Clin Transl Oncol (2010) 12:346-355
DOI 10.1007/s12094-010-0516-6

Evidence-based consensus recommendations to improve the quality of life in prostate cancer treatment

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Received: 2 September 2009 / Accepted: 18 October 2009

Abstract
Introduction Prostate cancer (PC) is one of the tumours with the highest incidence in recent years. PC therapies have several adverse effects. A panel consensus recommendation has been made to prevent or ameliorate complications in PC treatment to improve quality of life.
Material and methods Fifteen specialists have met to analyse the different toxicities associated with PC treatment. Each medical specialist performed a National Library of Medicine PubMed search citations searching about these secondary effects and his speciality from 1999 to 2009 to propose measures for their prevention/amelioration.
Results Surgery is associated with incontinence and impotence. Radiotherapy can produce acute, late urological and gastrointestinal toxicity. Brachytherapy can produce acute urinary retention. Chemotherapy is associated with haematotoxicity, peripheral neuropathy and diarrhoea, and hormone therapy can produce osteoporosis, metabolic syndrome, cognitive and muscular alterations, cardiotoxicity, etc.
Conclusions Improvement in surgical techniques and technology (IMRT/IGRT) can prevent surgical and radiotherapeutic toxicity, respectively. Brachytherapy toxicity can be prevented with precise techniques to preserve the urethra. Chemotherapy toxicity can be prevented with personalised schedules of treatment and close follow-up of iatrogenia and hormone therapy toxicity can be prevented with close follow-up of possible secondary effects.

Keywords Prostate cancer · Surgery · Radiotherapy · Chemotherapy · Hormone Deprivation · Toxicity · Quality of life

Introduction

Prostate cancer (PC) is one of the tumours with the highest incidence, which may be explained by the impact of populational ageing, the use of prostate-specific antigen (PSA) for early detection and a rise in the incidence. In Europe, 24.1% of the cancers in men are PC, with 301,500 new cases diagnosed in 2006 followed by lung cancer (15.5%) [1]. There has been an increase in the frequency and the absolute number of cases parallel to a rise in the rate adjusted by age which has gone from 38.5 per 100,000 inhabitants/year in 2002 to 62.6 in 2006. Another factor to explain this rise in incidence is the impact of PSA, which, on achieving early diagnosis, may produce an increase during a determined period of time [2]. The risks and benefits of the PSA test in early detection are controversial and this controversy has not ended with the recent results of the European and US randomised screening trials. The risk of screening is

*Supported by an unrestricted educational grant from MSD Oncology

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Table 1 Multidisciplinary consensus recommendations

	Toxicity	Consensus to prevent/ameliorate toxicity
Surgery	Incontinence [5], stenosis of anastomosis [6] and impotence [4]	Preservation of the bladder neck and neurovascular bundles [77–79]
Radiotherapy	Acute and late urological and gastrointenstinal toxicity (EORTC/RTOG) [8–12], impotence [13–15]	Technological improvement (IMRT/IGRT) [82]
Brachytherapy	Acute urinary retention and incontinence [18–20]	Evidence-based indication. Precise technique to preserve urethra [83]
Chemotherapy	Haematotoxicity (grade 3–4) [22], peripheral neuropathy [23], diarrhoea, emesis and oedema [24]	Personalised schedules of CHT close follow-up of secondary effects [84–88]
Hormone therapy	Osteoporosis [33–37]	Evidence-based indications [26–29], evaluation comorbidities [30–32]
	Metabolic syndrome [38–47]	Exercise [100], biphosphonates [94–97], SERMs (toremifene) [98]
	Cognitive alteration [48–55]	Support groups and/or psycho-oncologist [102–108]
	Muscular alteration [56, 57]	Personalised resistance exercise [109–114]
	Cardiotoxicity [58–67]	Exercise [114], SERMs (toremifeme) [115] and personalised drug treatment
	Anaemia [68–71]	Erythropoietin [118], exercise [120]
	Pulmonary and hepatic toxicity [72–76]	Close follow-up of these secondary effects and HD withdrawal

over-diagnosis and over-treatment, with unnecessary morbidity being associated with the latter.

Fifteen specialists have met to analyse the different toxicities associated with PC treatment to propose multidisciplinary consensus measures for their prevention/amelioration (Table 1) and thereby improve the quality of life (QoL) of these patients.

Indications and toxicities of the different treatments for prostate cancer

Surgery

Radical prostatectomy (RP) is the gold standard for treating localised PC, with a complex approach due to the anatomical placement of this gland, which is immediately below the bladder and is related to its superior fascia. The other extreme, the prostatic apex, ends at the distal segment of the prostatic urethra in the median perineal aponeurosis. Its posterior fascia is in contact with the anterior fascia of the rectum. The prostatic plexus reaches the prostate forming two neurovascular bundles. The cavernous nerves are between the prostatic capsule and the endopelvic fascia, located between the apex at the base to 9–12 mm from the urogenital diaphragm.

Alteration in QoL following RP is due to urinary incontinence and impotence. Total incontinence is of 1.5%, but 3% of the patients describe losses. Risk factors (RF) include: previous obstructive symptomatology, preservation or not of the neurovascular bundles, etc.

A cohort study evaluated 1291 men after RP [4]. Miction and sexual function were prospectively analysed. At 18 months, 8.4% reported incontinence and 59.9% impotence, both increasing with age (13.8% of men between 75 and 79 years of age vs. 0.7–3.6% in younger men). In another series, of 1141 RP [5], incontinence was defined as: (1) no or only occasional use of pads, (2) 0–1 pads/day but only for occasional urine leakage and (3) 0–1 pads/day. At two years of follow up, 83%, 92.3% and 93.4% of the patients, respectively, were continent. On multivariate analysis, age (p=0.009), sclerosis of the anastomosis and length of follow up (both p<0.001) were independent prognostic factors of incontinence.

Another complication is stenosis of the anastomosis with an incidence of 0.4–32% in relation to the surgical technique [6].

With regard to impotence, up to 50% already have erectile dysfunction (ED) on diagnosis of PC. The previous cohort study reported ED in 59% of the cases. At 18 months after RP, 39% of the patients <60 years of age had no sexual problems compared with 15.3–21.7% of the more elderly (p<0.001).

External radiotherapy

External radiotherapy (ERT) is effective in locally advanced PC, being an alternative to RP in intracapsular tumours. Comparison with RP may be based on survival and/or patient QoL. Given the slow evolution of PC, criteria of probability of cure are used. The PSA evaluates biochemical disease-free survival (BDFS) and negativity of prostatic biopsies following ERT predicts the probability of control of PC. An increase in doses provides a benefit but may represent a greater risk of complications [7]. The probability of grade 2 (G2) toxicity at 5 years depends on the total dose administered at both a gastrointestinal (≤70.2 Gy: 6%; ≥75.6 Gy: 17%) and urinary level (≤70.2 Gy: 8%; ≥75.6 Gy: 13%) [8].

The most commonly used classification of toxicity is the EORTC/RTOG [9]. Acute proctitis may occur within the first 6 weeks after ERT, usually being reversible and characterised by diarrhoea, urgency, tenesmus, rectal mu-

cous (10% G2, <1% G3) and, in rare cases, rectorrhagia (<1% G2). Late or chronic proctitis may occur following acute toxicity or as chronification, normally being self-limiting (1–2 years) and characterised by alteration of sphincter functionality or bleeding. G2 toxicity is 4–10% and G3 0–3%. The incidence of G2 rectorrhagia ranges from 2 to 15% and G3 <1 to 3% of the cases. RF include previous abdominal surgery, anticoagulant treatment, arterial hypertension (AH), diabetes, etc. Some RF may be related to the ERT derived from dose-volume histograms, which include the percentage of the rectum to receive intermediate–high doses (40–76 Gy) [10]. The inclusion of pelvic lymph nodes carries greater intestinal toxicity [11].

Cystitis may develop in the first 6 weeks, usually being self-limiting. Clinical manifestations are: nocturia, mictional urgency and dysuria. G2 cystitis ranges from 10 to 25% with <2 % in G3. The chronic phase may be produced following resolution of the acute phase or as chronification of the acute process. Clinical manifestations are sphincter dysfunction and potential haematuria. The rate of G2 toxicity is <15% and G3 <4%. The RF of urinary toxicity are previous local surgery [12], comorbidity by small vessel vascular insufficiency, anticoagulants, obesity and even hormone therapy (HT) [13].

Urinary incontinence is late following ERT and the incidence of G2–3 at 5 years is 1.3%. Evaluation of ED is difficult: lack of unanimous definition, previous sexual function, etc. with an incidence of 6–84% that seems to increase with time. In addition, in some series of ERT, neoadjuvant HT is used, causing 10% alteration. Three types of mechanisms of ED have been suggested: vascular lesion, neurological lesion due to reduction of nitric oxide synthetase in penial nerves and involvement of the penile bulb [14], with a correlation between the volume of this bulb receiving 45 Gy and late ED [15].

Brachytherapy

There are two types of prostatic implants: the permanent low-dose implant mainly performed with iodine-125 achieving a dose of 145 Gy to isodose the area surrounding the prostate and the temporary high-dose implant performed with iridium-192. The permanent implant as monotherapy is indicated in patients with low-risk disease, without obstructive urinary symptomatology and with small prostatic volumes. In patients with intermediate and high risk, some authors [16, 17] combine the permanent implant and ERT, in addition to HT. High-dose-rate prostate brachytherapy (PB) with 1 and up to 3 fractions is combined with ERT in patients with intermediate and high risk, although its use in monotherapy has been proposed even in low-risk patients.

Ten percent of the patients present acute urinary retention (AUR) and 80% present urinary symptoms in correlation with the dose received in urethra. Dysuria is not usually very intense and normally resolves [18]. Symptoms after PB measured by the IPSS are maximum at one month post-implant and improve within 12–24 months. Five years after the implant, IPSS scores are usually from 0 to 7 [19]. Previous transurethral resection (TUR) increases the risk of incontinence post-implant (up to 6%). Incontinence is low (1%), but some obstructive symptom may remain at one year leading to urethral stenosis in 5–10%. Between 4% and 11% of the patients may present intermittent rectorrhagias, with chronic proctitis in 2%. Rectourethral fistulas are rare (1%) [20]. In patients without previous ED, in 60% and 80% erection is sufficient at two years.

Chemotherapy

Hormone deprivation (HD) is the treatment of choice in patients with metastatic PC although a proportion evolves to a hormone-independent (HI) status. Following randomised studies [21], docetaxel (DCT) became the standard treatment in HIPC. In these studies, DCT every three weeks combined with prednisone or estramustine phosphate was more effective than mitoxantrone-prednisone [22]. DCT improves survival, palliates the symptoms and improves the QoL of these patients [23]. Nonetheless, half of the patients do not respond to DCT, which is not without toxicity in a disease with a median survival <20 months. The most observed severe toxicity (G3 and 4) is neutropenia, nausea and vomiting. In the TAX327 trial, 32% of the patients presented neutropenia G2–3, 3% febrile neutropenia and 50% asthenia. Diarrhoea, emesis and peripheral neuropathy appeared in 30% of the patients, peripheral oedema in 19% and mucositis in 20%.

Hormone therapy

The first hormone treatment was orchiectomy [24]. Thereafter, different compounds such as luteinising hormone-releasing hormone (LHRH) agonists, non-steroidal anti-androgens (NSAAs), LHRH antagonists and combined androgen blockade, etc. have been used producing a significant reduction in the total testosterone levels and a marked diminution in dihydrotestosterone and stradiol. The use of HD as the only treatment in the elderly has extended (48.4% with >70 years compared to 9% with <60 years) [25], even as rescue treatment following biochemical relapse to RT or RP.

HD is associated with secondary effects because testosterone intervenes in several metabolic pathways, with an impact on patients' QoL [26]. The elderly are more vulnerable, with prevalent comorbidities [27] influencing toxicity. Associated comorbidity, surpassing 65% in patients receiving ERT, is a prognostic factor for mortality [28].

Osteoporosis

Osteoporosis (OST) is an alteration of bone resistance predisposing patients to a greater risk of fracture. Few studies on OST have been performed in males, usually being "secondary" to other processes such as alcoholism, hypogonad-

Table 2 Definitions of the metabolic syndrome

	NCEP-ATP III	International Diabetes Federation
Waist circumference	>102 cm (males)	≥94 cm (males)
	>88 cm (females)	≥80 cm (females)
Triglycerides	≥150 mg/dl	≥150 mg/dl or drug treatment
HDL	<40 mg/dl (males)	<40 mg/dl (males) or drug treatment
	<50 mg/dl (females)	<50 mg/dl (females) or drug treatment
Blood pressure	≥130/≥85 mmHg	≥130/≥85 mmHg or drug treatment
Fasting glycaemia	≥110 mg/dl or diabetes	>100 mg/dl or diabetes

ism and glucocorticoid treatment. The consensus of the International Society for Clinical Densitometry agreed that OST may be considered in men >50 years when the value of bone density in the T-score is <–2.5. In those <50 years of age, a value <–2 using the Z-score is considered as bone density "inferior to that expected for this age". In patients receiving HD, fractures by OST are more frequent than those of metastatic origin. One pioneer study [29] evaluated 224 patients with PC treated with HD. In this group, 20 fractures were observed, 32% of osteoporotic origin, 36% following violent traumatism, 23% secondary to underlying OST associated with another trigger and 9% due to disease progression. The mortality associated with femur fracture in a population >75 years of age is 20%. Smith et al. [30] demonstrated that genetic, alimentary, metabolic or environmental causes triggering the clinical manifestation of PC also, by unknown mechanisms, produce a greater incidence of osteopenia (OSP) than that corresponding to age or other known risk factors.

Metabolic syndrome and diabetes

Hypoandrogenism by HD is associated with an increase in abdominal obesity, an impairment in the glucose and lipid metabolism that produces the metabolic syndrome (MS). This syndrome is a constellation of metabolic factors grouped to determine a greater risk of diabetes and cardiovascular disease. Since its description [31] different definitions have been made, including the measurement of insulin, since insulin resistance is considered the aetiopathogenic cause. The definition of the third report of the Adult Treatment Panel of the National Education Programme of Cholesterol (ATP III) [32] is the most commonly used because of its easy clinical application. Thereafter, the International Diabetes Federation [33] (IDF) proposed another with waist circumference being the requisite and central axis of the pathogenesis of the syndrome (Table 2). Values with the lower quartile of free testosterone and SHBG were associated with a 1.7–2.8-fold greater risk of developing diabetes [34]. In a study in patients with PC, those with HD presented a higher body mass index (BMI), waist circumference, triglycerides and hyperglycaemia compared to the group without HD [35] (55% vs. 22%). A longer duration of HD increases waist circumference and insulin resistance [36]. Plasma testosterone levels showed a negative correlation with the BMI, waist circumference, visceral fat, serum leptin levels, insulin, triglycerides, total cholesterol, LDL, free fatty acids, fibrinogen and PAI-1 and a positive correlation with HDL levels [37]. Testosterone produces a reduction in fat mass and an improvement in insulin action through the androgen receptor in the adipocytes, which activates the expression of adrenergic receptors, adenylate cyclase, protein kinase A and lipase sensitive to hormones, translating into a decrease in adipocyte lipid content [38]. Despite different significances between the classical MS and the metabolic alterations produced by HD [39], it may be conceptually useful to consider them together as important RF of death by cardiovascular events.

Cognitive alterations

Testosterone in men has a positive relationship with sexual behaviour, mood state and cognitive function [40]. HD may produce secondary effects in these functions with memory loss, lack of concentration and deterioration in verbal abilities [41], which were also found in a 6-month phase III study. However, Cherrier et al. [42] observed a beneficial effect in verbal fluency. Salminen et al. [43] reported changes in visual memory and recognition associated with a decline in stradiol at 6 months and improvement in verbal fluency at one year. Jenkins et al. [44] observed a decline in at least one of the cognitive tasks at 3 months in 47% of the HD subjects vs. 17% in the control group, with the most affected areas being spatial memory and verbal ability. However, in another study [45] no cognitive alterations were detected. This lack of consensus is due to small sample sizes, the difference in variable measurement, the interpretation of the data obtained, etc.

Muscular and functional alterations

HD in PC leads to a diminution in muscle mass (lean mass), which may be limited by physical exercise. The benefits of exercise on physical, mental and human social well-being have been demonstrated with one experimental study even reporting an improvement in immunity [46]. The alteration that age can cause on the following systems should also be taken into account:

Musculoskeletal system:

- Sarcopenia or loss of muscle mass. After 50 years of age, loss of 12% of muscle strength and 6% of muscle mass every 10 years.

Cardiac and circulatory system:
- Diminution of cardiac muscle contractibility.
- Diminishment of return circulation due to lesser pumping effect of the musculature of the lower limbs and venous valve insufficiency.

Respiratory system:
- Diminution of the alveolar and capillary surface (lesser interchange surface).
- Tendency to bronchial obstruction. Greater chest rigidity.

Cardiovascular disease

Keating et al. [47] warned about cardiovascular mortality, demonstrating a significant increase in ischaemic heart disease, acute myocardial infarction (AMI) and sudden death in patients treated with HD for PC possibly caused by metabolic alteration of glycides and lipids with an atherogenic profile (increase in LDL cholesterol and triglycerides, and a decrease in HDL cholesterol) in addition to alterations in cardiac rhythm. Another study [48] evaluated 1372 patients from 3 randomised studies based on the duration of HD. Patients receiving 0 vs. 6 months did not show a higher number of deaths in the HD arm but there was a significant decrease in the median time to death by AMI in the treatment group. Efstathiou et al. [49] did not confirm a direct relation between HD and death due to a cardiovascular cause. Nonetheless, D'Amico et al. [50] indicated that cardiac alterations may be more evident in patients with previous metabolic or cardiac comorbidities and, additionally, without a high competitive risk of death by PC. In more advanced stages of the disease the risk of mortality by cardiovascular causes would be surpassed by the probability of death by PC. This study reinforced a previous study indicating that in patients with important previous comorbidity, exclusive ERT is equivalent to combined treatment of ERT and HD by the excess deaths of causes other than PC [51]. Recent reanalysis of RTOG 8351, RTOG 8610 and RTOG 9202 showed no differences in cardiovascular mortality in longer HD time [52].

Androgen receptors at the level of vascular tissue exercise a vasoregulator effect and coronary vasodilatation [53]. Thus, androgen depletion would, with the atherogenesis of age itself, contribute to an even lesser capacity of dilatation. The lack of androgens and oestrogens may have a deleterious effect on endothelial function and lead to vessel rigidity, thereby favouring accelerated development of vascular disease [54]. Three-month treatment with HD has shown a diminution in vascular elasticity in the peripheral vessels [55]. A report by Trachtenberg et al. [56] is of note. An increase was observed in the ECG QT interval of 30–60 ms up to 46% with goserelin and bicalutamide and 26% with leuprolide and bicalutamide. Additionally, changes >60 ms were found in 8% of the patients treated with goserelin and bicalutamide and 6% with leuprolide alone. HD was considered to induce a lengthening in the QT interval. In patients with QT intervals >450 ms a variation in these values may induce arrhythmias such as "torsades de pointes", and they may produce ventricular fibrillation and sudden death. Moreover, the epidemiological prevalence of long QT in the elderly population may reach 20%, further increasing the risk of cardiac-related mortality.

Anaemia

Androgens stimulate erythropoiesis and their diminution reduces Hb concentrations. Asbell et al. [57] observed that HD represented a reduction of >1 g/dl in Hb levels at 2 months of initiation in 75% of the patients. In a prospective study on intermediate- and high-risk PC submitted to HD and ERT, D'Amico et al. [58] reported worse biochemical control in cases with previous anaemia. However, Pai et al. [59] did not observe this effect on the control of the disease.

Pulmonary and hepatic toxicity

Clinical manifestations of cough and dyspnoea with or without fever and diffuse crackling on auscultation in a patient with HD suggest possible interstitial pneumonitis. The incidence is of 2–4.5% [60] with a median time from the initiation of treatment of 2 months [61]. A diffuse bilateral infiltrate may be seen on chest X-ray and a bilateral nodular reticulum pattern may be observed on CT scan.

Hepatotoxicity is associated with the administration of antiandrogens. At 150 mg/day flutamide presents hepatotoxicity within the range of 3/10,000 up to 9%. Fulminant hepatotoxicity has also been described. The hepatic toxicity of flutamide has been related to the cytochrome P450 pathway and intracellular reduced glutathione (GSH) content in hepatocytes [62]. Ciproteron acetate has even been related to hepatocarcinoma [63].

Consensus in prevention of secondary effects

Consensus in prevention of secondary effects of surgery

A minimally invasive technique such as laparoscopic RP improves postoperative pain, recovery capacity and blood loss. Nonetheless, independently of the approach (open or laparoscopic), we will focus on specific surgical procedures for the prevention of toxicity. Firstly, preservation of the bladder neck improves postoperative continence [64]. Preservation of the neurovascular bundles is a meticulous technique [65] and in addition to preventing impotence, it improves urinary continence [66].

Consensus in prevention of the secondary effects of ERT

With 2D-ERT of doses of up to >70 Gy, the rate of chronic rectal toxicity ≥G2 is high (26–32%), being reduced to 6–9% with 3D-ERT. With IMRT and doses ≥80 Gy, rectal

toxicity ≥G2 is 1–4%. Image-guided radiotherapy (IGRT) allows the dose to be increased with low toxicity.

The randomised study of the RTOG 9413 [67] demonstrated a significant benefit in BDFS, combining lymph node irradiation with neoadjuvant concomitant HD in patients with risk of lymph node invasion >15% [68]. This benefit is limited by greater toxicity due to intestinal irradiation when pelvic lymph nodes are included using 2D-RT. Irradiation with IMRT adapted to lymph node volume [69] diminishes this toxicity.

Consensus in prevention of the secondary effects of PB

For prevention of *de novo* toxicity, a precise technique that delimits the urethra and the rectal wall well is essential to reduce the dose in these organs. An IPSS from 0 to 7 represents a lower risk of AUR and prolonged urethritis. An IPSS score >15 has a probability of AUR of 25%. A Spanish cooperative study on the QoL of patients treated for PC showed a worsening in urinary function in patients with RP, BT and ERT at one month after completing the treatment. Worse scores were observed in all the procedures in all the patients on Expanded Prostate Cancer Index Composite (EPIC) questionnaires and IPSS for surgical treatment related to incontinence and posterior recovery without significant differences [70].

Consensus in prevention of the secondary effects of CHT

Granulocytic growth factors (G-CSF) reduce the risk of febrile neutropenia. Dietetic and hygienic recommendations are essential to minimise oral and digestive toxicity. A close follow-up of secondary effects such as hydric retention and peripheral neuropathy is necessary for early detection. A strategy under investigation is that of intermittent CHT [71]. The optimal length of treatment with DCT has not been established [72]. The number of cycles necessary to achieve response or stable disease is achieved with an intermittent schedule followed by a stage of rest. On progression, DCT is reintroduced. Intermittent CHT may achieve a control comparable to that of continuous treatment and a better QoL with periods without CHT to recover from acute toxicity and diminish that accumulated. Another method is metronomic CHT [73] in which low doses are continuously administered. This may be due to the antiangiogenic effect of metronomic treatment. It is important to identify clinical or biological factors which discriminate patients who will not respond to DCT.

Consensus in prevention of secondary effects of HD

Consensus in prevention and/or treatment of OST

It is useful to optimise calcium (1000–1500 mg/day) and vitamin D (400–800 IU/day) intake, exercise programmes and behaviour modification as in smoking or drinking alcohol [74]. The treatment depends on the associated cause, although antiresorptive drugs such as bisphosphonates (BP) increase bone density, independently of age or gonadal function [75]. The use of PTH may also increase bone mineral density (BMD) in men with OST [76]. In the elderly, calcium and vitamin D supplements are necessary to correct hypovitaminosis D and reduce parathyroid hyperfunction and bone remodelling [77]. A hip protector may be useful to prevent hip fractures [78].

The use of BP has been studied in patients with PC submitted to HD [79]. Those receiving BP presented an increase in BMD of 7.8±1.5 and of 2.0±0.9 at the level of the lumbar spine and the femoral neck, respectively. Smith et al. [80] randomised patients to receive LHRH agonist or LHRH agonists plus pamidronate 60 mg endovenously every 12 weeks with a reduction in the BMD of 3.3% and 8.5% in the femoral neck and lumbar spine, respectively, in the group without BP.

Another study randomised 106 patients with HD [81] to receive either placebo or 4 mg of zoledronic acid. A significant increase in BMD was observed in all the localisations in the zoledronic group. However, these trials with zoledronic acid oral BP alone have approved use and may be indicated in patients with PC and OST prior to HD [82].

Another line under study is selective oestrogen receptor modulators (SERMs), since it has been observed that HD produces a decrease in testosterone and oestrogens with the latter seemingly playing a central role in male bone metabolism [83]. The action of toremifen, one of these SERMs, has already been demonstrated in the prevention of OST in patients with HD [84].

Consensus in prevention of the MS

Studies on insulin sensitisers, glitazones and metformin are underway and at present recommendations of a change in lifestyle, including a nutritional plan with an adequate distribution of nutrients associated with regular physical activity constitute the fundamental pillar of the treatment. It has been shown that a physical resistance training programme in the elderly produces a significant decline in abdominal fat and an improvement in the sensitivity to endogenous insulin [85]. A phase III study on the Mediterranean diet supplemented with nuts has shown it to be useful to effectively fight against the MS [86]. The use of antihypertensive, hypolipidic and platelet antiaggregant drugs and statins is advised based on the individualised data.

Consensus in prevention of cognitive alterations

The diagnosis of cancer causes emotional disturbance and support groups facilitate psychological adaptation [87]. The information concerning PC is crucial [88] since most patients are unhappy with aspects of communication established with their physicians [89]. Support groups satisfy the need for information, provide emotional support and improve QoL [90].

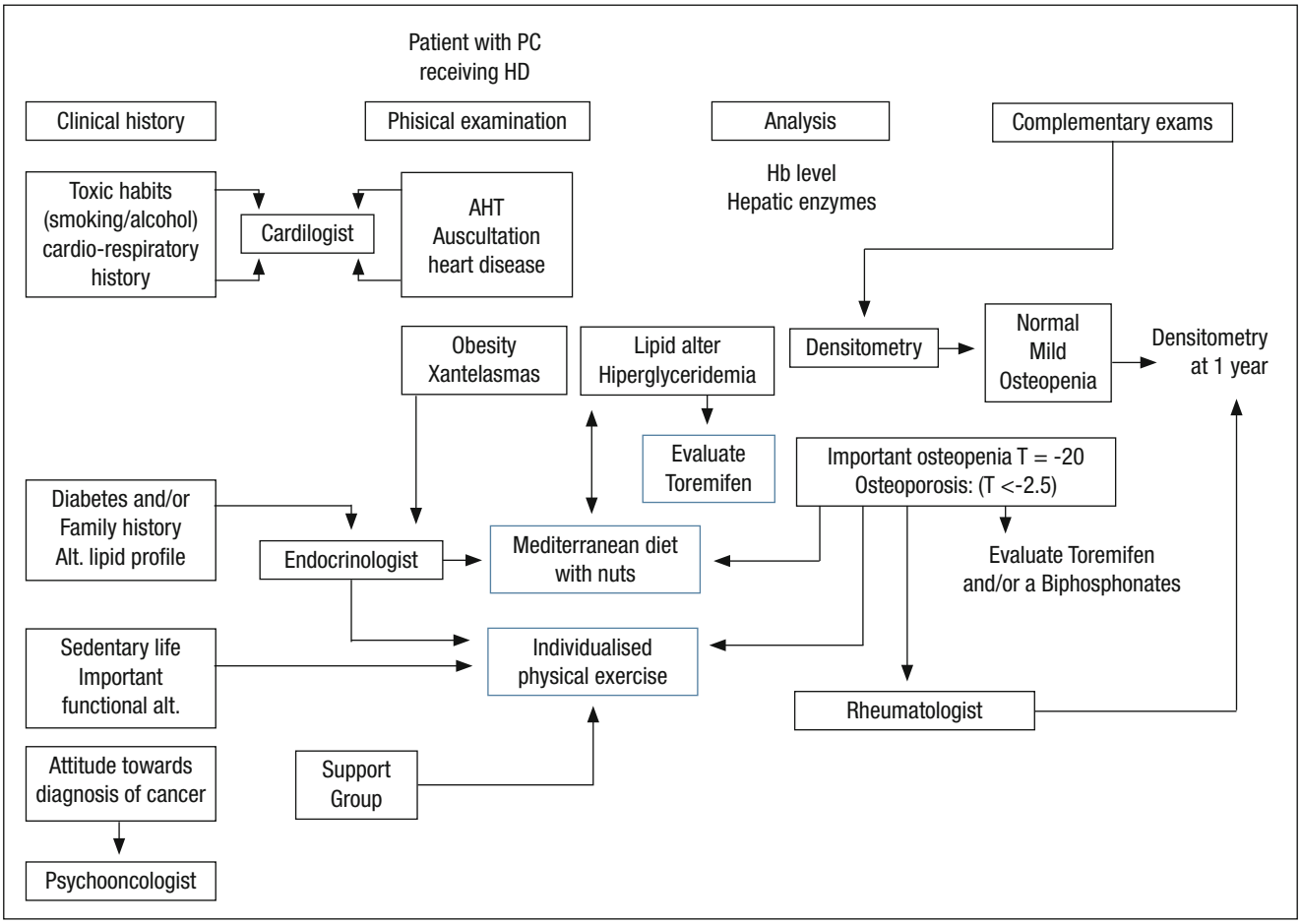


Fig. 1 Practical recommendations for clinical evaluation of patients who must receive HD

The diagnosis of cancer causes emotional disturbance due to the uncertainty it provokes and in some cases psycho-oncologist intervention is necessary.

Consensus in prevention and treatment of muscular and functional alterations

Physical exercise may improve the QoL of patients with alterations such as sarcopenia, particularly in elderly patients [91], since exercise reduces body fat and achieves a greater sensitivity to endogenous insulin [92]. Although physical exercise may increase free testosterone concentrations in young people, the same effect is not produced in the elderly [93].

It is basic to adopt active habits to progressively increase energy expense. For instants, from house hold tasks to sports of low intensity, <70% maximum cardiac frequency (MCF).

In elderly patients [94], resistance exercise for 3 months (3 days/week) improved muscle strength and mass by 30%, compensating for their loss in the previous decades.

The MCF expresses cardiac potency. The Karvone formula allows an approximate calculation of the MCF:

Calculation of MCF (hypothetical) = (220 men/226 women)–age

The calculation is performed in beats/minute and should lie between the CF at rest (or baseline) and the maximum. The aerobic threshold corresponds to the margin for energy consumption with the presence of oxygen (O_2). It should normally be between 60% and 75% of the MCF or max. O_2V. The anaerobic threshold is between this threshold and the MCF and corresponds to the intensity of effort at which the organism only obtains energy without the presence of oxygen due to the high intensity and the short length of time of demand. This should be between 80% and 95% of the MCF or max.O_2V.

Consensus in prevention of cardiac toxicity

The positive results of exercise during cancer treatment have also been sufficiently described [95]. Exercises designed to provide anabolic effects in the muscle and bone, to improve cardiovascular function, favour the loss of fat mass and preserve muscle mass are basic to counteract some of the secondary effects of HD and thereby improve the QoL. One hypothesis of investigation is whether statin administration to patients receiving HD could prevent this cardiovascular risk. The cardiac protector effect of tomerifen, which has been found to be useful in improving the lipid profile in patients with HD is of note [96].

Consensus in prevention of anaemia

The recovery of Hb depends on the recovery of testosterone levels, which may take more than one year in 50% of patients (after 6 months of HD) and are only completely recovered in 65% [97]. These levels may be recovered in patients with symptomatic anaemia after erythropoietin administration [98]. However, a possible stimulator effect of tumour cell proliferation by STAT proteins (signal transducers and activators of transcription) [99] is under debate. Again, a structured physical exercise programme may help to maintain or compensate for secondary alterations in Hb values, improving asthenia [100].

Consensus in prevention of pulmonary and hepatic toxicity

First, we consider these toxicities and withdrawal of HD. In the case of previous hepatic comorbidity it is important to limit antiandrogen administration (specifically flutamide) and to use bicatulamide. The administration of corticoid and oxygenotherapy produce rapid recovery of respiratory symptoms.

Consensus summary and final recommendations

Continuous evaluation of the clinical results obtained in each centre with curative treatments of RP, ERT and PB, with the incorporation of contrasted novel technologies, allows advances to be made in the control of PC and in the possible toxicity secondary to these treatments. In relation to CHT and HD, their therapeutic index may be negative if the toxicity associated with their use is not adequately weighed. In CHT it is basic to monitor the possible secondary effects in elderly patients with associated comorbidities.

Alterations such as OSTP, MS-like, cognitive alterations, functional or muscular alterations, etc. may have an important effect on patient QoL and may even threaten their survival more than PC itself.

We suggest that in patients who must receive HD, all the comorbidities found in the clinical history and on physical examination should be carefully evaluated (Fig. 1) and this clinical history should be directed towards determined aspects such as bone mineral status with densitometry. In cases of important OSP ($T<-2.0$) or OST ($T<-2.5$), the patient should undergo rheumatologic study or treatment. The patient should be interrogated about hyperglycaemia and a complete blood analysis is essential to provide information on other important aspects such as Hb values, lipid profile, etc. In cases with diabetes or hyperglycaemia, we should inform the endocrinologist that a treatment which may lead to a MS-like alteration will be initiated. Cardiac, vascular and AH histories will be collected. If these are already known, a new adaptation of the pharmacological treatment or evaluation by a cardiologist will be required. The emotional impact of the diagnosis on the patient should be evaluated, to seek help from disease support groups or even a psycho-oncologist. Exercises designed to provide anabolic effects in the muscle and bone, to improve cardiovascular function, favour the loss of fat mass and preserve muscle mass are essential to counteract some of the secondary effects and thereby improve QoL. Diet is important in relation to hyperglycaemia and the induced metabolic-like syndrome. The Mediterranean diet has been shown to be useful. However, it should be taken into account that human alimentation goes beyond a simple physiological act since it also implies a ludic and cultural act involving and describing the society around us. It should also be stressed that there are no bad or forbidden foods but rather bad use of foods and/or their quantities. Finally, the transitory use of different pharmacological treatments, especially statins, bisphosphonates and toremifen, should be individually and scientifically evaluated.

Acknowledgement In memory of Rafael Gutiérrez del Pozo (July 1953–December 2008), an exceptional urologist and faithful colleague and in memory of his great working capacity and continued and integrated commitment to his patients.

Conflict of interest The authors declare that they have no conflict of interest relating to the publication of this manuscript.

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