LASEK, Patryk, KOWALCZYK, Klaudia, TRĄBKA, Natalia, LASOTA, Nina, SMERDZYŃSKI, Maciej, ŁACH, Katarzyna, ŚCIURKA, Kinga, DEMIDOWICZ, Gabriela, PANUCIAK, Kinga and KOZICKA, Karolina. Combined Anticancer Therapy for Prostate Cancer - Literature Review. Journal of Education, Health and Sport. 2024;60:104-117. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.60.007
https://apcz.umk.pl/JEHS/article/view/48179
https://zenodo.org/records/10663433

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).
The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.01.2023. Revised: 08.02.2024. Accepted: 15.02.2024. Published: 15.02.2024.

Combined Anticancer Therapy for Prostate Cancer – Literature Review

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Abstract:
Prostate cancers represent a significant health problem, and their etiology is complex and multifaceted. It is estimated that in 2018, 1.3 million new cases and 359,000 deaths due to prostate cancer were diagnosed. They constitute the second most common group of cancers and the fifth most common cause of cancer-related deaths in men worldwide. The present study encompasses a literature review aimed at conducting an analysis of the potential of combined anticancer therapy as a prospective method for enhancing treatment efficacy, minimizing side effects, and improving long-term survival outcomes for prostate cancer patients. Combinations of compounds such as sunitinib with docetaxel, carboplatin with paclitaxel, estramustine or flutamide with luteinizing hormone-releasing hormone agonists, as well as docetaxel in conjunction with dexamethasone and octreotide, have demonstrated synergistic effects and an augmentation of therapeutic effectiveness. It is noteworthy to emphasize the potential enhancement of docetaxel's anticancer activity with concurrent

administration of dexamethasone and octreotide, as well as combined therapy involving docetaxel, prednisone, and curcumin.

Key words: prostate cancer; neoplasm; combination therapy; docetaxel; sunitinib; carboplatin; paclitaxel; estramustine; flutamide; dexamethasone; octreotide; prednisone; curcumin; adjuvant therapy.

Aim of the study: The aim of this literature review is to analyze the potential of combined anticancer therapy as a prospective approach to enhance treatment effectiveness, minimize side effects, and improve long-term survival for patients with prostate cancer.

Materials and methods: A comprehensive literature search was conducted across multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search timeframe extended from January 2000 to December 2023. Keywords and phrases used in the search included specific terms relevant to the subject matter of the review. These terms were adapted according to the specific syntax and requirements of each database. Additionally, a manual search was conducted to identify articles from the reference lists of included studies, ensuring a thorough capture of relevant literature.

Introduction:

Prostate cancers represent a significant health problem, and their etiology is complex and multifaceted. It is estimated that in 2018, 1.3 million new cases of prostate cancer were diagnosed, and 359,000 patients died because of it. They constitute the second most common group of cancers and the fifth most common cause of cancer-related deaths in men worldwide [1]. Risk factors primarily include age, genetics, and hormonal factors, particularly elevated testosterone levels [2,3,4,5,6]. Environmental influence, a diet rich in trans-fatty acid, and hormonal factors such as decreased vitamin D levels have also been identified as potential determinants in the development of prostate cancer [7,8,9,10,11,12]. Combined anticancer therapy appears as a promising approach capable of improving treatment outcomes, minimizing side effects, and potentially enhancing the long-term survival prospects of patients [13,14,15,16,17,18]. Therefore, research on combined therapy for prostate cancer seems to be a key element in the progress of male reproductive oncology. The aim of this work is to provide a literature review of reports on the therapeutic potential of combined therapies that could be applied in the treatment of prostate cancers.

Sunitinib and docetaxel

Cumashi and colleagues [19] conducted research comparing the effectiveness of monotherapy with the use of sunitinib and docetaxel with the effectiveness of combination

therapy using both of these substances. They carried out studies using DU-145 human hormone-refractory prostate cancer xenografts in nude mice [19]. Sunitinib, an inhibitor of tyrosine kinase receptors involved in tumor growth, pathological angiogenesis, and metastasis [20,21], was evaluated at a pre-established effective dose of 40 mg/kg/day. Administered alone orally through gavage (p.o.) for 3 weeks, this agent caused a significant regression of the initial tumor volume (efficacy level = 59%) [19]. Whereas, docetaxel, exhibiting cytostatic activity through the inhibition of cell divisions [22], administered intravenously (i.v.) at doses of 10 and 30 mg/kg/week for 3 weeks, resulting in tumor reduction of 49% and 76%, respectively. In combination therapy, sunitinib with docetaxel was administered at a dose of 40 mg/kg (p.o.) and 10 mg/kg (i.v.), respectively. At the end of treatment with this combination, the tumor volume decreased by 75%, much more than with docetaxel alone at a dose of 10 mg/kg (49%) and sunitinib in monotherapy (59%) [19].

In the above study, the activity of docetaxel and sunitinib was also examined in tumors regrowing after exposure to three cycles of weekly docetaxel (30 mg/kg/week), followed by sunitinib (40 mg/kg/day), or vice versa, administering sunitinib for 3 weeks (40 mg/kg/day) and then docetaxel (30 mg/kg/week). The mean regrowth time from the lowest value to the pre-treatment volume was 10.4 weeks for the docetaxel-sunitinib sequence and 0.5 weeks for the sunitinib-docetaxel sequence, indicating that as a first-line treatment, docetaxel is more effective in delaying tumor regrowth than sunitinib. It was also observed that regardless of the sequence used, each drug similarly inhibited tumor regrowth [19]. The findings from this study suggest the need for clinical trials to assess novel approaches in treating advanced hormone-resistant prostate cancer (HRPC).

Carboplatin with paclitaxel

In 2019, Fujiwara and co-workers published a study focusing on the efficacy and safety of using carboplatin (which induces DNA and mitochondrial damage, endoplasmic reticulum stress, up-regulates micro-RNA activity, and enhances intrinsic apoptosis [23]) with paclitaxel (which interferes with the normal microtubule growth through hyper-stabilize its structure and contributes to destroying the cell's ability to use its cytoskeleton in a flexible manner [24,25]) as first, second, and third-line chemotherapy in men with castration-resistant prostate cancer (CRPC) [26]. Data were collected from 58 patients with CRPC (excluding those with neuroendocrine prostate cancer) who received the carboplatin and paclitaxel regimen at Kyoto University between 2001 and 2018. Patients were i.v. treated with paclitaxel at a dose of 175 mg/m^2 of body surface area over a 3-hour infusion, followed by carboplatin (area under the curve 5 mg/ml/min) every day of a 28-day cycle. Treatment was continued until tumor progression or the occurrence of severe adverse events in patients. Twenty-seven patients underwent first-line chemotherapy with carboplatin-paclitaxel before docetaxel, 21 received carboplatin-paclitaxel as second-line chemotherapy after docetaxel and before cabazitaxel (it binds to the N-terminal amino acids of the beta-tubulin subunit and promotes microtubule polymerization while simultaneously inhibiting disassembly; this results in the stabilization of microtubules, preventing microtubule cell division [27]), and 10 received carboplatin-paclitaxel as third-line chemotherapy after docetaxel and cabazitaxel

[26]. In patients undergoing treatment with the carboplatin-paclitaxel regimen across different lines of therapy, the proportion experiencing a reduction of 50% or more in prostate-specific antigen (PSA) levels varied. Specifically, 55.6% of patients in the first-line treatment, 19.0% in the second-line, and 10.0% in the third-line achieved this level of PSA reduction at any point during treatment. Furthermore, a PSA response of 50% or greater after 12 weeks was noted in 48.1%, 14.3% and 10% patients in whom carboplatin-paclitaxel was used as the first-, second- and third-line of anticancer therapy, respectively. The researchers also observed an exceptional response in one out of ten patients who received carboplatin-paclitaxel as third-line chemotherapy [26]. In this particular clinical case, there was a remarkably good response to carboplatin-paclitaxel chemotherapy despite prior resistance to both docetaxel and cabazitaxel treatments. The PSA reduction of ≥50% persisted for over 8 months without evidence of radiological or clinical progression [26]. Subsequent studies identified a heterozygous, deleterious nonsense mutation in the tumor suppressor gene BRCA2 (5645C>A; S1882*), responsible for DNA damage repair in the patient's body. These findings highlight the significant efficacy of first-line carboplatin-paclitaxel therapy in treating patients with CRPC and the potential effectiveness of a novel treatment approach for patients with a heterozygous, deleterious nonsense mutation in the BRCA2 gene (5645C>A; S1882*) [26].

Estramustine phosphate and flutamide with luteinizing hormone-releasing hormone (LHRH) agonist

Noguchi and colleagues [28] conducted a comparative analysis of the effectiveness of combined therapy with luteinizing hormone-releasing hormone (LHRH) agonist and estramustine phosphate, which alkylates DNA and in consequence leads to apoptosis and cell death [29], versus flutamide – nonsteroidal antiandrogen that blocks the action of both endogenous and exogenous testosterone by binding to the androgen receptor and potent inhibitor of testosterone-stimulated prostatic DNA synthesis [30], in patients with newly diagnosed and pathologically confirmed prostate adenocarcinoma (stages D1 or D2) according to the American Cancer Society Classification. Patients previously treated with orchidectomy, hormones, anticancer chemotherapy, or radiotherapy were excluded. Additionally, patients with an Eastern Cooperative Oncology Group performance status greater than 3, brain metastases, an expected life span less than 3 months, another malignancy, or severe comorbidities (renal, hepatic, cardiovascular, or neuropsychiatric disorders) were ineligible for the study [28]. Enrolled patients (57) were then divided into two groups and were treated with either (I) oral administration of 280 mg estramustine phosphate twice daily or (II) oral administration of 125 mg flutamide three times daily. Concurrently, both therapies included LHRH antagonists (goserelin acetate 3.60 mg depot or leuprolide acetate 3.75 mg depot) administered subcutaneously every 4 weeks. The median observation time for both groups was 26 months (range 3–56 months). Both treatment regimens were well-tolerated, and the incidence of adverse events was similar. The overall response rate (complete and partial response) after 12 weeks of treatment in the estramustine and flutamide groups was 76% and 55%, respectively. The median time to objective progression in the estramustine group (25.4 months) was longer than in the flutamide group (14.6 months). Moreover,

follicle-stimulating hormone and testosterone serum levels were significantly lower in the estramustine group. Progression-free survival rates were consistently higher in the estramustine group compared to the flutamide group. However, no significant differences were observed in overall survival and time to death due to prostate cancer between the groups, as determined by log-rank statistical analysis [28]. The results of the cited studies are promising, however, as the authors emphasize to determine whether the former regimen offers greater benefits compared to the latter for newly diagnosed patients with advanced prostate cancer, a trial on a larger scale with increased statistical power is necessary for clearer insights.

Docetaxel with dexamethasone and octreotide

The research carried out by Dalezis et al. [31] demonstrated that combining dexamethasone and octreotide with docetaxel therapy enhances its efficacy against prostate cancer in the transgenic prostate cancer cells of mice (TRAMP-C1) model. Single treatment regimens showed that the invasion capacity of TRAMP-C1 cells was inhibited by 7.8% with dexamethasone (inhibitor of neutrophil apoptosis and demargination, which in lower doses provides an anti-inflammatory, while in higher doses an immunosuppressive effect [32]), 25.5% with octreotide (suppressor of luteinizing hormone [33]), and 13.2% with docetaxel. Further experiments with simultaneous application of different concentration ratios of tested substances provided evidence of their important synergistic action in vitro. Specifically, the triple combined treatment regimen (dexamethasone + osctreotide + docetaxel) significantly reduced the required concentration of doxetaxel for maximum inhibition of TRAMP-C1 cell growth [31].
Dalezis et al. [31] also investigated the in vivo impact of dexamethasone, octreotide, and docetaxelin monotherapy and combinations on reducing the degree of bone damage induced by TRAMP-C1 cells in male C57B1 mice. In the placebo group, imaging studies revealed bone damage of grade C (100%) in the animals. A single docetaxel treatment regimen reduced the degree of bone changes to grade C (20%) and B (80%), which was most effective compared to any other single treatment regimen. Furthermore, the combined use of dexamethasone and octreotide yielded a good response in bone assessment, similar to docetaxel [grade B (80%) and grade C (20%)]. Neoadjuvant application of dexamethasone + octreotide before docetaxel treatment further improved the anticancer effectiveness of both the single docetaxel treatment regimen and the combined dexamethasone + octreotide regimen, reducing the degree of bone changes to C (20%), B (60%), and preventing the development of bone changes in 20% of TRAMP-C1-inoculated animals [31]. These findings indicated that neoadjuvant administration with a combination of dexamethasone and octreotide may enhance the therapeutic impact of docetaxel on the TRAMP-C1 prostate cancer model. In the future, this may contribute to more effective and safe treatment of patients suffering from prostate cancer.

Docetaxel or prednisone and curcumin in patients with castration-resistant prostate cancer (CRPC)

In 2016, Mahammedi and colleagues presented their phase II study on combination therapy with docetaxel or prednisone and curcumin in patients with CRPC [34]. Thirty adult patients (median age 69 years, range 58-83) from three French centers with progressive CRPC and rising PSA received docetaxel at a dose of 75 mg/m^2 of body surface area as a 1-hour i.v. infusion every 21 days for 6 cycles. Premedication with dexamethasone at a dose of 8 mg was administered 12, 3, and 1 hour before the docetaxel infusion. All patients also received oral prednisone or prednisolone at 5 mg twice daily throughout the 21-day cycle starting from the first day. Purified oral curcumin, a yellow pigment of turmeric (Curcuma longa) with proven potential as a chemopreventive agent and beneficial effects on all stages of carcinogenesis [35,36,37], was formulated into 500 mg capsules, each containing 450 mg of curcumin, after evaluation by high-performance liquid chromatography and tandem mass spectrometry. Each patient received 6000 mg of curcumin daily for 7 consecutive days in each cycle (from day -4 to day +2, day 0 was the day of chemotherapy administration). The researchers aimed to "saturate" the body in the period before and after chemotherapy, avoiding continuous curcumin treatment.
An objective PSA response (a decrease in serum PSA levels by at least 50%) was achieved in 17 patients, constituting 59% of the participants. Normalization of PSA was observed in 14%, PSA levels remained stable in 34% of patients, and progression was noted in 7%. Most participants exhibited a rapid PSA response (median time to response was 1.38 months, range 0.53-5.50). In 15 patients, the response occurred within the first three cycles. Among men enrolled in the study, 6 experienced a PSA decline of 50-80%, and 11 a decline of > 80%. The median duration of the PSA response was 4.7 months [34]. This research provided further evidence supporting the use of curcumin in cancer therapy, demonstrating a significant response rate, favorable tolerability, and high patient acceptability. These findings may become an inspiration to undertake further research on the effectiveness and safety of adjuvant therapy with curcumin in patients with prostate cancer.

Conclusions

The results presented in the above literature review indicate a promising potential for combination anticancer therapy in the treatment of prostate tumors. Combinations of substances such as sunitinib with docetaxel, carboplatin with paclitaxel, estramustine or flutamide with LHRH agonists, and docetaxel in combination with dexamethasone and octreotide demonstrate synergistic effects, enhancing therapeutic efficacy. It is worth noting the potential intensification of the anticancer effects of docetaxel through simultaneous therapy with dexamethasone and octreotide, as well as combined therapy with docetaxel, prednisone, and curcumin. However, due to the complexity of the mechanisms of action and the heterogeneity of prostate tumors, further clinical research is needed to better understand the optimal combinations of drugs, doses, and therapeutic sequences. This will enable the development of a more personalized approach to the treatment of various prostate cancer entities.

Disclosure

The authors declare that they have no financial or non-financial conflicts of interest that could influence the interpretation of the study results or the content of this manuscript. This work was carried out independently, without external funding or support.

Author's contribution

Conceptualization: PL

Methodology: PL, KK, MS

Software: GD

Checked by: NT, KK, NL, KP

Formal analysis: KŁ

Investigation: PL

Resources: KŚ

Data storage: PL

Writing – rough preparation: PL, NL

Writing – review and editing: KK, NT, MS,KŁ, KŚ, GD, KP, KK

Visualization: PL, GD

Supervision: KKO

Project administration: PL

Obtaining financing: Not applicable

All authors have read and agreed with the published version of the manuscript.

Financing statement

The authors declare that there are no conflicts of interest or financial disclosures associated with this scientific work.

Institutional Review Board Statement

Not applicable

Statement of informed consent

Our work did not involve direct research on humans or obtaining their consent to participate in the study.

Data Availability Statement

As a review, our work does not contain new data or analyses. Therefore, there are no specific data sets or data availability for reporting. The information and findings presented in this review are based on previously published research, which can be accessed through the appropriate sources cited in the reference section.

Declaration of conflict of interest

The authors declare that there are no significant conflicts of interest related to this research work.

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