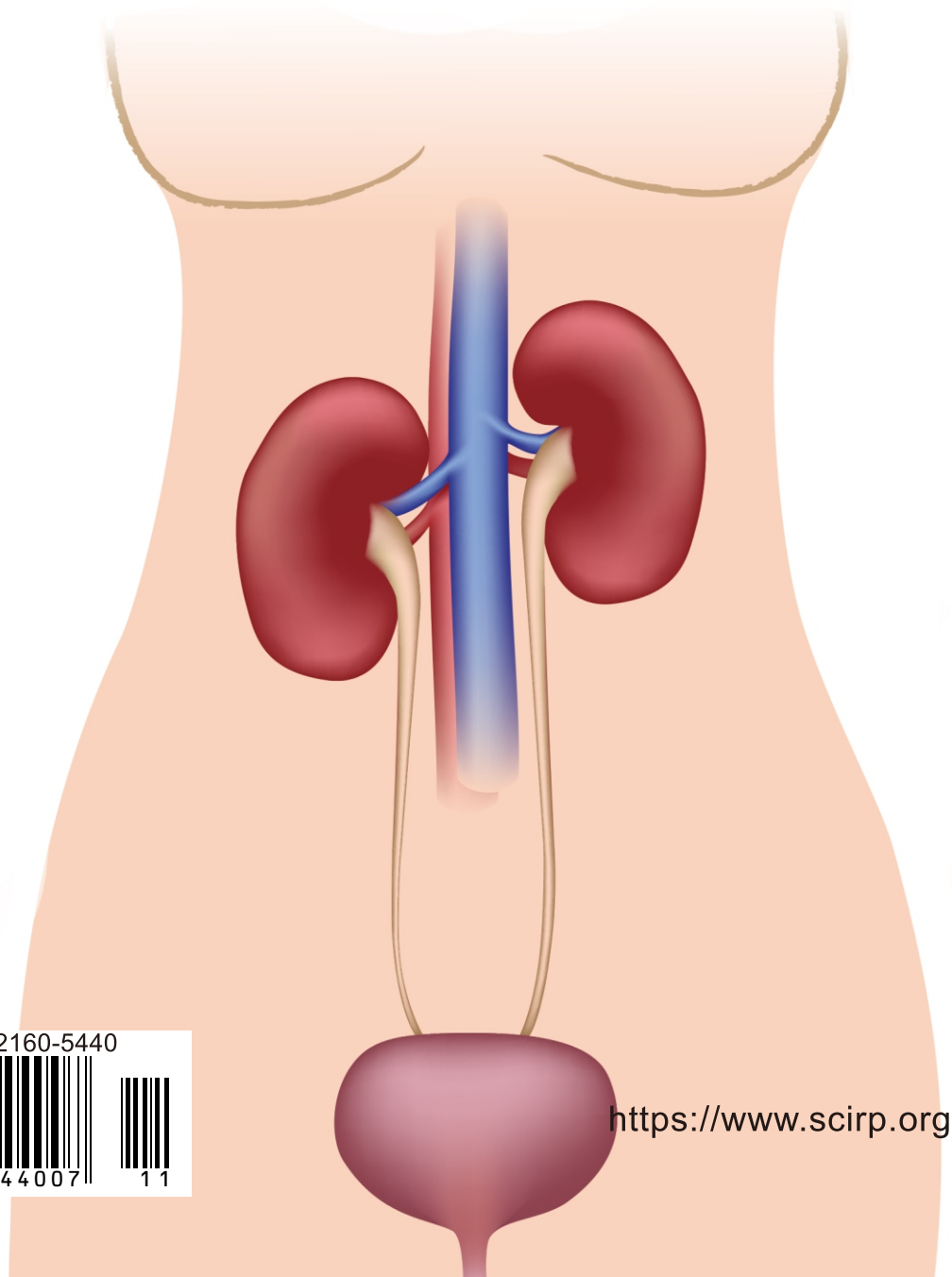

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Transection Type, Vesico-Vaginal Fistula Surgery

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Abstract

The objective of the study was to report the results of the surgery of the Vesico-vaginal fistula (VVF) transection types at CHU Conakry. **Methods:** This was a prospective descriptive study that focused on 64 patients operated for VVF transection type at the Urology department of CHU Conakry between January 2013 and December 2015. Four types of transection were defined according to the state of the urethra and vagina, the size of the fistula, the peri-fistulous tissue and associated lesions. The variables studied were the proportion of transection, age, the type of transection, the number of previous cures, the operative technique, the complications and the results after a follow-up of 3 months. **Results:** Transection accounted for 47.05% of the obstetric fistulas. The average age was 25.18 years old (14-43 years old). This was a Type I transection (11 cases), type II (27 cases), type III (19 cases) and type IV (7 cases). The surgical approach was vaginal in 64 cases. Fistulorraphy with a confection of a new cervix and cervico-urethral anastomosis was conducted in 19 patients, combined with bladder flap urethroplasty (30 patients) or vaginal flap (15 others). We recorded healing in 37 cases. **Conclusion:** Transection type VVF is a severe VVF. The preferential surgical approach was vaginal. Technical difficulties were related to associate lesions and the continence system affected.

Keywords

Vesico-Vaginal Fistula, Transection, Surgery

1. Introduction

In developing countries, vesico-vaginal fistulas are secondary to an ischaemic le-

sion on fetopelvic dystocia resulting from a long delay between the onset of labour and access to a caesarean section [1] [2] [3]. They are public health problems in countries with low medical services and where urgent obstetrics cares are insufficient [4] [5]. The WHO estimated between 2 and 3.5 million women victims of obstetric fistula in the world, mainly in Africa [5].

The transections types vesico-vaginal fistulas are severe obstetric fistula due to their extensions, associated lesions and the damage of the continence system [3] [4]. Several classifications of the obstetric fistula were reported in the literature but few authors were interested in transection only.

The classification of Waaldijk [6] describes three types of fistulas:

- Type I: Fistulas do not involve the urethral closing mechanism;
- Type II: Fistulas involve the urethral closing mechanism. It has divided the type II in type IIA without urethral damage, type IIB with urethral damage and subdivided the type IIB in type IIB(a) without circumferential defect IIB (b) with circumferential defect;
- Type III: Ureters and other fistulas.

Falandry's classification [7] takes into consideration the seat of the fistula, the sclero-inflammatory reshuffle and the sphincterial damage. It divides the obstetric fistulas into three groups:

- Group I: Simple fistulas, representing less than 15% of cases. The fistulous orifice is distant from the urethra or the cervix whatever its size. The tissues are flexible and the prognosis is excellent if only the provided postoperative care is satisfactory;
- Group II: Fistulas representing more than 50% of cases. They are more or less complex by the extent or by the damage of the Sphincterial device. The sclerosis of the tissues makes the exposure more or less difficult. The prognosis is good, but often at the price of several interventions with sometimes complex techniques (plasty, grafts, artifices) to obtain a seal and continence;
- Group III: About 30% of cases. These are true extended tissue destruction towards the genital device, urinary and sometimes the ano-rectal sector within scarf tissues whose surgical exposure is difficult, sometimes at the price of incisions that consume time and blood reserves. Some are described as "impossible" beyond the usual surgical techniques. The transsection would correspond to the type II(B) of Waaldijk or Group III of Falandry, that means a fistula with pure cervix disinsertion or cervico-urethral associated with a more or less extended destruction of the urethra. The tissue destruction concerns the posterior wall but also the anterior wall of the bladder, the cervix on all its conference. The urethra is sometimes cut nearest to the cervix and in this case it is normally usable. More often, the urethra is partially destroyed in its proximal part with a closed posterior orifice. The lower edge of the symphysis is no longer covered by a vaginal neo-epithelium. Sclerosis and loss of substance are often major, making the approach and the dissection extremely difficult. At the ultimate stage, the vagina is represented only

by a sclerous parade in the background of which there is a vesical stump. The associated rectal damages are most often large decay interesting the Sphincter.

All transsection does not come up with such dramatic lesions. Some concern only the cervix with a fistula overflowing a little on the trigone, an urethra fairly well maintained with a moderate sclerosis. Nevertheless, they have in common a circular damage at least at the level of the cervix, where the lower edge of the pubis is nacked [7]. All these anatomic clinical varieties require classification and require surgical experience in the repair of fistulas as in addition to the difficulties of access, the vesical neck to rebuild we can be brought to achieve uretroplasty from bladder or vaginal tissue in order to restore anatomy and urinary continent.

2. Methodology

It was a prospective descriptive study of three years duration, ranging from January 1st, 2013 to December 31, 2015. All the women operated of VVF transection type during the study period and having a complete medical file with a follow-up of at least 3 months were included.

A sample of 64 patients was the subject of this study. The study variables were: the proportion of transection compared to other obstetric fistula, age, reasons for consultation, the number of previous cures, the type of transection, the operation technique, the preoperative and postoperative complications. The review under the valve in the operating block has made it possible to highlight four types of transsection that have been defined according to the state of the urethra and vagina, the size of the fistula, the nature of the peri-fistuluous tissue and associated damages. These were:

- **Type I Transection** (Figure 1)**:** the urethra is being sectioned close to the cervix. The destruction of the proximal urethra was less than or equal to 1cm. The fistulous orifice and the vagina were flexible.
- **Type II Transection** (Figure 2)**:** The fistula the interest is in the Trigono-Cervico-Urerthral region with partial destruction of the urethra that was between 1 and 2 cm. There was a loss of substance and a vaginal flange.
- **Type III Transection** (Figure 3)**:** In this type, vaginal sclerosis and the loss of substance were major, sometimes making the vagina unpermeable. The remaining urethra was less than a centimeter. The surgery pathway and dissection were difficult.
- **Type IV Transection:** When the transection was associated with either a vesico-uterine fistula (VUF) or an uretero-vagina fistula (UVF) or a recto-vaginal fistula (RVF).

We have retained the patients in accordance with this classification adopted in our service for transections. After a follow-up of at least three months, the results were judged:

- Good: when the fistula was closed and the urination was restored.
- Poor: When urinal incontinence is persisting despite the closure of the fistula.
- Failure: When the fistula was not or incompletely closed.

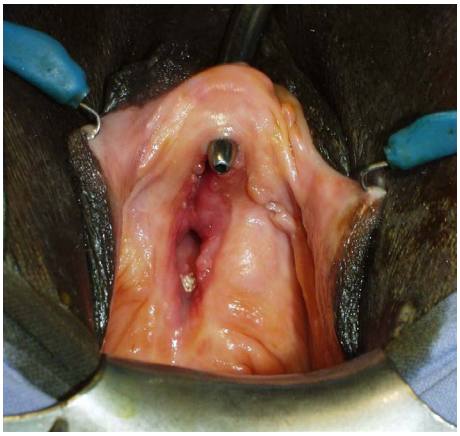

Figure 1. Type I complete transection (urethra section close to the cervix, the fistulous orifice and the vagina remain flexible).

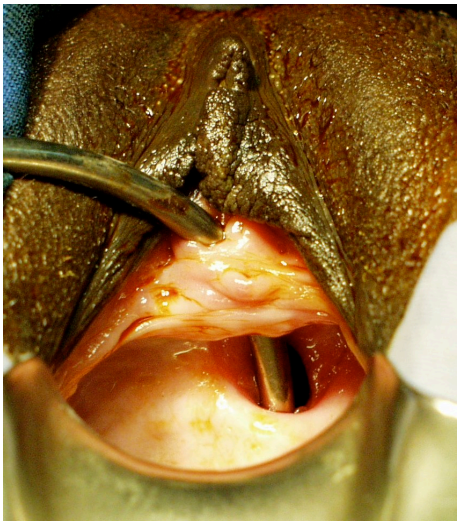

Figure 2. Type II Transection (Loss of substance and a vaginal flange, 2cm of urethra remaining).

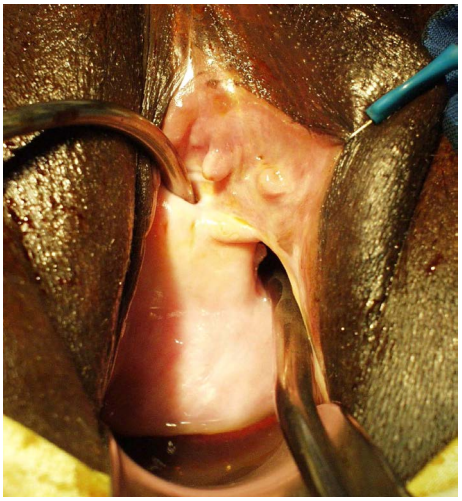

Figure 3. Type III Transection (complete destruction of the urethra, large vaginal bride, difficult approach and dissection).

These results were reviewed according to the type of transection, the number of previous cures, the status of the vagina and the operation technique.

3. Results

During the study period, we raised 64 cases of VVF transection type representing 47.05% of obstetric fistula. The recto-vaginal fistula were all obstetrics and associated with a VVF (Table 1).

Table 1. Socio-demographic and clinical characteristics of the patients.

Socio-demographic and clinical characteristics	effectif	%
Age*		
14 - 23	32	50
24 - 33	21	32.80
34 - 43	11	17.20
Profession		
House wife	59	92.20
Taylor	3	4.68
Trader	1	1.56
Student	1	1.56
gravidity		
Primiparous	32	50
Pauciparous	15	23.44
Multiparous	17	26.56
Place of delivery		
Hospital	34	53.12
Home	27	42.20
Health center	3	4.68
Route of delivery		
Vaginal delivery	48	75
Caesarean section	16	25
Reason for consultation		
Urine leaking from the vagina	64	100
Loss of feces from the vagina	4	6.25
Cyclic hematuria	1	1.56
Nomber of previous cure**		
once	15	23.43
Two times	9	14.06
Three times	4	6.25

*The average age of patients at the moment of the diagnosis was 25 years with the extrem of 14 and 43 years. **More than half (n = 36) have never been operated of the fistula.

The average age of the patients at the time of the fistula was 25.18 years old with extremes of 14 and 43 years. Half of the patients (32 cases) had an age between 14 and 23 years old. The profession was that of housewives in 92.1% (n = 59) and one patient had a primary level of education.

Vaginal urine leak was noted in all patients (64 cases) and was associated with loss of feces through the vulva in 4 cases and a cyclic hematuria in one case.

Vaginal delivery was reported from 48 patients (75%) and by Caesarean from 16 patients (25%). After dystocic work, the delivery was held at the hospital for 34 patients (53.1%), at home for 27 patients (42.2%), at the health center for 3 patients. The fistula occurred in a primiparous in the half of cases (n = 32), in a pauciparous within 23.43% of cases (n = 15) and in a multiparous in 26.56% of cases (n = 17 cases).

In the history of the fistula cure, the first cure has been reported in 15 patients, two cures in 9 patients and three cures in 4 patients. Thirty six patients had no previous cure.

At the examination under valve, the urethra was partially destroyed in 31 patients, totally in 15 patients and intact in 18 patients. It was also permeable in 41 patients and blind in 8 patients. The vagina was flexible in 23 patients, sclerotic in 37 patients and unpermeable in 4 patients.

The transection was associated with a RVF in 4 patients, a UVF in 2 patients and a VUF in a patient.

The types II and III of the transection were the most represented with 42.2% and 29.7% respectively. Types I and IV were found in 17.2% and 10.9% of cases respectively.

We used a spinal anesthesia in 58 patients (90.6%), a general anesthesia in 3 patients (4.7%) and an addition of a spinal anesthesia in 3 other cases.

The surgical approach was vaginal with 64 patients and mixed with 2 patients (3%) for the cure of a vesico-uterine fistula and an uretero-vesical reimplantation.

Fistulorraphy with a confection of a new-vervix and cervico-urethral anastomosis was the basic technique in 19 patients, combined with bladder flap urethroplasty in 30 patients or vaginal flap in 15 others. Among the associated gestures, a large bilateral or later posterior episiotomy had been required 39 times, the urethral trocardization 8 times, the rectal fistulorraphy 5 times, the uretero-vesical reimplantation 2 times. The Vesico-uterine fistulorraphy and the replacement of a flap was needed once in each case.

The operating suites were simple in 84.4% (n = 54). Among ten patients (15.6%) we noted complications such as vomiting + fever (4 times), lumbar pain + vomiting (2 times), headache + fever (2 times), ileus (1 time) and calcification on hair (1 time).

For the 64 patients, we made 96 surgical procedures, giving a repeated surgery survey of 33% of cases.

The vesical drainage was carried out by urethral catheterism and lasted 14 days for 19 patients and 21 days for 45 patients according to whether the transection was isolated or associated with urethroplasty.

The results of this transection surgery were deemed good in 37 patients (58%), failure in 21 patients and poor in 6 patients.

The comparative analysis of the overall results compared to the type of transection has raised that the best results were obtained with the I and II types (Table 2).

Out of 36 patients who had no previous surgery, 22 were cured giving a success rate of 61.11%. The failure rate increased from 25% when there was no restorative surgery and to 50% when there were 3 times of surgical cure (Table 3).

According to the status of the vagina, all the failure cases were associated with a sclerotic or unpermeable vagina (Table 4).

According to the operative technique, the fistulorraphy associated with urethroplasty with vaginal flap grouped the highest failure rate (Table 5).

Table 2. Distribution of the surgery results compared to the types of transection.

Types of transsection	Results			
	Good	Poor	Failure	TOTAL
Type I	11 (100%)	-	-	11 (100%)
Type II	22 (81%)	-	5 (19%)	27 (100%)
Type III	-	6 (32%)	13 (68%)	19 (100%)
Type IV	4 (57,1%)	-	3 (42.9%)	7 (100%)

Table 3. Distribution of the surgery results compared to the number of previous cures.

Number of previous cures	Results			
	Good	Poor	Failure	TOTAL
0	27 (75%)	0	9 (25%)	36 (100%)
1	8 (53%)	3 (20%)	4 (27%)	15 (100%)
2	3 (33.3%)	2 (22.2%)	4 (44.4%)	9 (100%)
3	1 (25%)	1 (25%)	2 (50%)	4 (100%)

Table 4. Distribution of the surgery results compared to the state of the vagina.

State of the Vagina	Results			
	Good	Poor	Failure	TOTAL
Flexible/soft	21 (91.3%)	2 (8.7%)	-	23 (100%)
Sclerotic	16 (43%)	4 (11%)	17 (46%)	37 (100%)
Waterproof/impermeable	-	-	4 (100%)	4 (100%)

Table 5. Distribution of the surgery results compared to the operating techniques.

Operating techniques	Good	Poor	Failure	Total
Fistulorraphy + urethra in vagina	-	6 (40%)	9 (60%)	15 (100%)
Fistulorraphy + urethra in bladder	21 (70%)	-	9 (30%)	30 (100%)
Fistulorraphy + neo-neck + cervico-urethral anastomosis	16 (84.2%)	-	3 (15.8%)	19 (100%)

4. Discussion

Between January 2013 and December 2015, we raised 64 cases of VVF transection type, representing 47.05% of all obstetric fistulas. In 1995, Guirassy *et al.* [8] reported that complex fistulas grouped 64% of cases. Diallo *et al.* [9] in a study of support of obstetric fistula realized in 3 sites out of our service reported that complex fistulas were 66% of cases. In a series of 1050 patients from Benchekroun *et al.* [10], Type I and Type II, corresponding to the transection accounted for 30% and 22% of which cases.

The average age of our patients was 25, 18 years with extremes of 14 and 43 years. Ruminjo *et al.* [11] As well as Frajzyungier *et al.* [12] reported an average age of 25-year. The young age participates in the foeto-maternal disproportion, responsible for the occurrence of the obstetric fistula [3]. Several authors [4] [10] [13] are unanimous on the occurrence of the fistula in young sexual active patients.

The choice of the surgical approach is not univocal [14] [15] [16]. Fistula may be approached either by vaginal or by trans-vesical or transperitoneal-vesical [15]. Bodner-Adler *et al.* [17] in a meta-analysis had reported the laparoscopic lane and robot assisted in 15% of cases with an estimated success rate at 98.87% of cases. Their choice is based on the complacency of the vagina, the seat of the fistula and associated lesions. It requires a good preoperative assessment, which is based on a vaginal examination carefully made, an assessment of the state of the high urinary device and the flexibility of the tissues. The vaginal path was our main surgery pathway.

Kambou *et al.* [18] used the vaginal chirurgical approach in 61.4% of cases. For Moudouni *et al.* [15], it was used in 70% of cases.

The vaginal chirurgical approach for us seems to be the best for transections because it gives an operating comfort, direct access to the lesions of the bladder and the urethra. It also allows the tissue interposition and simultaneous surgical approach of an associated RVF. This simultaneous surgical approach was made in the 4 cases of RVF associated with success in half of cases. For Gueye *et al.* [14], almost all types of vesico-vaginal fistulas can be repaired vaginal surgical approach. There are technical ways to expand the vaginal path:

- The Schuckhar side episiotomy
- The posterior episiotomy of the picot-Couvelaire
- Disinsertion of the anterior face of the bladder to the pubis.

A large bilateral or posterior episiotomy was used in 39 patients and the disinsertion of the anterior face of bladder in all patients.

However the vaginal surgical approach, has a disadvantage, that of not allowing the identification of the ureters except in the large fistula where all the vesical floor is visible.

High chirurgical track or transperitoneal-vesical route is indicated in the high vesico-vaginal fistula or in case of associated lesion such as a vesico-uterine fistula or an uretero-vaginal fistula [10] [14] [16]. In our series, it was associated

with the vaginal surgical approach in 2 cases.

The simplest technique for repairing VVF is to split and sew separately from the two planes (vesical and vaginal) after reviving the embankment [16]. But this technique that is of great simplicity and low morbidity is not easy in transections. The principle of surgical treatment in our series was fistulorraphy with a confection of a new cervix and cervico-urethral anastomosis in all patients. Urethroplasty was associated with fistulorraphy in 45 patients.

Postoperative vesical drainage was carried out by a urethral probe for several authors [14] [15] [19]. For the blinder reported by MOUDOUNI *et al.* [15], urine is used to drain by a urethral probe in case of high fistula far from the bladder cervix and a cystostomy in cervical and urethral low fistulas. The duration of the bladder drainage were not recommended by these authors. In our series, drainage lasted 14 days for 19 patients and 21 days for 45 patients according to the transection cure was insolated or associated with urethroplasty. Ruminjo *et al.* [11] reported a median duration of urethral catheterism of 21 days (14 - 27). The success rate in our series is in the range of literature where it ranges from 57 to 96% of cases [10] [12] [13] [15] [20]. For Falandry, the healing rate varies depending on the extent of the necrotic damage and can reach 100% for Group I, 75% for Group II and 50% for Group III [7].

This healing is sometimes obtained from the outset from the first intervention, other times at the end of complex surgery, repeated and traumatic for patient very affected psychologically as confirmed by the study made by the Wilson and Harouna *et al.* [2] [21]. The repeated surgery rate in our series (33%) was higher than that of Guirassy *et al.* [8] in the same service in 1995 reporting 20%. Indeed, each failure results in a sclerosis that is added to the primitive sclerosis, with less irrigated tissues [14] [19].

Urine continence failure after the fistula closes was 9% in our series against 10.4% for Sludge [22], 11% for Arrowsmith [23], 18.9% for Ruminjo [11] and 23.1% for Kimassoum *et al.* [24]. In any case where urethroplasty used vaginal tissue (vaginal flap urethroplasty) we observed bad results. The high failure rate in our 33% series could be related to the destruction of the urethra (type II and III of transections) and the sclerotic state of the vagina. Overall, about 15% of vaginal fistulas are incurable, despite the use of various surgical techniques. These cases are results either from enterocyctoplasty enlargement or replacement from urinary derivatives [12]. Palliatives interventions that seem best suited to our context are continent urinary derivatives such as continent vesicostomy or the ileoecoecale bladder continent of Benchekroun [10] [12].

5. Conclusion

The vesico-vaginal fistula transection type is severe obstetric fistulas as a result of their extention, associated lesions and the continence system damage. They are secondary to prolonged hard labour during delivery among young parturients. The preferential surgical approach was vaginal. Fistulorraphy with a con-

ception of a new cervix and cervico-urethral anastomosis was the basic technique that can be associated with urethroplasty by bladder or vaginal flap. The poor results were related to the type of transection (Type III and IV), the sclerotic state of the vagina, the number of previous cures and to the vagynal flap uretrhoplasty. Adequate support of delivery favours the reduction of the vesico-vaginal fistula.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Rochat, C.-H., Gueye, S.M., Colas, J.-M., Dumurgier, C., Falandry, L., Blanchot, J., Eglin, G. and Tebeu, P.-M. (2011) Vesicovaginal Fistulas and Obstetrical Fistulas—EMC Surgical Techniques. *Urology*, 41-175.

[2] Wilson, S.M., Sikkema, K.J., Watt, M.H., Masenga, G.G. and Mosha, M.V. (2016) Psychological Symptoms and Social Functioning Following Repair of Obstetric Fistula in a Low-Income Setting. *Maternal and Child Health Journal*, **20**, 941-945. https://doi.org/10.1007/s10995-016-1950-z

[3] Anoukoum, T., Attipou, K., Agodakoussemou, L.K., Akpadza, K. and Aayite, E.A. (2010) Epidemiological, Etiological and Therapeutic Aspects of Obstetric Fistula in Togo. *Progrès en Urologie*, **20**, 71-76. https://doi.org/10.1016/j.purol.2009.08.038

[4] Ndiaye, P., Amoul Kini, G., Adama, F., Idrissa, A. and Tal-Dia, A. (2009) Urogenital Fistula of Obstetric Origin (Fugo): Cost of Care at the Niamey National Hospital (Niger). *Revue d'épidémiologie et de Santé Publique*, **57**, 374-379. https://doi.org/10.1016/j.respe.2009.04.010

[5] Aristide Kabore, F., Kambou, T., Ouattara, A., Zango, B., Yameogo, C., Kirakoya, B., *et al.* (2014) Epidemiological, Etiological and Psychosocial Aspects of Urogenital Fistula in a Cohort of 170 Consecutive Patients, Taken Care of in Three Centers of Burkina Faso from 2010 to 2012. *Progrès en Urologie*, **24**, 526-532. https://doi.org/10.1016/j.purol.2014.03.001

[6] Waaldijk, K. and Armiya'u, Y.D. (1993) The Obstetric Fistula: A Major Public Health Problem Still Unsolved. *International Urogynecology Journal*, **4**, 126-128. https://doi.org/10.1007/BF00376428

[7] Falandry, L. (1992) Treatment of Post-Partum Uro-Genital Fistulas in Africa. 261 Cases Observed in Ten Years. *Progrès en Urologie*, **2**, 861-873.

[8] Guirassy, S., Diallo, I.S., Bah, I., Diallo, M.B., Sow, K.B., Diabate, I., *et al.* (1995) Epidemiological and Therapeutic Aspects of Uro-Genital Fistulas in Guinea. *Progrès en Urologie*, **5**, 684-689.

[9] Diallo, A.B., Sy, T., Bah, M.D., Diallo, T.M.O., Barry, M.S., Bah, I., Barry, T.H., Blanchot, J., Rochat, C.-H. and Diallo, M.B. (2016) Obstetric Vesico-Vaginal Fistula in Guinea: Analysis of Data from 3 Sites of Management of the NGO Engender Health. *Progrès en Urologie*, **26**, 145-151. https://doi.org/10.1016/j.purol.2016.01.006

[10] Benchekroun, A., El Alj, H.A, El Sayegh, H., Lachkar, A., Nouini, Y., Benslimane, L., Belahnech, Z., Marzouk, M. and Faik, M. (2003) Vesico-Vaginal Fistula: About 1050 Cases. *Annales d'Urologie*, **37**, 194-9198.

https://doi.org/10.1016/S0003-4401(03)00053-6

[11] Ruminjo, J.K., Frajzyngier, V., Abdullahi, M.B., Asiimwe, F., Barry, T.H., Bello, A., Danladi, D., *et al.* (2014) Clinical Procedures and Practices Used in the Perioperative Treatment of Female Genital Fistula during a Prospective Cohort Study. *BMC Pregnancy and Childbirth*, **14**, Article No. 220.
http://www.biomedcentral.com/1471-2393/14/220
https://doi.org/10.1186/1471-2393-14-220

[12] Frajzyngier, V., Ruminjo, J., Asiimwe, F., Barry, T., Bello, A., Danladi, D., Ganda, S., *et al.* (2012) Factors Influencing Choice of Surgical Route of Repair of Genitourinary Fistula, and the Influence of Route of Repair on Surgical Outcomes: Findings from a Prospective Cohort Study. *BJOG*, **119**, 1344-1353.
https://doi.org/10.1111/j.1471-0528.2012.03461.x

[13] Chelli, D., Boudaya, F., Hammedi, N., Ines, N., Bouchoucha, S., Chibani, M., Ben Zineb, N., FalfouL, A., Chelli, H. and Channoufi, M.B. (2010) Vesico-Vaginal Fistulae of Obstetric Origin. About 131 Cases. *La Tunisie Medicale*, **88**, 414-419.

[14] Gueye, S.M., Diagne, B.A. and Mensah, A. (1992) Les Fistules Vésico-Vaginales: Etiopathogenic and Therapeutic Aspects in Senegal. *Les Médecine d'Afrique Noire*, **39**, 8-9.

[15] Moudouni, S., Nouri, M., Koutani, A., Ibn Attya, A., Hachimi, M. and Lakrissa, A. (2001) Obstetric Vesicovaginal Fistulas. About 114 Cases. *Progrès en Urologie*, **11**, 103-108.

[16] Tazi, K., EL Fassi, J., Karmouni, T., Koutani, A., Ibn Attya, A.A., Hachimi, M. and Lakrissa, A. (2001) Complex Vesicovaginal Fistulas. About 55 Cases. *Annales d'Urologie*, **35**, 339-343. https://doi.org/10.1016/S0003-4401(01)00056-0

[17] Bodner-Adler, B., Hanzal, E., Pablik, E., Koelbl, H. and Bodner, K. (2017) Management of Vesicovaginal Fistulas (VVFs) in Women Following Benign Gynaecologic Surgery: A Systematic Review and Meta-Analysis. *PLoS ONE*, **12**, e0171554.
https://doi.org/10.1371/journal.pone.0171554

[18] Kambou, T., Zango, B., Ouattara, T.A., Diao, B., and Sanou, D. (2006) Update on the Management of Urogenital Fistulas Souro Sanou University Hospital in Bobo Dioulasso: Study 57 Cases Operated in 2 Years. *Médecine d'Afrique Noire*, **53**, 665-673.

[19] Schlienger, G., Laroche, J., Karsenty, G., Bertrand, S., Dulac, J.P., Fournier, R. and Savoie, P.H. (2012) Obstetric Vesico-Vaginal Fistulas for an Isolated Surgeon in Africa. *Médecine et Santé Tropicales*, **22**, 126-130.
https://doi.org/10.1684/mst.2012.0060

[20] Delamou, A., Diallo, M., Beavogui, A.H., Delvaux, T., Millimono, S., Kourouma, M., Beattie, K., Barone, M., *et al.* (2015) Outcomes of Fistula Repair in Guinea. *Tropical Medicine and International Health*, **20**, 813-819.
https://doi.org/10.1111/tmi.12489

[21] Harouna, Y.D., Seibou, A., Maikano, S., Djambeidou, J., Sangaré, A., Bilane, S.S. and Abdou, H.M. (2001) Obstetric Vesico-Vaginal Fistula: Investigation of 52 Women Admitted to the Village of Fistula. *Les Médecine d'Afrique Noire*, **48**, 55-59.

[22] Sombie, I., Kambou, T., Conombo, S.G., Sankara, O., Ouedraogo, L., Zoungrana, T., Hounton, S. and Meda, N. (2007) A Retrospective Review of Obstetric Urogenital Fistula from 2001 to 2003 in Burkina Faso. *Médecine Tropicale*, **67**, 48-52.

[23] Arrowsmith, S.D., Ruminjo, J. and Landry, E.G. (2010) Current Practices in Treatment of Female Genital Fistula: A Cross Sectional Study. *BMC Pregnancy and Childbirth*, **10**, Article No. 73. http://www.biomedcentral.com/1471-2393/10/73
https://doi.org/10.1186/1471-2393-10-73

[24] Kimassoum, R., Franklin, D.S., Arya, Z.A.T. and Kaboro, M. (2016) Evaluation of the Treatment of Urinary Incontinence after Obstetric Fistula Cure. *Uro'Andro*, **1**, 242-246.

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A Double-Blind, Placebo-Controlled Study of the Effectiveness of Mate Endurance TM Dietary Supplement on Sexual Satisfaction, Ejaculatory Control, and Distress in Men with Premature Ejaculation

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Abstract

Background: To assess the efficacy of the dietary supplement Mate Endurance on sexual satisfaction, ejaculatory control, and sexually related personal distress in patients with premature ejaculation. **Methods:** In a double-blind, randomized, placebo-controlled study, 68 patients between 21 and 60 years old with premature ejaculation were randomized to receive either Mate Endurance or placebo treatment for three months. The patients were provided a questionnaire at the start of the study and again three months post commencement of the study. The questionnaires were comprised of the Index of Premature Ejaculation (IPE) and the PE Diagnostic Tool (PEDT). **Results:** Participants in the treatment group experienced a significant improvement in symptoms often associated with premature ejaculation versus those in the placebo group. The treatment was widely used with limited adverse effects. **Conclusions:** The results of the study demonstrate the effectiveness of the dietary supplement Mate Endurance in improving symptoms associated with premature ejaculation, including general sexual satisfaction and distress associated with sexual encounters.

Keywords

Premature Ejaculation, Sexual Dysfunctions, Herbal, Ejaculation, Orgasm

1. Introduction

Premature ejaculation (PE) is the most common male sexual dysfunction affect-

ing men and their partners, impacting 30% - 40% of men at some point in their lives [1]. There are three common symptoms that affect individuals with PE: a short time interval between penetration and ejaculation; little or no voluntary control of timing of ejaculation; and negative emotional consequences such as anxiety, embarrassment, reduced sexual satisfaction, the avoidance of sexual encounters, personal and/or partner distress, and interpersonal difficulties [2]. Premature ejaculation can be defined as persistent or recurrent ejaculation and orgasm before or immediately after vaginal penetration, and before the individual desires [3].

Assessment measures for PE include stopwatch measurements of intravaginal ejaculatory latency time (IELT) and the use of validated questionnaires [2]. While various studies have proposed that a PE diagnosis should be based solely on intravaginal ejaculatory latency time (IELT), the presence of other more subjective factors (such as perceived lack of control over ejaculation) has been directly associated with elevated personal distress related to ejaculation and decreased satisfaction with sexual intercourse, whereas the effects of IELT on these parameters are indirect [4]. Moreover, IELT has not been recommended for use in the clinical management of PE due to its potentially disruptive impact on sexual performance and pleasure. Currently, there are five validated questionnaires available for the assessment of PE. The Index of Premature Ejaculation (IPE) and the Premature Ejaculation Diagnostic Tool (PEDT) are the two most widely used questionnaires, given their extensive databases [5].

Effectively treating symptoms of PE is important, because sexual dysfunction can have a significant psychological impact on an individual's confidence, as well as a negative effect on an overall relationship. Available treatments for PE include psychological and behavioral therapy, topical therapy (e.g., Benzocaine wipes), and systemic treatments such as adrenergic antagonists, gamma-aminobutyric acid (GABA), and selective serotonin reuptake inhibitors (SSRIs). The success of these agents in addressing premature ejaculation has been variable, and the agents are associated with a host of side effects [6] [7]. Despite the prevalence of premature ejaculation, few therapies exist that offer minimal to no downside risk. Traditional Chinese Medicine, including herbal and natural products, is drug-free alternatives that have been suggested to improve sexual satisfaction with limited side effects in certain instances [8].

Mate Endurance is a dietary supplement that contains an herbal aphrodisiac blend concentrate with primary ingredients including L-Tryptophan, L-Citrulline, Cassia (Cinnamon) Bark Powder, Tribulus Fruit Extract, Grape Seed Extract, Vitamin B6, Vitamin B12, Pantothenic Acid, and L-Tyrosine. This study involved a randomized, double-blind placebo-controlled trial to evaluate the efficacy of the dietary supplement (Mate Endurance) on the improvement of sexual satisfaction, ejaculatory control, and distress associated with premature ejaculation.

2. Methods

2.1. The Herbal Compound

The herbal compound (Mate Endurance) investigated in this study consisted of a blend of natural herbal concentrates packed in a gel capsule. Ingredients included in one serving were 3 mg Niacin, 2 mg Vitamin B6 (as Pyridoxine HCl), 900 mcg Vitamin B12 (as Cyanocobalamin), 5 mg Pantothenic Acid (as Calcium-D-Pantothenate), 100 mcg Selenium (as L-Selenomethionine) and a 224 mg proprietary blend of L-Tryptophan, L-Citrulline, Cassia (Cinnamon) Bark Powder, Fenugreek Seed Powder, Tribulus Fruit Extract, Grape Seed Extract, and L-Tyrosine.

2.2. Placebo

The placebo used in this study consisted of a tasteless starch compound with no active ingredients. The placebo was delivered in the same capsules used for the active herbal compound.

2.3. Study Subjects

Eligible subjects were healthy men aged 21 to 60 years old diagnosed with primary PE (based on the DSM-V criteria of premature ejaculation) [9]. Eligible subjects were also in a stable sexual relationship in which they engaged in sexual relations one or more times per week for a minimum of the last six months.

Exclusion criteria included: previous genital trauma or surgery, the presence of erectile dysfunction and inhibited male orgasm, a severe physical or mental illness, serious relationship problems, inability to engage in sexual intercourse once a week during the study period, current history of alcohol or drug abuse, and any history of diabetes mellitus, psychiatric disorders, renal insufficiency, liver diseases, dyslipidemia, hypertension, hypothyroidism or hyperthyroidism, or cardiac arrhythmias.

Sixty-eight men were deemed eligible for the study. All participants provided written informed consent prior to participating and after having been explained the possible risks and benefits associated with participation in the study. This study was approved by our institution's ethics committee.

2.4. Study Procedures

In a randomized, double-blind, placebo-controlled study conducted from December 2019 to March 2020, 68 male subjects complaining of primary PE were randomly assigned to two test groups (group 1 and group 2). Individuals in Group 1 received the herbal compound, and individuals in Group 2 received the placebo. Treatment was administered in a randomized sequence that remained unknown to the patient and the researchers. Subjects were instructed to take one capsule of their assigned treatment once daily on an empty stomach prior to their evening meal at approximately the same time every day. The use of medications or the consumption of alcoholic beverages within six hours of sexual ac-

tivity was prohibited. Couples were instructed not to use condoms or topical anesthetic cream, to not pause during intercourse, or to have interrupted intromission. None of the subjects underwent formal psychosexual counseling.

Subjects were asked to complete the Index of Premature Ejaculation (IPE) and the Premature Ejaculation Diagnostic Tool (PEDT) both prior to and at the end of the study.

The Cronbach's alpha measure of internal consistency of the IPE scale in our studied population was 0.81 which indicated high reliability.

2.5. Study Endpoints & Method of Data Analysis

The primary endpoints were increases in IPE scores and a decrease in PEDT scores, corresponding to a decrease in PE symptoms (*i.e.*, more ejaculatory control, more sexual satisfaction, and less distress associated with sexual encounters). Safety endpoints included queries on potential adverse events. To compare two groups at different time points as well as the percent of changes during treatment, the Mann-Whitney test was used. The Wilcoxon singed-rank test was also applied to assess the within-group changes. Moreover, to evaluate the differences between groups after treatment while adjusting for measurement at baseline, the analysis of covariance (ANCOVA) was conducted. Differences were considered statistically significant at the level of a *P*-value of ≤0.05. Statistical analysis was done using IBM SPSS 25.0.

3. Results

A total of 68 subjects were recruited; only 62 (91%) completed the trial study. Six patients (9%) dropped out of the study and were excluded from the final analysis (Figure 1). Mean patient age was 31.1 ± 4.7 years (range 24 - 41) in Group 1 and 32.6 ± 4.9 years (range 23 - 44) in Group 2.

The mean pretreatment weekly intercourse episodes were 2.05 times per week for the herbal compound group compared to 2.03 times per week for the placebo group. The mean intercourse frequency at 12-week treatment was 2.14 times per week and 2.12 times per week for group 1 and group 2, respectively, which was not significantly different ($p = 0.9$).

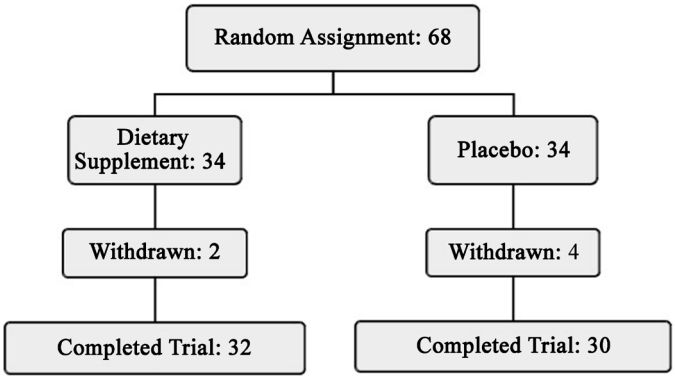

Figure 1. Study design.

To analyze the PEDT results, baseline versus 12-week mean PEDT scores were compared. A score of 0 to 4 was attributed to each answer option in the PEDT questionnaire. A total score is calculated by taking the sum of each of the individual scores. A score of 11 or more is commonly found in men with PE.

The baseline mean PEDT score was 18 and 17 in Groups 1 and 2, respectively, at the commencement of the study. After 12 weeks of treatment, the mean PEDT score significantly decreased (18 to 10) in the treatment group ($p < 0.02$), compared to only a mild decrease in the placebo group (17 to 15) ($p = 0.06$) (Table 1).

Baseline and 12-week mean IPE Scores were also measured. In all three domains of sexual satisfaction, control, and distress, the two groups reported similar IPE scores at the commencement of the study ($p > 0.05$). The scores in both the sexual satisfaction domain as well as in the distress domain showed statistically significant results 12 weeks after treatment both in unadjusted and adjusted analysis ($p < 0.05$), while the differences between the two groups was not statistically significant in the control domain ($p = 0.524$). The within-group changes were also assessed using the Wilcoxon signed-rank test. The increase in all domains, and both groups, were significant, but it was significantly higher in the treatment group (Table 2). A higher score represents more ejaculatory control, more sexual satisfaction, and less distress.

Adverse Effects

There were a slightly greater number of instances of adverse effects associated with the dietary supplement treatment compared to the placebo. Four individuals using the dietary supplement and one individual using the placebo reported treatment-related adverse events, including constipation (3 cases in Group 1), nausea (1 case in Group 2), and headache (1 case in Group 1).

4. Discussion

In this study, we evaluated the efficacy of Mate Endurance as a sexual complementary dietary supplement. To measure results, we used validated questionnaires, including the IPE and PEDT, as opposed to stopwatch measures of IELT. The use of validated questionnaires not only provided a more accurate means of measuring the subjective factors associated with PE, such as lack of ejaculatory

Table 1. Comparing PEDT results between two groups of mate endurance and Placebo.

Variable	Time	Group		p-value
		Mate Endurance (n = 32)	Placebo (n = 30)	
PEDT[a]	Start of intervention	18.0 ± 1.0	17.0 ± 1.0	<0.001[b]
	12 weeks past intervention	10.0 ± 2.0	15.0 ± 1.0	<0.001[b]
	Mean differential	8.0 ± 2.0	2.0 ± 1.0	<0.001[b]
	p-value	< 0.02[c]	0.06[c]	

Data presented as Mean ± SD. [a]PEDT, Premature Ejaculation Diagnostic Tool; [b]Based on t-test; [c]Based on paired t-test.

Table 2. Comparing Index of Premature Ejaculation (IPE) results between two groups of Mate Endurance and Placebo.

Domain	Time	Group		Unadjusted p-value	Adjusted p-value
		Mate Endurance (n = 32)	Placebo (n = 30)		
Sexual Satisfaction	Start of intervention	26.6 ± 9.1 25.0 (12.5 - 50.0)	25.2 ± 4.8 25.0 (18.7 - 37.5)	0.547[a]	<0.001[b]
	12 weeks past intervention	44.7 ± 14.3 50.0 (25.0 - 68.7)	30.0 ± 9.9 25.0 (12.5 - 50.0)	<0.001[a]	
	Mean differential	18.2 ± 16.3 15.6 (0.0 - 43.7)	4.8 ± 11.1 0.0 (−12.5 - 31.2)	<0.001[a]	
	p-value	<0.001[c]	0.033[c]		
Control	Start of intervention	10.3 ± 9.1 6.2 (0.0 - 25.0)	11.7 ± 6.7 12.5 (0.0 - 25.0)	0.397[a]	0.524[b]
	12 weeks past intervention	17.2 ± 8.2 18.7 (0.0 - 25.0)	16.7 ± 8.3 18.7 (0.0 - 31.2)	0.705[a]	
	Mean differential	6.8 ± 8.6 3.1 (0.0 - 25.0)	5.0 ± 7.7 0.0 (−6.2 - 18.7)	0.401[a]	
	p-value	<0.001[c]	0.003[c]		
Distress	Start of intervention	9.8 ± 9.9 12.5 (0.0 - 25.0)	11.7 ± 9.2 12.5 (0.0 - 25.0)	0.403[a]	<0.001[b]
	12 weeks past intervention	31.6 ± 17.4 25.0 (0.0 - 50.0)	18.3 ± 10.7 25.0 (0.0 - 25.0)	0.005[a]	
	Mean differential	21.9 ± 17.7 18.7 (0.0 - 50.0)	6.7 ± 12.2 0.0 (−12.5 - 25.0)	0.001[a]	
	p-value	<0.001[c]	0.007[c]		

Data presented as Mean ± SD, Median (min-max). [a]Based on Mann-Whitney test; [b]Based on ANCOVA adjusted for measurements at the start of measurement; [c]Based on Wilcoxon signed-rank test.

control and personal distress, but also eliminated the potentially disruptive impact on sexual performance and pleasure associated with stopwatch measurements.

At the commencement of the study, the treatment versus the placebo group showed no significant differences in mean age or mean IPE score. In addition, both Group A and Group B reported similar frequencies of weekly intercourse episodes pretreatment and during the 12-week treatment period. This suggests that both randomized groups had no significant differences prior to the treatment, allowing them to be compared fairly during the treatment period.

After 12 weeks of treatment, it was found that there was a significant decrease ($p < 0.05$) in the mean PEDT score and a significant increase ($p < 0.05$) in the mean IPE score in subjects in the dietary supplement treatment group, whereas there was a significantly smaller decrease in PEDT score and increase in IPE score in the placebo group. The reported changes in the placebo group can likely be attributed to the placebo effect. This suggests that the dietary supplement was more effective than a placebo in decreasing symptoms associated with PE as

shown by the subject's responses to the questionnaire. Specifically, the supplement was effective in improving sexual satisfaction and decreasing distress stemming from sexual encounters in patients suffering from PE.

Various facets of Mate Endurance's formulation may have attributed to the overall effectiveness of the dietary supplement in all three domains of the IPE. First, tryptophan is a compound which enters the brain, where it is then converted to 5-Hydroxytryptophan (5-HTP), which increases the synthesis of serotonin [10]. Many neurotransmitters and receptors are found at the ejaculatory neuroaxis including dopamine, nitric oxide, and 5-hydroxytryptamine (5-HT), the precursor to serotonin [11]. Whereas dopamine causes excitation of the ejaculatory neuroaxis, serotonin causes inhibition [12]. Therefore, the increased presence of serotonin as a result of the consumption of L-Tryptophan may play an important role in ejaculatory control [13].

Next, L-citrulline is an ingredient which the body converts to L-arginine, an amino acid that improves blood flow through increased nitric oxide production. The increased presence of nitric oxide improves blood circulation, thereby improving erectile function [14].

Lastly, a combination of herbal ingredients presents in the dietary supplement such as fenugreek and tribulus terrestris have been suggested to increase sexual drive and libido in men [15].

The double-blind, placebo-controlled design, paired with the statistically significant results to improvements in factors often associated with premature ejaculation measured through the use of the IPE and PEDT, provides evidence of efficacy of the natural dietary supplement Mate Endurance for improvement of sexual satisfaction and decreased distress associated with premature ejaculation.

Limitation

Our study was limited by its small sample size, limited duration of follow-up, and using only self-reports to assess improvements in symptoms associated with PE.

5. Conclusion

Premature ejaculation continues to be one of the most predominant male sexual dysfunctions, affecting nearly 40% of men at one point in their lives. While it was believed that herbal supplements could provide a drug-free alternative solution, few studies have investigated the effectiveness of herbal supplements. The results of this study demonstrate the effectiveness of the dietary supplement Mate Endurance in improving some subjective symptoms of PE compared to placebo. Furthermore, Mate Endurance was well-tolerated by the subjects with minimum reported side effects.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Patrick, D.L., Althof, S.E., Pryor, J.L., Rosen, R., Rowland, D.L., Ho, K.F., McNulty, P., Rothman, M. and Jamieson, C. (2005) Premature Ejaculation: An Observational Study of Men and Their Partners. *The Journal of Sexual Medicine*, **2**, 358-367. https://doi.org/10.1111/j.1743-6109.2005.20353.x

[2] Althof, S.E., McMahon, C.G., Waldinger, M.D., Serefoglu, E.C., Shindel, A.W., Adaikan, P.G., Becher, E., Dean, J., Giuliano, F., Hellstrom, W.J.G., Giraldi, A., Glina, S., Incrocci, L., Jannini, E., McCabe, M., Parish, S., Rowland, D., Segraves, R.T., Sharlip, I. and Torres, L.O. (2014) An Update of the International Society of Sexual Medicine's Guidelines for the Diagnosis and Treatment of Premature Ejaculation (PE). *Sexual Medicine*, **2**, 60-90. https://doi.org/10.1002/sm2.28

[3] Serefoglu, E.C., McMahon, C.G., Waldinger, M.D., Althof, S.E., Shindel, A., Adaikan, G., Becher, E.F., Dean, J., Giuliano, F., Hellstrom, W.J.G., Giraldi, A., Glina, S., Incrocci, L., Jannini, E., McCabe, M., Parish, S., Rowland, D., Taylor Segraves, R., Sharlip, I. and Torres, L.O. (2014) An Evidence-Based Unified Definition of Lifelong and Acquired Premature Ejaculation: Report of the Second International Society for Sexual Medicine Ad Hoc Committee for the Definition of Premature Ejaculation. *The Journal of Sexual Medicine*, **11**, 1423-1441. https://doi.org/10.1111/jsm.12524

[4] Shabsigh, R. and Rowland, D. (2007) The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision as an Appropriate Diagnostic for Premature Ejaculation. *The Journal of Sexual Medicine*, **4**, 1468-1478. https://doi.org/10.1111/j.1743-6109.2007.00557.x

[5] Althof, S., Rosen, R., Symonds, T., Mundayat, R., May, K. and Abraham, L. (2006) Development and Validation of a New Questionnaire to Assess Sexual Satisfaction, Control, and Distress Associated with Premature Ejaculation. *The Journal of Sexual Medicine*, **3**, 465-475. https://doi.org/10.1111/j.1743-6109.2006.00239.x

[6] Atikeler, M.K., Gecit, I. and Senol, F.A. (2002) Optimum Usage of Prilocaine-Lidocaine Cream in Premature Ejaculation. *Andrologia*, **34**, 356-359. https://doi.org/10.1046/j.1439-0272.2002.00511.x

[7] Higgins, A. (2010) Antidepressant-Associated Sexual Dysfunction: Impact, Effects, and Treatment. *Drug, Healthcare and Patient Safety*, **2**, 141-150. https://doi.org/10.2147/DHPS.S7634

[8] Li, Y., Duan, Y., Yu, X., Wang, J., Yao, Z., Gong, X., Gong, X., Zheng, W., Xue, Y. and Guo, J. (2019) Traditional Chinese Medicine on Treating Premature Ejaculation. *Medicine*, **98**, e15379. https://doi.org/10.1097/MD.0000000000015379

[9] American Psychiatric Association (2013) Diagnostic and Statistical Manual of Mental Disorders. 5th Edition. https://doi.org/10.1176/appi.books.9780890425596

[10] Richard, D.M., Dawes, M.A., Mathias, C.W., Acheson, A., Hill-Kapturczak, N. and Dougherty, D.M. (2009) L-Tryptophan: Basic Metabolic Functions, Behavioral Research and Therapeutic Indications. *International Journal of Tryptophan Research*, **2**, 45-60. https://doi.org/10.4137/IJTR.S2129

[11] Giuliano, F. and Clément, P. (2012) Pharmacology for the Treatment of Premature Ejaculation. *Pharmacological Reviews*, **64**, 621-644. https://doi.org/10.1124/pr.111.004952

[12] Aggarwal, A., Lal Jethani, S., Rohatgi, R. and Kalra, J. (2017) The Role of Selective Serotonin Reuptake Inhibitors in Premature Ejaculation. *European Medical Journal*, **2**, 78-81.

[13] Giuliano, F. and Clément, P. (2006) Serotonin and Premature Ejaculation: From

Physiology to Patient Management. *European Urology*, **50**, 454-466. https://doi.org/10.1016/j.eururo.2006.05.055

[14] Shirai, M., Hiramatsu, I., Aoki, Y., Shimoyama, H., Mizuno, T., Nozaki, T., Fukuhara, S., Iwasa, A., Kageyama, S. and Tsujimura, A. (2018) Oral L-Citrulline and Transresveratrol Supplementation Improves Erectile Function in Men with Phosphodiesterase 5 Inhibitors: A Randomized, Double-Blind, Placebo-Controlled Crossover Pilot Study. *Sexual Medicine*, **6**, 291-296. https://doi.org/10.1016/j.esxm.2018.07.001

[15] Ali, J., Ansari, S. and Kotta, S. (2013) Exploring Scientifically Proven Herbal Aphrodisiacs. *Pharmacognosy Reviews*, **7**, 1. https://doi.org/10.4103/0973-7847.112832

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Upfront Docetaxel with LH-RH Antagonist for Metastatic Hormone Sensitive Prostate Cancer Considering Epithelial to Mesenchymal Transition

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Abstract

Objective: Upfront docetaxel use for hormone naïve advanced prostate cancer is reported that it successfully delayed the progression to hormone refractory stage, though the adequate methodology to obtain the maximum effect is unclear. We investigated these issues from our experiences of upfront docetaxel use with LH-RH antagonist for metastatic hormone sensitive prostate cancer, aiming at the prevention of epithelial-mesenchymal transition (EMT) for apoptosis tolerance. **Patients and Methods:** Of 31 stage IV new prostate cancer patients treated with upfront docetaxel and LH-RH antagonist (Degarelix), 25 patients who could be followed more than 12 months (mean 36.2 months) were analyzed. Docetaxel was used two to three courses basically 75 mg/m^2 dose initializing two weeks after the induction of first Degarelix. **Results:** The clinical course was divided clearly to two groups according to prostate specific antigen (PSA) values. Of 25 patients, 12 patient's PSA did not decrease below 0.1 ng/ml within 6 months (group A) and gradually rose afterwards. PSA in another 13 patients (group B) decreased below 0.1 within 6 months and kept below 0.1 during the follow up period. Although statistically not significant, the initial group A's PSA was higher than group B's (average 1308 and 353 ng/ml), however, number of metastasis, Gleason sum, and bone metastatic extent of disease showed no difference between them. Among group B patients, 7 cases had only upfront docetaxel and hormonal therapy, and some of these patients showed only atrophic gland and fibrotic tissue at second prostate biopsy (specimens after more than two years of therapy), suggesting complete response. **Conclusion:** Our study suggested that PSA value at 6 months may predict the outcome of whole therapy. Patients showing PSA less than 0.1 ng/ml at 6 months and requiring

no therapy other than docetaxel and hormone may be induced to complete response. Upfront docetaxel with LH-RH antagonist may prevent EMT for obtaining apoptosis tolerance, in case the patient does not have the castration-resistant clone at the beginning of the therapy (group B).

Keywords

Docetaxel, Prostate Cancer, Epithelial to Mesenchymal Transition, Degarelix

1. Introduction

Although early detection of non-metastatic prostate cancer improved overall and disease specific survival for all prostate cancer patients, no apparent evidence of survival improvement was shown for de novo metastatic prostate cancer patients [1]. The GETUG-AFU-15 [2], CHAARTED [3] and STAMPEDE NCT00268476 [4] RCT studies proved the efficacy of upfront docetaxel use for metastatic hormone-sensitive prostate cancer (mHSPC) in median progression free survival and/or median overall survival. Following the evidences of these studies, upfront docetaxel therapy is becoming a standard care for patients with mHSPC [5] [6]. However, the best timing to start docetaxel and/or the duration of chemotherapy have not to be cleared [7] [8]. The reason why androgen deprivation therapy (ADT) must be continued eternally is said that small numbers of cancer cells obtain apoptosis tolerance at the beginning of the ADT, and keep alive at cell arrest phase as long as ADT continues, while most of the hormone-sensitive cancer cells go into apoptosis [9]. And these remaining cells have a chance to get an ability to proliferate even in low hormonal environment in some future, and become castrate resistant prostate cancer [10]. The LHRH-antagonist, Degarelix is proved to cut androgen to castrate level as early as surgical castration [11]. We use docetaxel as tubulin-targeting chemotherapy at the beginning of Degarelix hormonal therapy aiming at "no cancer cells" obtaining apoptosis tolerance. We here report an interesting result that may lead to more effective upfront docetaxel use as a methodology.

2. Patients and Methods

Of 31 stage IV new prostate cancer patients during the period of Oct. 2014 to Oct. 2019, treated with upfront docetaxel and LH-RH antagonist (Degarelix), 25 patients who could be followed more than 12 months (mean 36.2 months) were analyzed. Patients who had been treated surgically or radiologically as localized prostate cancer and advanced thereafter were excluded, because mostly they had already been hormonally treated when prostate specific antigen (PSA) recurrence. No age limitation was provided if the patient could approve chemotherapy. Docetaxel was used two to three courses monthly basically 75 mg/m^2 dose initializing two weeks after the induction of first Degarelix. As this study was not

a controlled study but an observational study, for the patients underwent upfront docetaxel and Degarelix, attending physician added other drugs and therapies afterwards according to necessity, such as regional irradiation, abiraterone, enzalutamide and cabazitaxel. Patients, whose initial chief complaint was progressive limb paralysis due to vertebral metastasis, underwent irradiation for the metastatic site and Degarelix as a first therapy. Transrectal prostate biopsy was performed for all patients before treatment, and second prostate biopsy was also made for selected patients showing good clinical course for more than two years. Statistical analysis was made by Student's t-test for the initial PSA values between A and B. This study was approved by the hospital's IRB committee (Institutional Review Board of Tokyo Medical University, Ibaraki Medical Center, approved # 14 - 39) and all the attendees accepted this study and report by signature.

3. Results

The clinical course of this therapy was divided clearly into two groups according to PSA values. Of 25 patients, 12 patient's PSA did not decrease below 0.1 ng/ml within 6 months and gradually rose afterwards. These patients were categorized as group A. PSA in another 13 patients decreased below 0.1 within 6 months and kept below 0.1 during the follow up period. These patients were categorized as group B (**Figure 1(a)**, **Figure 1(b)**). Although statistically not significant, the initial group A's PSA were higher than group B's (average 1308 and 353 ng/ml), however, number of metastasis, Gleason sum, and bone metastatic extent of disease showed no difference between them (**Table 1**). Though group A patients had various additional therapy after PSA failure by physician's decision, among group B patients, seven patients only underwent hormonal and upfront docetaxel therapy. Of those, two patients showed only atrophic gland and fibrotic tissue at second prostate biopsy after more than two years follow up, suggesting complete response only by hormonal and upfront docetaxel therapy (**Figure 2(a)**, **Figure 2(b)**).

4. Discussion

The evolving treatment progress have occurred for metastatic prostate cancer by the development of new generation anti-androgens [12], abiraterone acetate which inhibit adrenal testosterone biosynthesis more effectively than non-specific CYP 17 inhibitor such as ketoconazole and aminoglutethimide [13], and taxanes that bind beta-tubuline and stabilize the microtubule cytoskeleton leading an apoptotic cell death [14]. These agents have been used for hormone refractory advanced prostate cancer, and attribute to improve overall survival and progression free survival. However, in recent years, upfront use of these agents for hormone-sensitive prostate cancer, showed significant retardation of the development to hormone-refractory state [15]. Usefulness of upfront docetaxel for mHSPC was proved by randomized prospective studies such as GETUG-AFU-15

NCT00104715 [2], CHAARTED NCT00309985 [3], STAMPEDE NCT00268476 [4], though the best timing and duration of additional chemotherapy have not been determined [16]. As a hormonal agent, LHRH agonist was mainly used for these studies. The timing to start upfront chemotherapy varied from simultaneous to several months from the beginning of hormonal therapy by these study design. We used Degarelix (LHRH-antagonist), because it was proved to reduce androgen to castrate level as early as surgical castration, and induce apoptosis simultaneously for all hormone-sensitive benign and malignant prostatic cells [11].

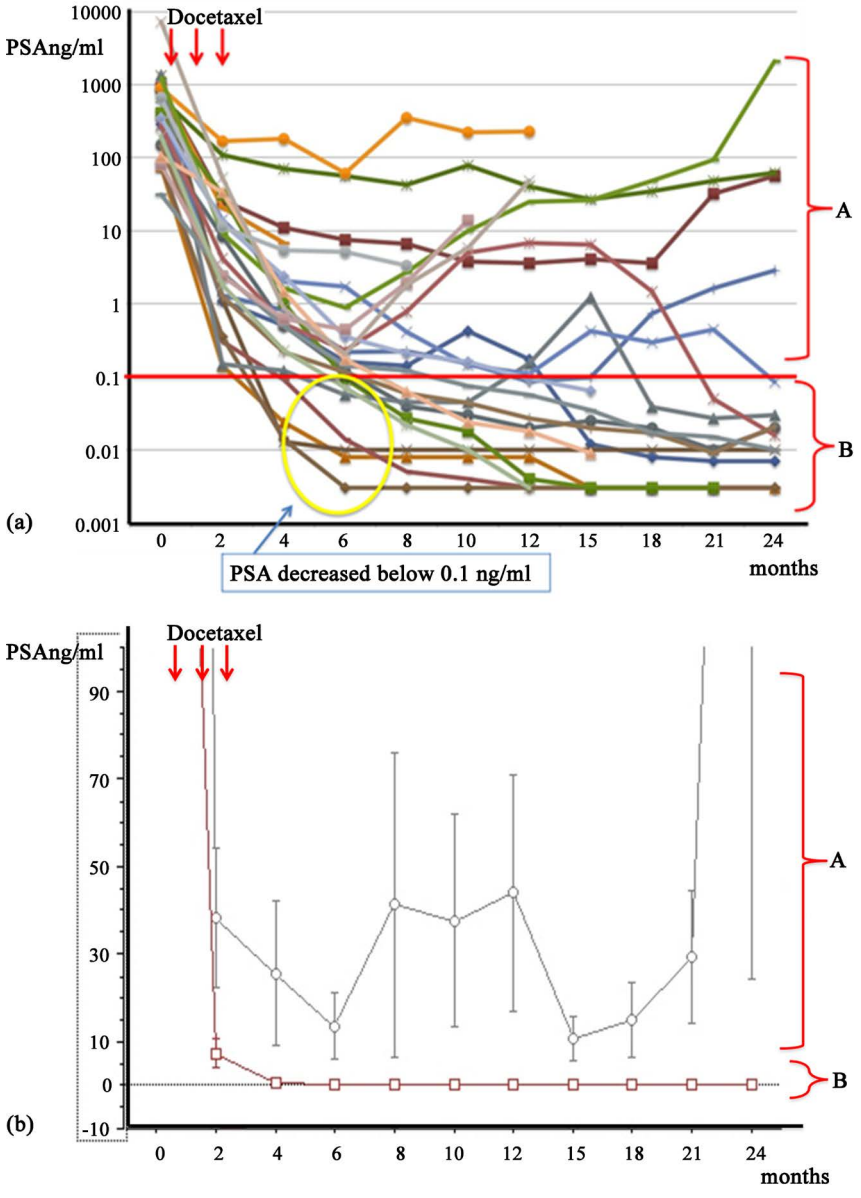

Figure 1. (a) Clinical course by PSA values of all patients are indicated in Semi-log plot. Patients whose PSA did not decrease below 0.1 ng/ml within 6 months were categorized as group A, and the others as group B. (b) Clinical course by PSA values of group average ± SD in lineal plot.

Table 1. Patient profiles of group A and B.

		A	B
No. of patients		12	13
Average age (min-max)y/o		71.7 (60 - 83)	66.9 (52 - 77)
Initial PSA (ng/ml) Average (min-max)		1308.5 (80 - 7184)	353.4 (31 - 1371)
Gleason Grade Group	3	0	1
	4	4	5
	5	7	6
Bone Mets EOD	1 - 2	3	5
	3 - 4	5	5

No statistical differences were observed between A and B in these profiles. EOD: extent of disease.

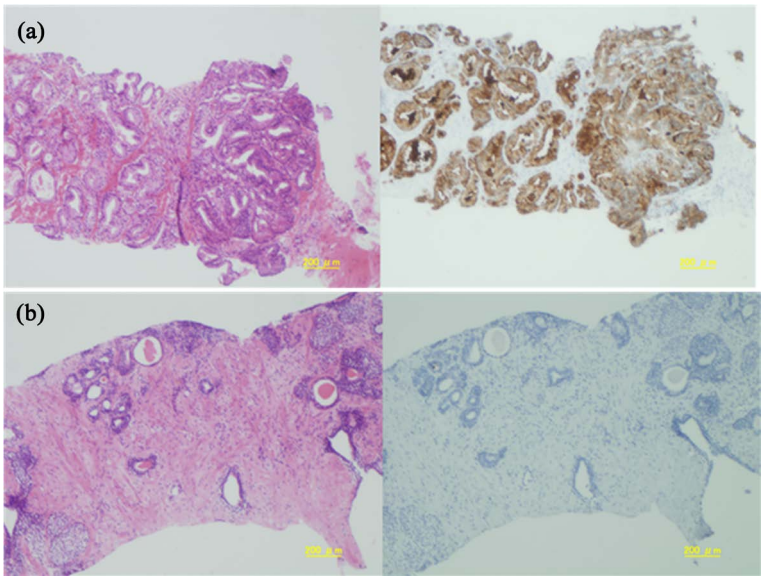

Figure 2. (a) Representative histological findings of group B patients showing initial (pre-treatment) prostate biopsy. Gleason 4 + 3 adenocarcinoma observed in H & E (left), and immunohistochemical staining for PSA (right). Reduced from 20×. (b) Second (post treatment more than two years) prostate biopsy from the same patient as **Figure 2(a)**. Only atrophic glands with negative PSA staining (right) were shown. Reduced from 20×.

The mechanism and timing of development of castration resistance are still debatable. Two models were proposed such as; "adaptation emergence" and "clonal selection". The former model suggested that prostate cancer is composed of homogenous hormone dependent cells, and castration resistance emerges through genetic/epigenetic conversion of cells from androgen-dependent to independent status. Whereas the latter model indicates that prostate cancer is composed of heterogenous major hormone dependent and minor hormone independent cells. Under an androgen-deprived environment, the castration-resistant cells are selected for survival and obtain proliferative advantage, and finally all cells composed of hormone independent [17]. Especially to the

former adaptation emergence process, the contribution of epithelial to mesenchymal transition (EMT) has been proved in the several basic studies [18]. And for the purpose of inhibiting EMT and/or mutation of androgen receptor, microtubule-targeting agents; docetaxel is reported effective [19] [20]. We consider that docetaxel should be used at the timing of the first hormonal use, that is the timing of adaptation emergence to acquire apoptotic tolerance for hormonal therapy [21]. Eigl *et al.* (2005) reported an in vivo synergistic effect of taxans and ADT. They found that homogenous hormone-sensitive tumor engrafted mice receiving paclitaxel and simultaneous castration, exhibited a delayed median time to progression compared to those treated with sequential ADT and chemotherapy [22]. Our results suggested that in group A, small numbers of survived castration resistant prostate cancer, those existed at the first visit, continued proliferation after the chemotherapy as a "clonal selection". Whereas in group B, especially in patients applying no other treatment modality other than ADT and docetaxel, upfront docetaxel prevented EMT to obtain "adaptation emergence", and induced total cell kill. Second prostate biopsy for those PSA value below 0.1 ng/ml for more than two years and quitted ADT, indicated no residual cancer on specimens. This result may prove our total kill cell theory. Sasaki and Sugimura (2018) summarized the relation of prognosis between nadir PSA value and time to PSA nadir after primary ADT for advanced hormone-naïve prostate cancer. They concluded that higher PSA nadir and shorter time to PSA nadir represents poor prognostic factor, suggesting more androgen and androgen-receptor independent cancer cells at the first visit [23]. Moreover, our results suggested that the decrease of PSA less than 0.1 ng/ml within 6 months predicted good prognosis. It was presumed that rapid PSA reduction indicated high proportion of hormone-sensitive cancer cells at the first visit [23]. Group B patients were thought to have high proportion of hormone-sensitive cancer. In experimental animal study consisted all hormone-sensitive cancer cells, a closely timed sequence of chemo-hormonal therapy appeared to induce maximum synergy effect [22]. Our results might prove clinical model of Eigl's study in group B patients. According to the results of CHAARTED and GETUG-AFU15 studies, upfront docetaxel was more beneficial for high volume mHSPC rather than low volume cancer [24]. However, considering EMT, Eigl's and our results it is suggested that even for low volume mHSPC, upfront docetaxel will be beneficial. The timing of upfront docetaxel initiation should start two weeks after the first LHRH antagonist, to disturb EMT of hormone naïve cells for the acquisition of apoptosis tolerance.

5. Conclusion

Although the number of patients and follow up period were limited, our study suggested that PSA value at 6 months may predict the outcome of whole therapy. Patients showing PSA less than 0.1 ng/ml at 6 months and requiring no therapy other than docetaxel and hormone may be induced to complete response. Upfront docetaxel with LH-RH antagonist may prevent EMT for ob-

taining apoptosis tolerance, in case the patient does not have the castration-resistant clone at the beginning of the therapy (group B).

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wu, J.N., Fish, K.M., Evans, C.P., White, R.W. and Dall'Era, M.A. (2014) No Improvement Noted in Overall or Cause-Specific Survival for Men Presenting with Metastatic Prostate Cancer over a 20-Year Period. *Cancer*, **120**, 818-823. https://doi.org/10.1002/cncr.28485

[2] Gravis, G., Fizzazi, K., Joly, F., Oudard, S., Priou, F., Esterni, B., *et al.* (2013) Androgen-Deprivation Therapy Alone or with Docetaxel in Non-Castrate Metastatic Prostate Cancer (GETUG-AFU 15): A Randomized, Open-Label, Phase 3 Trial. *The Lancet Oncology*, **14**, 149-158. https://doi.org/10.1016/S1470-2045(12)70560-0

[3] Sweeney, C.J., Chen, Y.H., Carducci, M., Liu, G., Jarrard, D.F., Eisenberger, M., *et al.* (2015) Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *The New England Journal of Medicine*, **373**, 737-746. https://doi.org/10.1056/NEJMoa1503747

[4] James, N.D., Sydes, M.R., Mason, M.D., Clarke, N.W., Anderson, J., Dearnaley, D.P., *et al.* (2015) Docetaxel and/or Zoledronic Acid for Hormone-Naïve Prostate Cancer: First Overall Survival Results from STAMPEDE (NCT00268476). *Journal of Clinical Oncology*, **33**, 5001. https://doi.org/10.1200/jco.2015.33.15_suppl.5001

[5] Mottet, N., van den Bergh, R.C.N., Briers, E., Bourke, L., *et al.* (2018) EAU-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. 6.4.5.2 ADT Combined with Chemotherapy. 70. https://uroweb.org/wp-content/uploads/EAU-ESUR-ESTRO-SIOG-Guidelines-on-Prostate-Cancer-large-text-V2.pdf

[6] Committee for Medicinal Products for Human Use (CHMP) Opinion "TAXOTERE in Combination with Androgen-Deprovation Therapy (ADT), with or without Prednisone or Prednisolone, Is Indicated for the Treatment of Patients with Metastatic Hormone-Sensitive Prostate Cancer." https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-taxotere-ws-1550_en.pdf

[7] Sun, G., Zhang, X., Chen, J., Liao, B., *et al.* (2018) What Kind of Patients with Castration-Naïve Prostate Cancer Can Benefit from Upfront Docetaxel and Abiraterone: A Systematic Review and a Network Meta-Analysis. *Urologic Oncology*, **36**, 505-517. https://doi.org/10.1016/j.urolonc.2018.09.005

[8] Gravis, G., Audenet, F., Irani, J., Timsit, M.O., *et al.* (2017) Chemotherapy in Hormone-Sensitive Metastatic Prostate Cancer: Evidences and Uncertainties from the Literature. *Cancer Treatment Reviews*, **55**, 211-217. https://doi.org/10.1016/j.ctrv.2016.09.008

[9] Akakura, K., Bruchovsky, N., Goldenberg, S.L., Rennie, P.S., Buckley, A.R. and Sullivan, L.D. (1993) Effects of Intermittent Androgen Suppression on Amdrogen-Dependent Tumors. Apoptosis and Serum Prostate-Specific Antigen. *Cancer*, **71**, 2782-2790. https://doi.org/10.1002/1097-0142(19930501)71:9<2782::AID-CNCR2820710916>3.

0.CO;2-Z

[10] Huang, Y., Jiang, X., Liang, X. and Jiang, G. (2018) Molecular and Cellular Mechanism of Castration Resistant Prostate Cancer (Review). *Oncology Letters*, **15**, 6063-6076. https://doi.org/10.3892/ol.2018.8123

[11] Shore, N.D. (2013) Experience with Degarelix in the Treatment of Prostate Cancer. *Therapeutic Advances in Urology*, **5**, 11-24. https://doi.org/10.1177/1756287212461048

[12] Crawford, E.D., Schellhammer, P.F., McLeod, D.G., Moul, J.W., Higano, C.S., Shore, N., *et al.* (2018) Androgen Receptor Targeted Treatments of Prostate Cancer; 35 Years of Progress with Antiandrogens. *Journal of Urology*, **200**, 956-966. https://doi.org/10.1016/j.juro.2018.04.083

[13] Ryan, C.J., Smith, M.R., de Bono, J.S., Molina, A., Logothetis, C.J., de Souza, P., *et al.* (2013) Randomized Phase 3 Trial of Abiraterone Acetate in Men with Metastatic Castration-Resistant Prostate Cancer and No Prior Chemotherapy. *New England Journal of Medicine*, **368**, 138-148.

[14] Darshan, M.S., Loftus, M.S., Thadani-Mulero, M., Levy, B.P., Escuin, D., Zhou, X.K., *et al.* (2011) Taxane-Induced Blockade to Nuclear Accumulation of the Androgen Receptor Predicts Clinical Response in Metastatic Prostate Cancer. *Cancer Research*, **71**, 6019-6029. https://doi.org/10.1158/0008-5472.CAN-11-1417

[15] Fizazi, K., Jenkins, C. and Tannock, I.F. (2015) Should Docetaxel Be Standard of Care for Patients with Metastatic Hormone-Sensitive Prostate Cancer? Pro and Contra. *Annals of Oncology*, **26**, 1660-1667. https://doi.org/10.1093/annonc/mdv245

[16] Shiota, M., Yokomizo, A. and Eto, M. (2016) Taxane Chemotherapy for Hormone-Naïve Prostate Cancer with Its Expanding Role as Breakthrough Strategy. *Frontiers in Oncology*, **5**, 304. https://doi.org/10.3389/fonc.2015.00304

[17] Ahmed, M. and Li, L.C. (2013) Adaptation and Clonal Selection Models of Castration-Resistant Prostate Cancer: Current Perspective. *International Journal of Urology*, **20**, 362-371. https://doi.org/10.1111/iju.12005

[18] Li, P., Yang, R. and Gao, W. (2014) Contributions of Epithelial-Mesenchymal Transition and Cancer Stem Cells to the Development of Castration Resistance of Prostate Cancer. *Molecular Cancer*, **13**, 55. https://doi.org/10.1186/1476-4598-13-55

[19] Martin, S.K., Kamelgarn, M. and Kyprianou, N. (2014) Cytosleleton Targeting Value in Prostate Cancer Treatment. *American Journal of Clinical and Experimental Urology*, **2**, 15-26. https://pubmed.ncbi.nlm.nih.gov/25374905/

[20] Zhu, M.L., Horbinski, C.M., Garzotto, M., Qian, D.Z., Beer, T.M. and Kyprianou, N. (2010) Tubulin-Targeting Chemotherapy Impairs Androgen Receptor Activity in Prostate Cancer. *Cancer Research*, **70**, 7992-8002. https://doi.org/10.1158/0008-5472.CAN-10-0585

[21] Jaworska, D. and Szliszka, E. (2017) Targeting Apoptotic Activity against Prostate Cancer Stem Cells. *International Journal of Molecular Sciences*, **18**, 1648. https://doi.org/10.3390/ijms18081648

[22] Eigl, B.J.C., Eggener, S.E., Baybik, J., Ettinger, S., Chi, K.N., Nelson, C., *et al.* (2005) Timing Is Everything: Preclinical Evidence Supporting Simultaneous Rather than Sequential Chemohormonal Therapy. *Clinical Cancer Research*, **11**, 4905-4911. https://doi.org/10.1158/1078-0432.CCR-04-2140

[23] Sasaki, T. and Sugimura, Y. (2018) The Importance of Time to Prostate-Specific Antigen (PSA) Nadir after Primary Androgen Deprivation Therapy in Hormone-Naïve Prostate Cancer Patients. *Journal of Clinical Medicine*, **7**, 565.

https://doi.org/10.3390/jcm7120565

[24] Gravis, G., Boher, J.M., Chen, Y.H., *et al.* (2018) Burden of Metastatic Castrate Naïve Prostate Cancer Patients, to Identify Men More Likely to Benefit from Early Docetaxel: Further Analysis of CHAARTED and GETUG-AFU15 Studies. *European Urology*, **73**, 847-855. https://doi.org/10.1016/j.eururo.2018.02.001

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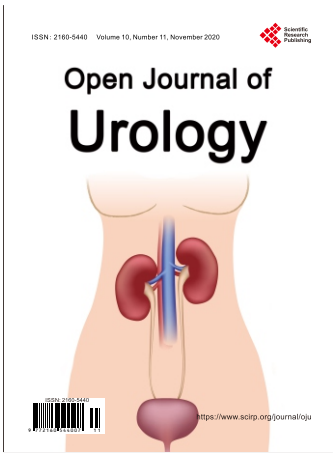

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