Herbal Supplement PC-Spes for Prostate Cancer

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OBJECTIVE: To determine the efficacy and toxicity of the herbal supplement PC-Spes in prostate cancer patients.

METHODS: Literature search through MEDLINE (1966–October 2001), PubMed, and abstracts from the Annual Meeting of the American Society of Clinical Oncology (1995–2001).

RESULTS: PC-Spes was associated with biochemical and clinical response in some prostate cancer patients. The mechanisms of action of PC-Spes appeared to be related to its estrogenic activity.

CONCLUSIONS: PC-Spes is associated with some efficacy in prostate cancer patients. Due to the limited data available, it should not be used to replace standard androgen suppression therapy in androgen-dependent patients. PC-Spes may have a role for patients who have failed standard treatments for androgen-independent disease and have no history of thromboembolism or abnormal bleeding. PC-Spes has a toxicity profile similar to those of androgen suppression and estrogen therapy.

KEY WORDS: herbal supplements, PC-Spes, prostate cancer, thromboembolism.

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REQUEST

What is the clinical efficacy and toxicity of the herbal product PC-Spes in prostate cancer patients?

RESPONSE

Background

Prostate cancer is the most prevalent cancer and second leading cause of cancer death in men in North America. In the US and Canada, it is estimated that >1 million men are currently diagnosed with prostate cancer, with 215 000 new cases and 35 700 deaths annually, and an associated annual drug cost of >$1.4 billion US.[1,2] With an aging population and the trend to earlier detection, the impact of prostate cancer on the healthcare system is likely to increase in significance.

Approximately 70% of prostate cancer patients have localized disease (stages 0–I and II) at the time of the diagnosis, while 20% may already have advanced disease (stages III and IV), with approximately half of the cases being metastatic.[3] Localized disease is potentially curable with radical prostatectomy or radiation. However, up to 20% and 35% of patients after surgery and radiation, respectively, may have disease recurrence.[4] Metastatic prostate cancer is not curable and is mainly managed symptomatically with androgen suppression, either by orchiectomy or pharmacologic agents. Historically, estrogen in the form of diethylstilbestrol is an effective agent for androgen suppression, but is associated with significant cardiovascular toxicity. It has been largely replaced by the safer luteinizing-hormone releasing hormone (LHRH) agonists, which can be used alone or with an antiandrogen (androgen-receptor antagonist). Although the response rate to androgen suppression is >90%,[5] the median duration of response is only approximately 18 months.[6] Over time, most patients develop disease progression. Currently, there are few effective treatments for androgen-independent prostate cancer.[7]

Complementary and alternative medicine is used in approximately 30–40% of prostate cancer patients.[8] PC-Spes, a patented herbal formulation (BotanicLab, Brea, CA), has been available as a nutritional supplement since 1995 and is popular among prostate cancer patients.[9] It is supplied as 320-mg gelatin capsules made of extracts from 8 herbs which, according to the manufacturer, "have been documented in many plant pharmacopeias for their anti-tumor, antiviral, and immune stimulating activity." The product label recommends 3–6 capsules per day for "prostate health."[10]

The in vitro and animal data of PC-Spes have been reviewed elsewhere.[11] Given that herbs can have significant pharmacologic effects, healthcare professionals need to be

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aware of the current clinical data of this popular herbal product used for a common disease.

Literature Review

A search on MEDLINE (1966–October 2001), PubMed, and Proceedings of the Annual Meeting of the American Society of Clinical Oncology (ASCO) (1995–2001) was conducted in October 2001. Search terms used were PC-Spes (all fields), PC Spes (all fields), and a combination of the medical subject heading prostatic neoplasms with plant extracts, Chinese herbal drugs, Chinese traditional medicine, Oriental traditional medicine, medicinal plants, herbs, and alternative medicine.

The interpretation of study results on metastatic prostate cancer is associated with several difficulties. Only 20–30% of patients have measurable soft-tissue lesions, while bone lesions, although more common, are difficult to measure. Serum prostate-specific antigen (PSA) is a popular surrogate marker for measuring response to treatment in prostate cancer. However, various criteria have been used to define PSA response. In addition, androgen-independent prostate cancer may be defined differently in different clinical trials. Hence, the National Cancer Institute Prostate-Specific Antigen Working Group criteria[12] were used to help evaluate the data of PC-Spes. Specifically, these criteria were used to assess the PSA response (Table 1) and androgen-independent disease with no measurable soft-tissue lesions or difficult-to-measure bone lesions.

Androgen-independent disease is defined as disease progression (either of measurable lesions or PSA) despite castration concentration of serum testosterone (<50 ng/mL). Any antiandrogen (i.e., androgen-receptor antagonist) should also be stopped prior to starting a new therapy, since this may cause paradoxical clinical and PSA responses in 21% of patients, with a median response of 3.5–5 months.[12] Ideally, androgen-independent patients should continue their androgen suppression (e.g., LHRH agonists) while being treated with a new therapy, although this is not required in the PSA Working Group guidelines. Continued androgen suppression has 2 theoretical merits. First, it can prevent regrowth of any androgen-dependent prostate cancer cells.[7] Secondly, it makes it easier to ascertain that a response to a new therapy is due to its activity against androgen-independent cancer cells and not the regrowth of androgen-dependent cells.

Clinical Trials

No randomized controlled trials were found. Seventeen clinical reports were identified: 11 published articles,[13-22] 5 ASCO abstracts,[23-27] and 1 conference presentation[28] (Table 2). Data from the 5 abstracts[23-37] were derived from 3 published reports.[13,16,18] Data from 2 studies[19,20] were included in 1 follow-up report.[15] In addition, 2 surveys[9,29,30] by a patient support group were found. Since these surveys were not clinical reports, their data are presented separately.

A total of 205 patients were included in the clinical reports, with 98% having metastatic disease.[13,15-18,21,22,28] All studies were uncontrolled case series, with data collected prospectively in all but 1 study.[18] Daily intake of PC-Spes ranged from 3 (34%)[15,20] to 9 capsules (43%),[14,16,17,22] usually in 3 divided doses (76%).[15-17,22] Two patients were reported to be taking 12 capsules daily.[21,22] One study[16] specified that the PC-Spes capsules used were from a single batch. Sixty-two percent of the patients were followed for 5–10 months, with 34% followed up to 16 months[16] and 2 patients for approximately 2 years.[20] All studies used a decline of PSA as the primary response endpoint, with 54% of the patients fulfilling all the PSA Working Group criteria for PSA response.[16-18]

Data on 105 androgen-dependent patients were reported. PSA response was seen in 90% of the patients,[13-16,28] and the onset of response was 1–2 months.[13-15] Based on data for 34% of the patients, the duration of PSA response was approximately 14 months.[16] One patient experienced disappearance of a measurable bladder mass.[16] Serum testosterone concentrations were measured in 40 patients (38%), all of whom had decreased concentrations during PC-Spes therapy, with 34 (85%) reaching castration concentrations. The onset and duration of castration testosterone concentrations were found to correlate with the onset and duration of PSA response.[13,16]

Data on 100 androgen-independent patients were reported.[15-18,21,22] One case report[21] described only the toxicity and was therefore excluded in the denominator for assessing the efficacy. Seventy-seven patients (78%) had documented PSA progression despite prior androgen suppression,[16-18,20,22] with confirmed castration testosterone concentrations in 37 (37%). Sixty-two patients (63%) had stopped antiandrogen (i.e., androgen receptor antagonist) prior to PC-Spes,[16,18,20] and 54 (55%) were continued on androgen suppression (e.g., LHRH agonists) during PC-Spes therapy.[16,17,22] PSA response was seen in 65 patients (66%),[15-18,22] with individual study response rates ranging from 50% to 80%.[15-18] The onset of PSA response was similar to that seen in androgen-dependent patients. The median duration of PSA response was estimated to be 2–4.5 months.[16-18] In addition to PSA response, improved quality of life and pain relief

Table 1. Criteria for PSA Progression, PSA Response, and Duration of PSA Response[12]

Response Measures	Criteria
PSA progression	2 consecutive increases in PSA ≥1 wk apart PSA values ≥5 ng/mL
PSA response	PSA decline ≥50%, confirmed by a second PSA ≥4 wk later baseline PSA measured within 2 wk of new therapy no clinical or X-ray evidence of disease progression during PSA response
Duration of PSA response	from the first confirmed PSA decline of ≥50% until PSA has increased to 50% above the nadir

PSA = prostate-specific antigen.

were seen in 16 patients,[17] while improvement in symptom control was reported in 5 patients (5/13).[26] In one study,[16] 2 of 25 patients reported improvements in measurable bone lesions.

Most common adverse effects were mild and related to androgen suppression (Table 3).[13-19,21,22,28] Bone mineral density in 33 patients was unchanged after 1 year of follow-up.[27] However, 11 patients (5%) reported serious cardiovascular events over approximately 12 months of follow-up: 4 venous thrombosis,[13,17,19] 4 pulmonary embolism,[16,28] 2 peripheral edema,[14,18] and 1 angina[18] (Table 3). The incidence of thromboembolic events was 4% (3/70) in one study[16] that excluded patients with prior cardiovascular events.

Two cases of serious abnormal bleeding were reported.[21,22] Both patients had metastatic disease and had no previous or family history of abnormal bleeding or bruising. The first patient[21] self-medicated with unspecified multivitamins and PC-Spes 12 capsules daily for 1 month. He presented with syncope, tachycardia, epistaxis, hematuria, bloody stools, extensive ecchymoses, and a large retroperitoneal hematoma. Laboratory tests showed prolonged bleeding (prothrombin time >106 sec, activated partial thromboplastin time >120 sec) and a serum warfarin concentration of 0.69 µg/mL (therapeutic range 2–8). The patient fully recovered after PC-Spes was stopped and treatment with blood transfusion and vitamin K was started. The authors did not rechallenge the patient, but found a serum warfarin concentration of 0.87 ± 0.2 µg/mL in mice fed PC-Spes 500 mg/kg for 3 days.

The second patient[22] self-medicated with PC-Spes 9 capsules daily concurrent with LHRH agonist therapy. He developed self-limited epistaxis and bruises 9 days after he started taking PC-Spes. Two months later, he increased his PC-Spes daily dose to 12 capsules when his PSA continued to rise. One month after increasing his PC-Spes dose, the patient presented with uncontrolled epistaxis for 2 days and multiple ecchymoses. Laboratory tests showed thrombocytopenia, hypofibrinogenemia, prolonged bleeding (international normalized ratio 2.1), and increased D-dimers. The patient was diagnosed as having disseminated intravascular coagulation and fully recovered over the 2–3 weeks after PC-Spes was stopped.

Two surveys of patients taking PC-Spes were conducted by a patient support group through mailed questionnaires. An unknown number of respondents to the first survey[9,29] was included in the second survey.[30] Hence, the response and adverse event rates in these 2 surveys are based on overlapping patient data. Results of the first survey were published in 2 reports[9,29] and included updated data on 62 of the original 85 patients 2 years later.[9] The median daily PC-Spes dose used was approximately 6 capsules. Using unspecified PSA decline as endpoint, 75 patients (88%) reported a response to PC-Spes.[29] The response rates in patients never treated with androgen suppression was 97%.[9,29] The initial and follow-up response rates in patients with prior androgen suppression was 81%[29] and 85%,[9] respectively. The second survey reported data on 137 patients, 62% of whom had never been treated with androgen suppression.[30] The median PC-Spes daily dose used was similar to that in the first survey. Using unspecified PSA decline or stable PSA as endpoint, 128 of 137 patients (93%) reported a response to PC-Spes. Eighty-eight patients

Table 2. Summary of Studies

Population	PC-Spes Therapy	Response Rates	Reference
n = 8, AD: prior response to AS	4 capsules/d × >6 wk	PSA decline ≥50%: 100%, onset at 1 mo; castration testosterone concentrations: 38% of pts.	13,23
n = 1, AD: untreated localized disease	4–9 capsules/d × 7.5 mo	PSA decline ≥50%: onset at 3 wk, duration >7.5 mo	14
AD (n = 47): 4 localized untreated; 43 "received prior cryotherapy, radiation therapy, hormone therapy, and/or radical prostatectomy"	1 capsule tid × 8.5 mo	PSA decline ≥50%: 88% at 12 mo, onset at 2 mo	15,19,20
AI (n = 22): progression despite AS	1 capsule tid × 8.5 mo	PSA decline ≥50%: 74% at 6 mo, onset at 2 mo	
AD (n = 33): testosterone >120 ng/mL, no prior AS (except neo/adjuvant)	3 capsules tid × 64 wk	PSA decline ≥50%: 100%, duration >57 wk; measurable disease: 1 patient (1/3); castration testosterone concentrations: 97% of pts.	16,24,25,27
AI (n = 37): progression despite castration testosterone concentrations and antiandrogen withdrawal; AS continued during PC-Spes	3 capsules tid × 64 wk	PSA decline ≥50%: 54%, duration 18 wk; measurable disease: 2 pts. (2/25)	
n = 16, AD	unspecified daily dose × 6 mo	PSA decline ≥50%: 100%	28
n = 16, AI: progression despite AS; AS continued during PC-Spes	3 capsules tid × 5 mo	PSA decline ≥50%: 81%; pain relief: 100%; improved quality of life: 100%	17
n = 23, AI: progression despite AS and antiandrogen withdrawal	3 capsules bid × 10 mo	PSA decline ≥50%: 52%, median duration 2 mo; symptom control: 5 pts. (5/13)	18,26
n = 1, AI: described as "hormone-refractory"	12 capsules/d × 1 mo	response data not reported	21
n = 1, AI: progression despite AS; AS continued during PC-Spes	3 capsules tid × 2 mo, then 4 capsules tid × 1 mo	PSA continued to rise during PC-Spes	22

AD = androgen-dependent; AI = androgen-independent; AS = androgen suppression; PSA = prostate-specific antigen.

(64%) also reported PSA of <5 ng/mL after taking PC-Spes, although their baseline PSA values were not specified.

Adverse events reported were similar in both surveys. Reduced libido was reported in "most" patients.[9,30] Gynecomastia was reported in 40–60% of patients in the first survey[9] and was present in most patients in the second survey.[30] Leg cramps were reported in 31 of 127 patients (23%) in the second survey. Seven patients (11%) reported cardiovascular events in the first survey, including 4 cases (6%) of thromboembolism.[9] Eleven patients (8%) reported thromboembolic events in the second survey: 10 venous thrombosis and 1 pulmonary embolism.[30] Five of these cases were previously reported in the first survey.[9]

Discussion

PC-Spes is an herbal product that has been shown to produce PSA response in prostate cancer patients over approximately 1 year of follow-up. Like most complementary and alternative medicines, the available data on PC-Spes came predominantly from case series of poorly defined methodology.

A PSA response rate of 80–90% was consistently seen in androgen-dependent patients.[9,13-16,28-30] Although some reports had small numbers of patients[13,14,28] or unclear methodology,[9,13-15,28-30] the consistent response rates observed suggest that its effect on androgen-dependent patients may be significant at least over the first year of treatment. One probable mechanism of action of PC-Spes is through androgen suppression, since 90% of the patients developed loss of libido. In addition, 85% of the patients whose serum testosterone was measured reported castration concentrations during PC-Spes treatment, which appeared to correlate with PSA response.[13,16] The PSA response in turn was associated with improvements in quality of life,[17] pain relief,[17] symptom control,[18,26] and measurable disease[16] in some patients.

PC-Spes also appears to be beneficial in 65% of the androgen-independent patients.[15-18] However, response rates varied from study to study, with some reported as 50%[16,18] and others as high as 80%.[9,15,29] A possible explanation for this inconsistency is that various criteria were used to define androgen-independent disease in different studies. Indeed, <40% of the patients fulfilled all of the PSA Working Group criteria.[16] Similarly, the high response rates in the patient surveys could be due to poorly defined patient population[9,29] and the exclusion of patients lost to follow-up.[9]

There are 2 possible explanations for the apparent efficacy of PC-Spes on androgen-independent disease. First, PC-Spes could have induced a response through androgen suppression in patients who were not truly androgen-independent.[9,15,17,29] For example, 62 of 99 patients (63%) described as androgen-independent were not confirmed with castration testosterone concentrations.[15,17,18,22] Other confounding factors such as antiandrogen withdrawal, continued androgen suppression, or confirmed PSA rise prior to study were also not documented in all patients.[15,17,22] Secondly, PC-Spes may have truly additional, androgen-independent, antitumor effects. This is supported by pre-clinical data[11,31] and the 54% response rate seen in a clearly defined cohort of 37 androgen-independent patients.[16]

PC-Spes appears to produce significant estrogenic effects, which may partly explain its therapeutic and adverse effects, although the presence of other nonestrogenic mechanisms cannot be excluded. The estrogenic activity of PC-Spes is supported by 4 observations. First, most patients reported breast tenderness and gynecomastia, which are commonly seen with estrogen therapy used in androgen suppression.[32] Second, the approximate 5% incidence of thromboembolic events of PC-Spes[9,13,15-17,19,28,30] is of a magnitude similar to that seen with estrogen.[33] Although one may argue that patients with prostate cancer or undergoing androgen suppression are at increased risk of thromboembolic events, the annual incidence associated with these competing risk factors is <1%.[33,34] Third, clinical response to PC-Spes was seen in both androgen-dependent and -independent patients. Similar activities have been shown with estrogen, which may induce response in androgen-dependent patients via androgen suppression[32] and in androgen-independent patients by increased tumor apoptosis.[7] Finally, in vitro estrogenic activity has been reported with ethanolic extract of PC-Spes[13] and 2 of its ingredients, licorice and *Panax pseudoginseng*.[35,36]

Most nonthromboembolic adverse effects reported with PC-Spes were mild, including loss of libido, gynecomastia, and leg cramps (Table 3). However, 2 cases of serious abnormal bleeding were recently reported.[21,22] The association of these events with PC-Spes was strong based on the timing, absence of competing causes (apart from prostate cancer), and recovery. In addition, in vitro anticoagulant activity has been observed with *Scutellaria baicalensis,* a PC-Spes ingredient and a coumarin.[37]

Overall, the short-term response rates to PC-Spes in androgen-dependent patients[13-16,28] were similar to those seen in the large, randomized, controlled studies of LHRH agonists.[33] However, PC-Spes efficacy was derived from small, noncomparative studies,[13-16,28] mostly under uncontrolled settings.[9,13-15,28,30] The adverse effects of PC-Spes seem to be related to androgen suppression and estrogenic activity. Given that it has significant cardiovascular toxicity and that there are no comparative data, PC-Spes cannot be recommended as an alternative to LHRH agonists for andro-

Table 3. Adverse Effects of PC-Spes

Adverse Effects	Incidence % (n = 204)
Loss of libido[13,14,16,28]	90[a]
Breast tenderness or gynecomastia[13-18,28]	64
Leg cramps[16,18]	25
Diarrhea[16,18]	15
Cardiovascular events[13-19,28]	5
Hot flashes[15,18]	3
Gastrointestinal upset[18]	3
Abnormal bleeding[21,22]	1

[a]Androgen-dependent patients only (n = 105).

gen suppression. For patients who have failed androgen suppression, PC-Spes is associated with a relatively good response rate. Although the number of patients studied was small and covered a short follow-up compared with data on other standard treatments,[7] PC-Spes may be a possible alternative in patients who have failed second-line hormonal therapy and who cannot tolerate chemotherapy. It is unclear at present whether patients with prior thromboembolism may be more predisposed to cardiovascular toxicity with PC-Spes. It is therefore prudent to advise against its use in this population. Similarly, patients at risk for hemorrhagic events should avoid PC-Spes. Given the popularity of complementary and alternative medicine among cancer patients, clinicians should always ask patients if they are taking PC-Spes as it may confound the efficacy and toxicity outcomes of standard or experimental therapies.

Several aspects of PC-Spes warrant further studies. First, individual ingredients of PC-Spes should be tested to ascertain their respective roles on androgen suppression, estrogenic effects, antitumor activity, and other pharmacologic effects in prostate cancer. Second, an optimal dosage based on pharmacokinetic parameters (e.g., bioavailability, elimination rate) and clinical response needs to be determined. Third, the efficacy of PC-Spes in androgen-independent patients needs to be confirmed with more patients and longer follow-up before it can be compared with other current standard treatments.[7] Finally, various pharmaceutical concerns need to be addressed, including chemical stability and more precise standardization of the quality and potency between batches by comparing individual components rather than the overall pattern with HPLC.[11] This is particularly important in view of 2 unpublished reports[38,39] of diethylstilbestrol found in some PC-Spes batches.

Summary

PC-Spes may induce PSA response in patients with androgen-dependent prostate cancer. However, it cannot be recommended as an alternative to standard androgen suppression due to lack of comparative data with LHRH agonists and its significant cardiovascular toxicity. Short-term, limited PSA response to PC-Spes may be seen in some androgen-independent patients. There may be a role for PC-Spes in androgen-independent patients who have no history of thromboembolism or abnormal bleeding and have failed second-line hormonal therapy and/or chemotherapy. If PC-Spes is used, it should be monitored for the same adverse effects as found in androgen suppression and estrogen therapy, as well as abnormal bleeding. Further studies are needed to verify the active ingredients, optimal dosage, efficacy in androgen-independent patients, and methods used for pharmaceutical quality assurance.

ADDENDUM: Since the preparation of this review, the US Food and Drug Administration had issued a warning in February 2002 that laboratory analysis of PC-Spes by the California Department of Health Services found it contained warfarin. BotanicLab, the manufacturer of the product, had voluntarily recalled PC-Spes nationwide.

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EXTRACTO

OBJETIVO: Determinar la efectividad y toxicidad del suplemento a base de hierbas llamado PC-Spes en pacientes con cancer prostático.

MÉTODOS: Búsqueda de literatura a través del sistema MEDLINE, PubMed, y extractos de los reuniones anuales de la Sociedad Americana de Oncología.

RESULTADOS: PC-Spes fue asociado a respuesta bioquímica y clínica en algunos pacientes con cancer prostático. El mecanismo de acción de PC-Spes parece estar relacionado a su actividad estrogénica. El perfil de toxicidad de PC-Spes es similar al de los supresores de androgenos y al estrógeno, incluyendo riesgo de tromboembolismo, sangramiento, disminución de líbido, y ginecomastia.

CONCLUSIONES: Se ha observado alguna efectividad asociada al uso de PC-Spes en el tratamiento de cancer prostático. Debido a la limitación de información, no se debe usarse para reemplazar la terapia estandar de supresión de andrógenos en los pacientes con tumores dependientes de andrógenos. PC-Spes puede tener un rol en pacientes que han fallado a tratamientos convencionales con enfermedad independiente de andrógeno y que no tengan historial de tromboembolismo o sangramiento anormal. La toxicidad de PC-Spes es similar a la de los supresores de andrógenos y estrógenos.

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RÉSUMÉ

OBJECTIF: Evaluer l'efficacité et la toxicité du produit de phytothérapie PC-Spes chez des patients atteints de cancer de la prostate.

REVUE DE LITTÉRATURE: Littérature repérée par une recherche sur MEDLINE, PubMed, et les résumés des congrès annuels de la société américaine d'oncologie clinique.

RÉSUMÉ: Le PC-Spes est aux Etats-Unis un complément alimentaire qui a été présenté comme favorisant la santé de la prostate. Aucun essai contrôlé à son propos n'est disponible. Une dizaine de séries ouvertes de faibles effectifs font état d'une réponse biochimique (antigène prostatique spécifique et testostérone) chez des patients atteints de cancers de la prostate prenant des doses variées de PC-Spes. Des améliorations cliniques ont également été rapportées chez quelques patients. Le mécanisme d'action semble lié à l'activité estrogénique.

CONCLUSIONS: Le PC-Spes a été associé à une certaine efficacité chez des patients atteints de cancer de la prostate. En raison de la faiblesse des données disponibles, il ne devrait pas remplacer la thérapeutique habituelle de suppression androgénique chez les patients atteints de cancers hormono-dépendants. Les auteurs estiment toutefois que le PC-Spes pourrait avoir un rôle après échec des traitements standards chez des patients atteints de cancers non hormono-dépendants et sans antécédents ni risques thromboemboliques ou hémorragiques. Le PC-Spes semble avoir un profil de toxicité semblable à la suppression androgénique ou à la thérapeutique par estrogènes. Des questions sérieuses restent en suspens à propos de la qualité pharmaceutique de ce complément alimentaire (contaminations alléguées par diéthylstibéstrol et warfarine) et des études pharmacologiques et cliniques de méthodologie adaptée sont indispensables.

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