HORMONAL THERAPY COMBINED WITH RADIOTHERAPY IN LOCALLY ADVANCED PROSTATE CANCER

Piotr Milecki[1], Zbigniew Kwias[2]

[1]Department of Radiotherapy, Great Poland Cancer Centre, ul. Garbary St. 15, 61-866 Poznań, Poland
[2]Chair of Urology, University School of Medical Sciences, ul. Kurlandzka St. 1, 61-650 Poznań, Poland

Received June 04th, 2002; received in a revised form July 30th, 2002; accepted October 10th, 2002

ABSTRACT

At present radiation therapy and radical prostatectomy are considered to be the treatment of choice for clinical T1-T2 prostate cancer. In a more advanced stage of the disease (T3) 10-year overall survival is observed in approximately 40% of patients treated with conventional radiotherapy. So far only a few methods for improving the efficacy of radiotherapy have been introduced. One of them is a three-dimensional conformal radiotherapy with 3 dimensional treatment planning. These novel methods make it possible to escalate the dose to the target and protect healthy tissue at the same time. The optimal volume of irradiation, total dose, fraction dose, techniques of radiotherapy, and the end points used during the follow-up are open to debate. In recent years a few clinical trials involving hormonal therapy and radiotherapy have been carried out. The most important of these are: RTOG 8307, RTOG 8610, RTOG 9202, and EORTC 22863.

In the RTOG 8307 trial the comparison of outcomes of a combined treatment with a matched-control group of patients treated by radiotherapy alone has shown that adding hormonal therapy to radiotherapy resulted in a better outcome. Another trials RTOG 8531 and RTOG 8610 produced benefit due to the implementation of hormonal therapy in radiotherapy. The EORTC trial No. 22863 showed improvement in the 5-year overall survival when hormonal therapy after the completion of radiotherapy was continued for 3 years in the investigational arm. The RTOG 9202 study indicated benefit obtained from 2 years of adjuvant hormonal therapy.

The results of these trials have had a substantial impact on the management of locally advanced prostate cancer, but there are still questions that have to be answered. There is no doubt that hormonal therapy is an important component of the management of locally advanced prostate cancer. Still the optimal combination of drugs and the timing of such treatment remains controversial. Considering the potential side effects of a combined treatment on the quality of life of patients and care costs, additional properly designed randomised trials are needed to identify the subgroup of patients who will obtain the greatest benefit. Currently, it can be concluded that in the group of patients with a high risk of relapse by adding hormonal therapy to radiotherapy the outcome of treatment in patients with prostate cancer has improved.

Key words: prostate cancer, radiotherapy, hormonal therapy, combined treatment.

INTRODUCTION

From the urologist's point of view radical prostatectomy is a standard method of treatment in localized prostate cancer [1,2]. However, surgery is generally not an adequate mode of treatment for the advanced stage of the disease. In patients with locally prostate cancer the external beam radiation therapy, especially, 3-dimensional conformal radiotherapy (3D CRT) is a treatment which can provide the same results as surgery. Additionally, 3D CRT reduces side effects [3,4,5]. The third mode of treatment in patients with prostate cancer is hormonal therapy. This modality alone has generally only a palliative effect but in combination with radiotherapy it may lead to a cure or influence the prolongation of survival in the majority of patients. Based on the earliest studies carried by Huggins and Hodges [6], the male hormones are known to promote the growth of both prostate gland and cancer cells. The main androgen involved in the stimulation of growth of the prostate and cancer cells is dihydrotestosterone (DHT). Generally, hormonal the-

rapy refers to any treatment that reduces the level of biological activity of male hormones. Two mechanisms involved in androgen suppression strategy of treatment are distinguished. The first leads to eliminating the production of testosterone in testis by surgical castration (bilateral orchiectomy) or by chemical castration (LHRH analog). The latter mechanism gained popularity during the last few decades when LHRH analogs (Lutenazing Hormone Realizing Hormone) were introduced into clinical practice. However, the effects of LHRH agonists are limited to the blockage of testicular androgens, similar to surgical castration [7]. They cause the pituitary desensitisation and inhibition of sex steroid production. Agonists do not influence the production of dehydroepiandrosterone (DHEA) and dehydroepiandrosterone-sulfate (DHEA-S) by adrenal glands**.** Another group of drugs which is very popular in the treatment of patients with prostate cancer is antiandrogen medication. Mechanism of action of this class of drugs involves blocking of the intracellular androgen receptor, which is located in the tumour cell [8]. Currently, two groups are in clinical usage: steroidal (cyproterone acetate - CPA, medroxyprogesterone acetate - MPA) and nonsteroidal (flutamide and its metabolites such nilutamide and bicalutamide - Casodex).

Steroidal antiandrogens have a progesterone-like effect, which causes a decreease in the release of LH by the hypophysis. The non-steroidal antiandrogens block the binding of dihydrotestosterone with the intracellular androgens receptor.

There is general agreement that symptomatic men with a metastatic disease should receive hormonal therapy. Although, hormonal therapy for an advanced stage of cancer (metastatic) is not a curative method of treatment, but it may lead in some cases to the prolongation of the patient's life and improvement of the quality of life [9].

THE POSSIBLE MECHANISM OF INTERACTIONS BETWEEN ANDROGEN DEPRESSION AND RADIOTHERAPY

The idea that the addition of an androgen ablation therapy to radiotherapy may improve the results of combined treatment is based on earlier experience in the application of neoadjuvant hormonal therapy with surgery [10]. Neoadjuvant surgical trials have showed response rates (reduction in tumour volume) approaching 90% when hormonal treatment prior to surgery was applied, with both the prostate and the tumour becoming smaller. The result of such modality leads only to a reduced number of positive postoperative margins after radical prostatectomy without any influence on the patient's overall survival [11].

Androgen deprivation improved the outcomes of combined treatment as a result of local and systemic actions, which are represented by hormonal therapy. The mechanism of interaction between hormonal therapy and radiotherapy has not been precisely established, but the following areas of interaction can be identified:

1. Local interactions:
   (a). Androgen deprivation treatment leads to the shrinkage in the size of the entire enlarged prostate gland. It has a very practical implication for radiotherapy treatment. First, the dimensions of fields used in radiotherapy could be smaller, which would allow for administering a higher total dose with the decrease in side effects in a healthy tissue [12]. Data from numerous papers indicate that neoadjuvant hormonal therapy result in a substantial tumour volume reduction ranging from 30 to 40 % [13]. Substantial prolongation of hormonal therapy beyond 6 months gives only a slight reduction in volume.
   (b). The decrease in the number of clonogenic cancer cells due to androgen ablation therapy should lead to the enhancement of radiotherapy effects in the tumour at the same range of doses [14].
   (c). It is known that the tumour of the prostate cancer contains malignant cells which exist in the environment with a low level of oxygen [15]. Androgen deprivation

treatment leads to a decrease in the amount of cancer cells in the tumour and thus the improvement of the blood flow could cause enhancement in the oxygenation [16].

(d). Apoptosis induced by hormonal therapy involves cancer cells in which apoptosis failed to be activated by radiotherapy [17].

2. Systemic interaction: androgen deprivation may prevents subsequent distant micrometastases [18].

THE MOST IMPORTANT CLINICAL TRIALS WHICH ASSESSED COMBINED TREATMENT

One of the first trials, which tried to answer the question of the influence of additional hormonal therapy on the outcome of treatment in locally advanced prostate was carried out by Zagars et al. [19]. According to the trial, radiotherapy alone was compared to the radiotherapy + adjuvant hormonal therapy (diethylostilbestrol). A 15-year disease-free survival (DFS) in the adjuvant estrogen group was strikingly and significantly higher than that in the radiation-alone group (63% vs. 35%). However, there was no improvement in the overall survival (OS) because of greater intercurrent disease-related mortality in patients receiving estrogens.

In another trial, RTOG 8307 [20], patients with stages T2b and T3 were entered into the study and randomised to receive megestrol acetate 40 mg three times daily, or diethylostilbestrol (DES) 1 mg three times daily. The treatment started 2 months prior to the beginning of irradiation and continued through the whole course of radiotherapy. It should be underlined that the assessment of pretreatment PSA in this study was not available. Another fact worth underlining is that the time of androgen ablation treatment was very short lasting only 4 months.

Recently, the outcomes from a few prospective randomised trials have indicated that combined treatment (androgen ablation plus radiotherapy) leads to the prolongation of overall survival. One of these well-documented trials was carried out by Pilepich et co-workers [21]. In this trial (RTOG 8531) the influence of androgen depletion with combination with radiotherapy on results of treatment was evaluated. Patients in this trial were randomised to receive radiotherapy alone or radiotherapy plus adjuvant goserelin acetate (LHRH agonist) which was introduced in the last week of radiotherapy. The hormonal therapy was continued until the progression of disease occurred, or as long as it was tolerated by the patient. Radiotherapy fields in the first phase of treatment covered of the lymph nodes of the pelvis with a dose of 44 – 50 Gy and then an additional dose of 20 – 25 Gy to the prostate was added. At the median follow-up of 4.5 years (range 0.2 - 9.8 years), the actuarial projections showed that 84% of patients on the combined-therapy arm and 71% of those on the RT-alone arm had no evidence of local recurrence ($p < 0.0001$). The update of RTOG trial 85-31 presented in 1999 with a median follow-up of 5.6 years for all patients and 6 years for patients who were alive, showed improvement in cause specific survival (CSS) in the group of patients treated with hormonal therapy ($p = 0.019$).

In the next RTOG 8610 study carried out by Pilepich et al. [22], patients received neoadjuvant (2 months) and then, during radiotherapy, androgen ablation (goserelin + flutamide) in the investigational arm, and radiotherapy alone in the control arm. The results of this trial indicated that patients in the combined-therapy group had a better local control, with 5- and 8-year failure rates of 25% and 37%, respectively, compared with 36% and 49% in the RT group ($p< 0.002$).

The results of the well documented randomised trial conducted by the EORTC 22863 came from Europe. The difference between this trial and the trials mentioned above mainly involved the time duration of the androgen depletion therapy. In this study reported by Bolla et co-workers [23], the results of treatment in the two group of patients were compared, whereas, only in the investigational arm post radiotherapy androgen depletion therapy (LHRH analog) was continued for 3 years. In the first phase of the trial in both arms,

hormonal therapy prior to radiotherapy and during the irradiation goserelin acetate (LHRH analog) and cyproterone acetate (150 mg per day/1 month) was employed. Patients in both groups received 50 Gy of radiation to the pelvis lymph nodes, and then an additional dose of 20 Gy to the prostate. This report was particularly valuable because it incorporated short neoadjuvant androgen ablation treatment with long-term adjuvant therapy. The results of the trial indicated that local control in the investigational arm (combined treatment) was 97% in comparison with 77% in the control arm (radiotherapy alone) during the 45 months follow-up. The 5-year overall survival in the combined treatment arm was 79% vs. 62% in the radiotherapy alone group, retrospectively.

Another very important study, reported by Laverdiere et al. [24], compared the following methods of treatment:

- radiotherapy alone,
- neoadjuvant combined androgen blockade (3 months) + radiotherapy,
- neoadjuvant combined androgen blockade (3 months) + radiotherapy + adjuvant combined androgen blockade (10.5 months).

Results of this study showed the advantage of neoadjuvant and adjuvant hormonal therapy. According to these results patients treated with a dose of 64 Gy in combined fashion noted 28% of positive biopsies compared with 65% treated with radiotherapy alone. However, the neoadjuvant androgen deprivation given 3 months before and 6 months after the radiotherapy was associated with only 5% rate of positive biopsies.

The data concerning the assessment of the influence of combined therapy on the outcome of treatment was based on the results of observation of 1554 patients who were entered in to the RTOG – 9202 trial conducted by Hanks et al. [25]. According to the trial's protocol all patients received goserelin and eulexin 2 months before and then during radiotherapy, and later, after the completion of radiotherapy, were randomised without any further therapy or were administered additional goserelin alone for 24 months. This trial showed some significant improvement in the local progression rate (6.2% vs. 13%), disease-free survival (54% vs. 34%), freedom from distant metastases (11% vs. 17%), and biochemical control (46% vs. 21%) in the group long-term hormonally treated patients. It should be noted that the subset analysis (T3, T4 and T2 with Gleason 8-10) showed no significant overall survival difference (77% vs. 80%) in the period of 5-years. The second subset analysis (patients with Gleason 8-10 versus the group of patients from RTOG 85-31 study) indicated therapeutic gain due to long-term androgen ablation therapy (80% vs. 69% during a 5-year follow up).

The observation on the addition of hormonal therapy to radiotherapy which results in a better outcome of treatment raises a number of questions:

1. PSA is the most important indicator of the biochemical relapse of radiotherapy during the follow-up of patients with prostate cancer. In prostate cancer the introduction of hormonal therapy may lead to a rapid biochemical response (decrease of PSA level), usually after 2 - 3 months from the beginning of the treatment, which, in the phase of follow-up, makes it difficult to assess the response of radiotherapy. On the other hand, it should be noted that even in the case of undetectable serum PSA level is it uncertain that cancer is eradicated [26].
2. Toxicity:
   Hormonal therapy produces many side effects such as gynecomastia, breast tenderness, and osteoporosis. Another aspect concerns the sexual function, which is significantly depressed due to hormonal therapy [27]. Another interesting issue is the increase in toxicity of combined treatment in the bone (head of femoral bone), especially as the androgen suppression treatment caused a higher risk of osteoporosis [28, 29]. Combined treatment (neoadjuvant and concurrent hormonal therapy plus radiotherapy) might lead to the decrease in the volume of the prostate gland during the course of radiotherapy, bringing more rectal mucosa into the high dose. So far we have had no evidence using a multivariable analysis that the use of neo-

adjuvant and concurrent androgen suppression therapy is a significant predictor of rectal bleeding.

3. Timing of hormonal therapy:
   The first aspect of this issue is the relative timing of ablation and radiation therapy. According to the trials mentioned above the minimum time to begin hormonal therapy before radiotherapy (neoadjuvant) both for external beam therapy and brachytherapy is approximately 3 months. This is probably enough to achieve volume reduction of the prostate gland. The second issue concerns the duration of hormonal ablation. Currently, this period of time is not defined and the optimal time probably depends on the risk factors of the disease. Generally, in a patient with a higher risk of failure longer time of hormonal therapy is required. Patients with an earlier stage of the disease may probably benefit from short-term hormonal therapy.
   What kind of androgen blockade should be preferred (maximum androgen blockade or androgen suppression only) in combination with radiotherapy? In advanced prostate cancer, the addition of antiandrogen to androgen suppression by surgery or drugs improved the 5-year survival by about 2% or 3%, depending on whether the analysis includes or excludes the cryptoterone. In many trials the control group (radiotherapy alone) in case of disease progression received androgens ablation. Thus in reality, these trials addersed the issue of early versus late androgen suppression.
4. Economical aspect of combined treatment:
   For example, in 1993, the Health Care Financing Administration spent $ 328 million alone for LHRH agonist therapy [31]. The addition of flutamide to castration added approximately $ 3,427 per year to the cost of treatment in patients with prostate cancer.

CONCLUSIONS

On the basis of the data from literature it could be concluded that:

1. Androgen deprivation therapy is easy to administer and requires no special technology. Neoadjuvant and adjuvant androgen deprivation is a standard treatment in conjunction with radiation therapy in the group of patients with a high risk of failure (T3, PSA>20ng/ml, Gleason >7). It could be stated that the therapeutic gain of combined treatment is probably higher when the combined treatment is applied to patients in the higher-risk group.
2. The optimal timing of the application of androgen depletion has still not been determined. Currently, approximately 3 months for neoadjuvant therapy is probably the optimal strategy. The best mode of neoadjuvant hormonal therapy is represented by castration (surgery or chemical), probably plus antiandrogen. Adjuvant hormonal therapy should be advised in high-risk patients, but the duration of this treatment has not been established precisely, the probable minimal time of treatment should be around 12 months. Thus far the studies have shown that there is survival benefit for patients with a more advanced disease with a longer androgen suppression treatment applied, but in the group of lower risk, patients may benefit from a short-term hormonal therapy.

REFERENCES

1. Chodak GW, Thisted RA, Gerber GS, Johansson JE, Adolfsson J, Jones GW, et al. Results of conservative management of clinically localized prostate cancer. N Engl J Med 1994; 330:242-8.

2. Catalona WJ. Surgical management of prostate cancer. Cancer 1995;75: 1903-8.

3. Shipley WU, Thames HD, Sandler HM, Hanks GE, Zietman AL, Perez CA, et al. Radiation therapy for clinically localized prostate cancer. A multi-institutional pooled analysis. JAMA 1999;281:1598-604.

4. Hanks GE, Hanlon AL, Schulthesiss TE, Pinover WE, Movsas B, Epstein BE, et al. Dose escalation with 3D conformal treatment: Five-year outcomes, treatment optimization, and future directions. Int J Radiat Oncol Biol Phys 1998;41:501-10.

5. Zelefsky MJ, Leibel SA, Gaudin PB, Kutcher GJ, Fleshner NE, Ventakramen ES, et al. Dose escalation with three-dimensional conformal radiation therapy affects the outcome in prostate cancer. Int J Radiat Oncol Biol Phys 1998;41: 491-500.

6. Huggins C, Hodges C. Studies on prostatic cancer: The effect of castration, of estrogen, and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. Cancer Res 1941;1: 293-7.

7. Garnick MB. Hormonal therapy in the management of prostate cancer: from Huggins to the present. Urology 1997 (supp 3A);49:5-15.

8. McConnell JD. Physiologic basis of endocrine therapy for prostatic cancer. Urol Clin North Am 1991;18:1-7.

9. Janknegt RA, Abbou CC, Bartoletti R. Orchiectomy and Anandron (nilutamide) or placebo as treatment of metastatic prostate cancer in a multinational double-blinded randomized trial. J Urol 1993;149: 119-30.

10. Soloway M, Sharifi R, Wajsman Z, Mc Leod D, Wood DP Jr, Puras-Baez A. Randomized prospective study comparing radical prostatectomy alone versus radical prostatectomy preceded by androgen blockade in clinical stage B2 (T2bNxM0) prostate cancer. J Urol 1995;154:424–8.

11. Aus G, Abrahamsson PA, Ahlgren G, Hugosson J, Lundberg S, Schain M, et al. Hormonal treatment before radical prostatectomy: A 3-year follow-up. J Urol 1998; 159:2016–7.

12. Zelefsky MJ, Harrison A. Neoadjuvant androgen ablation prior to radiotherapy for prostate cancer: reducing the potential morbidity of therapy. Urology 1997;49(suppl 3 A):38-45.

13. Marcenaro M, Sanguineti G, Franzone P, Corvo R, et al. Neoadjuvant androgen deprivation and prostate gland shrinkage during conformal radiotherapy. Int J Radiat Oncol Biol Phys 2001;51(ASTRO): 18-9.

14. Eulau SM, Corn BW. Combinations of hormones and local therapies in locally advanced prostate carcinoma. Oncology 1996;10:1193-202.

15. Movsas B, Chapman JD, Hanlon AL, Horowitz EM, Pinover WH, Greenberg RE, et al. Hypoxic regions exist in human prostate carcinoma. Urology 1999;53: 11-8.

16. Cvetkovic D, Movsas B, Dicker AP, Hanlon AL, Greenberg RE, Chapman JD, et al. Increased hypoxia correlates with increased expression of the angiogenesis marker vascular endothelial growth factor in human prostate cancer. Urology 2001; 57:821-5.

17. Pollack A, Salem N, Ashoori F, Hachem P, et al. Lack of prostate cancer radiosensitization androgen deprivation. Int J Radiat Biol Phys Oncol 2001;51:1002-7.

18. Zietman AL, Prince EA, Nakfoor BM, Shipley WH. Neoadjuvant androgen supperssion with radiation in the management of locally advanced adenocarcinoma of the prostate: experimental and clinical results. Urology 1997;49 (3A suppl): 74-83.

19. Zagars GK, Johnson DE, von Eschenbach AC, Hussay DH. Adjuvant estrogen following radiation therapy for stage C adenocarcinoma of the prostate: Long-term results of a prospective randomized study. Int J Radiat Oncol Biol Phys 1988; 14:1085-91.

20. Pilepich MV, Krall JM, John MJ, Rubin P, Porter AT, Marcial VA, et al. Hormonal cytoreduction in locally advanced carcinoma of the prostate treated with definitive radiotherapy: Preliminary results of RTOG 83-07. Int J Radiat Oncol Biol Phys 1989;16:813-7.

21. Pilepich MV, Caplan R, Byhart RW, Lawton CA, Gallagher NJ, Mesic JB, et al. Phase III trial of androgen supression using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: Report of Radiation Oncology Group Protocol 85-31. J Clin Oncol 1997;15:1013-21.

22. Pilepich MV, Winter K, Russell AH i wsp. Phase III Radiation Therapy Oncology Group (RTOG) trial 86-10 of androgen deprivation before and during radiotherapy in locally advanced carcinoma of the prostate (abstract 1185). Proc Am Soc Clin Onciol 1998;17:308a.

23. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and gosorelin. N Engl J Med 1997,337:295-300.

24. Laverdiere J, Gomez JL, Cusan L, Suburu ER, Diamond P, Lernay M, et al. Beneficial effect of combined therapy administered prior and following external beam radiation therapy in localized prostate cancer. Int J Radiat Biol Phys 1997; 37:247-52.

25. Hanks GE, Lu JD, Machtay M, et al. RTOG protocol 92-02: a phase III trial of the use of long term total androgen supression following neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate. Int J Radiat Oncol Biol Phys. ASTRO 2000;48:3,112.

26. D'Amico AV, Schultz D, Loffredo M, Dugal R, Hurwitz M, Kaplan I, et al. Biochemical outcome following external beam radiation therapy with or without androgen suppression therapy for men with clinically localized prostate cancer. JAMA 2000;284:1280-3.

27. Singer PA, Tasch ES, Stocking C, Rubin S, Siegler M, et al. Sex or survival: trade offs between quality and quantity of life. J Clin Oncol 1991;9:328-34.

28. Daniell HW. Osteoporosis after orchiectomy for prostate cancer. J Urol 1997;157: 439-44.

29. Daniell HW, Tam EW. Increased testicular atrophy following prostate bed radiation therapy for prostate carcinoma. Cancer 1998;83:1174-9.

30. Gee WF, Holtgrewe HL, Albersten PC, Litwin MS, Manyak MJ, et al. Practice trends in the diagnosis and management of prostate cancer in the United States. J Urol 1995;…:207-8.