An oncology perspective on the benefits and cost of combined androgen blockade in advanced prostate cancer

Armen G Aprikian, MD,[1] Neil Fleshner, MD,[2] Adrian Langleben, MD,[3] Jeffrey Hames, BSc[4]

[1]Department of Surgery, McGill University, MUHC — Montréal General Hospital, Montréal, Québec, Canada
[2]Division of Urology, Department of Surgery, University of Toronto, University of Toronto Health Network Toronto, Ontario, Canada
[3]Departments of Medicine and Oncology, McGill University, Montréal, Québec, Canada
[4]Michael G. DeGroote, McMaster University, Hamilton, Ontario, Canada

APRIKIAN AG, FLESHNER N, LANGLEBEN A, HAMES J. An oncology perspective on the benefits and cost of combined androgen blockade in advanced prostate cancer. The Canadian Journal of Urology. 2003;10(5):1986-1994.

Objectives: *To provide context in oncology for the significance of the benefits and cost of combined androgen blockade (CAB) in the treatment of advanced prostate cancer.*

Methods: *Canadian drug costs for the survival benefit with CAB in advanced prostate cancer were compared with the costs of benefit with new treatments in advanced non-small-cell lung cancer (NSCLC), metastatic colorectal cancer, and metastatic breast cancer. Clinical toxicities were also compared.*

Results: *The survival benefit with CAB in advanced prostate cancer appears to be approximately 3 months. The survival benefit with the addition of vinorelbine to cisplatin for the treatment of advanced NSCLC is approximately 2 months, and the survival benefit with the addition of irinotecan to fluorouracil (and leucovorin) for the treatment of metastatic colorectal cancer is approximately 2 to 3 months. The survival benefit with anastrozole or exemestane in advanced breast cancer, or with the addition of trastuzumab to standard chemotherapy in metastatic breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2), is approximately 4 to 5 months. The calculated cost per month of survival benefit with bicalutamide in CAB for prostate cancer is $437 to $1107. The cost per month of survival benefit with vinorelbine for NSCLC is $1241 and with irinotecan for colorectal cancer is $6812 to $11,214. The calculated cost per month of survival benefit with anastrozole for breast cancer is $170, for exemestane is $185, and the cost per month with the addition of trastuzumab is $5230. Vinorelbine and irinotecan are associated with severe grade 3 or 4 clinical toxicities, and an increased frequency of heart failure has been observed when trastuzumab is added to anthracyclines. Anastrozole, exemestane and nonsteroidal antiandrogens are associated with mild to moderate side effects.*

Conclusions: *The advantages offered by CAB (including the cost per month of survival benefit and minimal associated clinical toxicities) are comparable to the reported advantages of new treatments for other common cancers such as NSCLC, colorectal cancer, and breast cancer.*

Key Words: advanced prostate cancer, combined androgen blockade, survival benefit, cost comparison

Accepted for publication August 2003

Acknowledgement
Supported in part by an educational grant from AstraZeneca.

Address correspondence to Armen G Aprikian, MD, MUHC — Montréal General Hospital, 1650 avenue Cedar, Montréal, Québec, H3G 1A4 Canada

Introduction

Prostate cancer is the most common cancer in Canadian men, with an estimated 17800 new cases in the year 2001.[1] The three leading cancers — prostate, lung, and colorectal — account for 48% of the potential years of life lost due to cancer in Canadian men.[1] For

Canadian women, breast, lung, and colorectal cancer account for 52% of potential years of life lost due to cancer .[1]

Since 1941, androgen deprivation has been the treatment of choice for advanced prostate cancer.[2] The mainstay of therapy is castration: either surgical (orchiectomy) or medical using a luteinizing hormone-releasing hormone analogue (LH-RHa). However, while castration suppresses androgens of testicular origin and reduces serum testosterone by 90%, it does not block the androgens released by the adrenals.[3]

The concept of combined androgen blockade (CAB) has been studied extensively.[4-7] Antiandrogens currently available in Canada include the steroidal antiandrogen cyproterone acetate and three nonsteroidal antiandrogens: bicalutamide, flutamide, and nilutamide.

Several randomized trials comparing castration alone (orchiectomy or LH-RHa) versus CAB using antiandrogens in combination with castration have been conducted over the past 15 years. Most of these trials have involved <300 patients, and this sample size may be insufficient to demonstrate or refute a survival benefit with CAB.[8,9] Although some physicians believe that CAB may be beneficial for some patients, the magnitude of benefit has often been considered modest at best and the cost considered elevated.

To provide context for the use of CAB in the treatment of advanced prostate cancer, comparisons were made with new treatments for the most common cancer in women (breast cancer) and the next two most commonly occurring cancers in the Canadian population (lung and colorectal cancer).[1] These comparisons included the magnitude of survival benefit with the new treatments, drug acquisition costs associated with the survival benefit, and clinical toxicities with the new treatments.

Methods

Randomized, controlled trials and meta-analyses assessing CAB in prostate cancer (up to February 2001, English only) were sourced using MEDLINE. Trials used in the meta-analyses (including the update of the Prostate Cancer Trialists' Collaborative Group)[10] were examined, and randomized, controlled trials enrolling >300 patients were reviewed.

Treatment comparisons

Published randomized, controlled trial data comparing new treatment regimens with a reference regimen were used to determine survival benefit, time to disease progression, and clinical toxicities with the new treatments. Therapies selected for comparison (in advanced lung, metastatic colorectal, and advanced or metastatic breast cancer) were approved by the regulatory authorities for the indications considered and reflected current practice in Canada.

The survival benefit of CAB in advanced prostate cancer was determined by comparison with surgical or medical castration. Data from several randomized studies with nonsteroidal antiandrogens were available, and therefore a range of values regarding survival and disease progression was used in the calculations. The corresponding time to disease progression reported in individual trials was then applied to determine length of treatment.

For non-small-cell lung cancer (NSCLC), the benefit of the new treatment vinorelbine plus cisplatin was assessed with clinical trial data using the reference regimen of cisplatin alone.

For colorectal cancer, two randomized, controlled trials were used to calculate the benefit of irinotecan versus two reference regimens: fluorouracil alone or fluorouracil with leucovorin.

Clinical trial data for two reference regimens were also used for advanced breast cancer. For treatment after tamoxifen failure, the reference regimen was megestrol acetate and the new regimen anastrozole. In addition, the benefit of exemestane in tamoxifen failures was reviewed. For breast cancer that overexpresses HER2, calculations were made comparing standard chemotherapy and standard chemotherapy plus trastuzumab.

Cost calculations

The cost of the new drug in Canadian dollars[11] for the length of treatment was divided by the number of months of survival benefit. The length of treatment was considered to be the median time to progression, as treatment is generally continued until disease progression. The dosing regimen used in the relevant clinical trial was applied to the cost calculations for lung, colorectal, and breast cancer. If necessary, doses were calculated based on a body surface area of 1.8 m^2. For prostate cancer, the cost of the nonsteroidal antiandrogen bicalutamide was used, and the dosing regimen was taken from the Compendium of Pharmaceuticals and Specialties.[12] Of the three nonsteroidal antiandrogens available in Canada, bicalutamide was selected, since it reflects

current practice and it did not bias the cost-per-month survival gain comparisons with new treatments for other cancers.[13,14]

Results

Survival benefit with new treatment regimens

CAB in advanced prostate cancer

CAB has been studied in eight clinical trials involving >300 patients Table 1a[15-22] Nonsteroidal antiandrogens were evaluated in six trials,[15-20] and cyproterone acetate in two trials.[21,22] In the six trials with nonsteroidal antiandrogens, there was a survival difference in favor of CAB ranging from 1.2 to 7.3 months, with three reaching statistical significance at 3.7 months,[20] 7 months,[19] and 7.3 months.[16] The two trials involving cyproterone acetate showed no survival benefit for CAB.

Four meta-analyses were reviewed. Survival differences were available in two Table 1b[10,24-26] with one reporting a 7.3-month difference favoring CAB.[24] A third meta-analysis calculated risk ratios and demonstrated a statistically significant 10% improvement in overall survival with CAB.[25] In the largest meta-analysis updated in 2000,[10] CAB with a

TABLE 1a. **Large, randomized clinical trials and meta-analyses of CAB in advanced prostate cancer. prostate cancer**

Antiandrogen in CAB	Trial design	Patients (N)	Disease progression
Flutamide[15]	orchiectomy + flutamide vs orchiectomy + placebo	1387	P-FS: 20.4 mo vs 18.6 mo 1.8 mo difference favoring CAB, P = .26
Flutamide[16]	leuprolide + flutamide vs leuprolide + placebo	603	P-FS: 16.5 mo vs 13.9 mo 2.6 mo difference favoring CAB, P = .039
Flutamide[17]	goserelin + flutamide vs goserelin	583	NA previous median 25 mo follow-up for survival reported no significant difference in TTP, P = .7423
Flutamide[18]	goserelin + flutamide vs goserelin	373	TTP: 24 mo vs 18 mo 6 mo difference favoring CAB, P = .09
Flutamide[19]	goserelin + flutamide vs orchiectomy	327	TTP favoring CAB, P = .009 P-FS favoring CAB, P = .02
Nilutamide[20]	orchiectomy + nilutamide vs orchiectomy + placebo	457	TTP: 21.2 mo vs 14.7 mo 6.5 mo difference favoring CAB, P = .002
Cyproterone acetate[21]	buserelin + CPA vs orchiectomy	354	TTP: median 15 mo, P = .28
Cyproterone acetate[22]	goserelin + CPA vs goserelin	328	TTP: median 14 mo, P = .68

non-steroidal antiandrogen was associated with a significant 3% increase in 5-year survival and CAB with cyproterone acetate was associated with a significant 3% decrease in 5-year survival.

Vinorelbine plus cisplatin in advanced NSCLC

A phase III study of 432 chemotherapy-naive patients randomized to vinorelbine plus cisplatin or cisplatin alone.was analyzed.[27] The combination of vinorelbine plus cisplatin resulted in a significant increase in median progression-free survival (4 months vs 2 months for cisplatin alone, P = .0001) and a significant 2-month increase in overall survival (8 months vs 6 months for cisplatin alone, P = .0018).

Large, randomized clinical trials of CAB in advanced

Median overall survival	Follow-up (months)
nonsignificant 3.6 mo difference favoring CAB, P = .14 33.5 mo vs 29.9 mo	median 49-50
significant 7.3 mo difference favoring CAB, P = .035 35.6 mo vs 28.3 mo	Kaplan-Meier plots truncated 42
nonsignificant 1.2 mo difference favoring CAB, P = .172 39.6 mo vs 38.4 mo	median 59
nonsignificant 2 mo difference favoring CAB 34 mo vs 32 mo	median 24
significant 7 mo difference favoring CAB, P = .04 34 mo vs 27 mo	median 86
significant 3.7 mo difference favoring CAB, P = .033 27.3 mo vs 23.6 mo	range 82-102
no significant difference in median survival, P = .98 approximately 24 mo	median 68
no significant difference in probability of survival, P = .26	mean 42

Irinotecan plus fluorouracil (and leucovorin) in metastatic colorectal cancer

A study involving chemotherapy-naive patients (N = 387) randomized patients to fluorouracil or irinotecan and fluorouracil.[28,29] Time to progression was significantly longer in the irinotecan-plus-fluorouracil group than in the fluorouracil-only group (median 6.7 months vs 4.4 months, respectively, P < .001). Overall survival was also significantly longer in the irinotecan-plus-fluorouracil group (median 17.4 months vs 14.1 months, respectively, P = .031).

The addition of irinotecan to the other more commonly used standard regimen, fluorouracil and leucovorin, was assessed in a randomized study (N = 683) (30). The addition of irinotecan resulted in significantly longer progression-free survival (median 7.0 months vs 4.3 months, respectively, P = .004) and a significant median 2.2-month increase in overall survival (14.8 months vs 12.6 months, respectively, P = .04).

Anastrozole, exemestane and trastuzumab in advanced breast cancer

A study of 764 postmenopausal patients failing tamoxifen therapy compared a standard regimen of megestrol acetate with anastrozole.[31] Anastrozole demonstrated a statistically significant 4.2-month survival advantage. The median time to death was 26.7 months for the 1 mg anastrozole group versus 22.5 months for the megestrol acetate group (P < .025). The difference for time to progression did not reach statistical significance (4.8 months vs 4.6 months, P = .49). The benefit of exemestane over megestrol acetate was demonstrated in a randomized controlled trial involving 769 postmenopausal patients failing tamoxifen.[32] Time to progression (20.3 weeks vs 16.6 weeks, P = 0.04) and median overall survival (not reached vs 123 weeks, P = 0.04, estimated survival benefit 4 months) were significantly longer with exemestane therapy.

Trastuzumab is a recombinant monoclonal antibody against HER2 that has been assessed in patients with metastatic breast cancer overexpressing HER2. The addition of trastuzumab to chemotherapy was compared with chemotherapy alone in 469 women.[33] Trastuzumab was associated with a significantly longer time to progression (median 7.4 months vs 4.6 months, P < .001) and a significant 4.8-

TABLE 1b. **Large, randomized clinical trials and meta-analyses of CAB in advanced prostate cancer. Meta-analyses of CAB in advanced prostate cancer.**

Treatment comparisons	Studies (N)	Patients (N)	Disease progression	Survival
LH-RHa or orchiectomy + antiandrogen (at least 1 yr) vs LH-RHa or orchiectomy[10]	27	8275 (metastatic or locally advanced prostate cancer)	NA	significant improvement in 5-yr survival with NSAA in CAB: 27.6% vs 24.7% (logrank 2p =.005) Significant decrease in 5-yr survival with CPA in CAB: 15.4% vs 18.1% (logrank 2p = 0.4 adverse) nonsignificant improvement in 5-yr survival for all CAB: 25.4%vs 23.6% (logrank 2p =.11)
LH-RHa or orchiectomy + NSAA vs LH-RHa or orchiectomy[24]	9	NA (advanced prostate cancer)	significant increase in TTP with CAB RR = 0.74 (95% CI, 0.63-0.86), P < .001	significant improvement in overall survival with CAB RR = 0.78 (95% CI, 0.67-0.90), P < .001
LH-RHa or orchiectomy + flutamide vs LH-RHa or orchiectomy[25]	9	4128 (advanced prostate cancer)	NA	significant 10% improvement in overall survival with CAB RR = 0.90 (95% CI, 0.79-1.00) P = .05
Orchiectomy + nilutamide vs Orchiectomy + placebo	7	1056 (stage D prostate cancer, no previous treatment)	significant 16% reduction in OR for progression of disease with CAB OR = 0.84 (95% CI, 0.71-1.00), P = .05	nonsignificant 11% reduction in annual odds of overall mortality with CAB OR = 0.89 (95% CI, 0.75-1.07)

Note: Terms significant and nonsignificant refer to statistical significance.
Abbreviations: CAB, combined androgen blockade; CI, confidence interval; CPA, cyproterone acetate; LH-RHa, luteinizing hormone-releasing hormone analogue; NA, not available; NSAA, nonsteroidal antiandrogen; OR, odds ratio; P-FS, progression-free survival; RR, risk reduction; TTP, time to progression.

month survival advantage (median 25.1 months vs 20.3 months, P = .046).

Costs of new treatments for each month of survival gain

The parameters used to calculate drug acquisition cost per month of survival gain are listed in Table 2.

Nonsteroidal antiandrogens in CAB for advanced prostate cancer

The median survival benefit ranged from 3.7 months[20] to 7.3 months,[16] and the corresponding median times to progression were 21.2 months[20] and 16.5 months.[16] The cost of bicalutamide at 50 mg/day in Canada is $193.20 per month.[11] Therefore, the cost for the addition of bicalutamide ranged from $437

to $1107 per month of survival gain.

Vinorelbine in advanced NSCLC

A randomized trial reported a median time to progression of 4 months in the cisplatin plus vinorelbine group and a median survival advantage of 2 months.[27] The cost of vinorelbine is $172.38 per 50 mg.[11] Calculations showed that the addition of vinorelbine costs $1241 per month of survival gain.

Irinotecan in metastatic colorectal cancer

A clinical trial comparing fluorouracil to fluorouracil plus irinotecan reported a median time to progression of 6.7 months in the irinotecan group and a median survival benefit of 3.3 months.[29] The cost of irinotecan is $548.26 per 100 mg.[11] Using these data, the addition of irinotecan costs $6812 per month of survival gain.

A randomized trial comparing the addition of irinotecan to fluorouracil and leucovorin reported a median time to progression in the irinotecan group of 7.0 months and a median survival benefit of 2.2 months.[30] Using these data, the addition of irinotecan costs $11214 per month of survival gain.

Anastrozole, exemestane or trastuzumab in breast cancer

A combined analysis of two trials comparing megestrol acetate versus anastrozole in patients after tamoxifen failure reported a survival advantage of 4.2 months and a median time to progression of 4.8 months with anastrozole 1 mg.[31] The cost of anastrozole is $148.50 per month.[11] Therefore, a cost of $170 per month of survival gain was calculated for anastrozole therapy. The cost per month associated with a 4 month survival gain with exemestane is estimated at $185.

Recently reported results from a randomized trial comparing standard chemotherapy with chemotherapy plus trastuzumab found a significant 4.8-month survival advantage and a median 7.4 months to progression with trastuzumab.[33] The cost of trastuzumab is $2913 per 440 mg,[11] resulting in a cost of $5230 per month of survival gain.

Clinical toxicity

Nonsteroidal antiandrogens in CAB for advanced prostate cancer

Overall, CAB with nonsteroidal antiandrogens is well tolerated. The three nonsteroidal antiandrogens available in Canada include bicalutamide, flutamide, and nilutamide.[34] Nilutamide has been associated with reversible visual abnormalities and alcohol intolerance in approximately 20% of patients.[9] Only one trial has directly compared toxicities of antiandrogens in the context of CAB; this randomized trial demonstrated a significantly higher incidence of diarrhea (26% vs 12%, $P < .001$) for the flutamide-plus-LH-RHa group compared with the bicalutamide-plus-LH-RHa group.[14] Minor adverse events reported most frequently in this trial included hot flashes, constipation, nausea, and diarrhea. No grade 3 or 4 toxicities were reported.

Vinorelbine for advanced NSCLC

The trial comparing cisplatin with cisplatin plus vinorelbine reported more hematological toxicity in the cisplatin plus vinorelbine treatment.[27] This included the following World Health Organization (WHO) grade 3 or 4 toxicities: granulocytopenia (81% cisplatin-plus-vinorelbine vs 5.5% cisplatin-only), thrombocytopenia (6% cisplatin-plus-vinorelbine vs 2.5% cisplatin-only), and anemia (24% cisplatin-plus-vinorelbine vs 8% cisplatin-only).

Irinotecan for metastatic colorectal cancer

The addition of irinotecan to fluorouracil resulted in a significantly higher frequency of grade 3 or 4 hematological and nonhematological toxic effects.[29] Toxic effects included grade 3 or 4 neutropenia (28.8% irinotecan-plus-fluorouracil vs 2.4% fluorouracil-only) and grade 3 or 4 leukopenia (20.4% irinotecan-plus-fluorouracil vs 2.4% fluorouracil-only). Nonhematological grade 3 or 4 effects that were significantly more frequent in the irinotecan group included diarrhea, asthenia, and infection.

Anastrozole and trastuzumab for advanced breast cancer

The combined analysis of anastrozole or exemestane versus megestrol acetate demonstrated that anastrozole and exemestane were generally well tolerated.[31,32] The most commonly reported adverse events were asthenia, nausea, headache, hot flushes, and dyspnea. These occurred in 11% to 18% of patients who received anastrozole 1 mg and 7% to 12% of patients receiving exemestane 25 mg/day.[32]

The trial assessing the addition of trastuzumab to chemotherapy reported the most important adverse event was cardiac dysfunction.[33] The addition of trastuzumab increased the frequency of heart failure (5% to 22%), leukopenia (26% to 41%), and anemia (19% to 27%). This increase in cardiac toxicity was observed mainly in association with anthracycline therapy.

TABLE 2. **Comparison of cost per month survival gain for CAB in advanced prostate cancer with new treatments advanced or metastatic breast cancer**

	Advanced prostate cancer	**Advanced non-small-cell lung cancer**	**Metastatic colorectal cancer**	
Reference regimen	castration (orchiectomy or LH-RHa)	cisplatin	fluorouracil	fluorouracil and leucovorin
New regimen	castration + NSAA	cisplatin + vinorelbine	fluorouracil + irinotecan	fluorouracil and leucovorin + irinotecan
Difference in median overall survival*	3.7 mo[20] to 7.3 mo[16]	2.0 mo[27]	3.3 mo[29]	2.2 mo[30]
Median time to progression for new regimen	21.2 mo[20] and 16.5 mo[16]	4 mo[27]	6.7 mo[29]	7.0 mo[30]
Dosing schedule	NSAA† 50 mg/day[12]	vinorelbine 25 mg/m^2/wk[27]	irinotecan 80 mg/m^2/wk or 180 mg/m^2 every 2 wk[29]	irinotecan 125 mg/m^2/wk x 4 wk q 6 wk[30]
Cost[11]	NSAA† $193.20/mo	vinorelbine 50 mg = $172.38	irinotecan 100 mg = $548.26	irinotecan 100 mg = $548.26
Cost per month survival gain	$437-1107	$1241	$6812	$11214

*Difference in median overall survival = overall survival with new regimen minus overall survival with reference reference regimen.
†Costs and dosing regimen of bicalutamide used for calculations.
Abbreviations: HER2 indicates human epidermal growth factor receptor 2; LH-RHa, luteinizing hormone-releasing antiandrogen.

Discussion

Treatment with CAB for advanced prostate cancer may provide a survival benefit of approximately 3 months. The number of months of survival benefit provided by nonsteroidal antiandrogens in CAB for advanced prostate cancer appears comparable to the survival benefit provided by new treatments for other common cancers. In addition, drug acquisition costs associated with that survival benefit are at least comparable to the cost per month of survival gain with new treatments for advanced NSCLC, metastatic colorectal cancer, and metastatic breast cancer. Moreover, cost differentials would likely increase much further if indirect costs were also taken into account (e.g., physician/nursing care, biochemical and imaging tests, hospital stay, intensive care, and supportive-care drugs). Management of the grade 3 or 4 toxicities associated with some of the therapies for advanced cancer would result in significantly higher costs than the relatively mild adverse effects associated with nonsteroidal antiandrogens.

for advanced NSCLC, metastatic colorectal cancer, and

Breast Cancer Advanced breast cancer (after tamoxifen failure)	**Advanced breast cancer (after tamoxifen failure)**	**Metastatic breast cancer that overexpresse s HER2**
megestrol acetate	megestrol acetate	standard chemotherapy
anastrozole	exemestane	standard chemotherapy + trastuzumab
4.2 mo[31]	4 months[32] (estimate)	4.8 mo[33]
4.8 mo[31]	5.0 months[32]	7.4 mo[33]
anastrozole 1 mg/day[31]	exemestane 25 mg/day[32]	trastuzumab loading dose of 4 mg/kg, then 2 mg/kg/wk[33]
anastrozole $148.50/mo	exemestane $148.00/mo	trastuzumab 440 mg = $2913
$170	$185	$5230

regimen. P < .05 for new regimen compared with

hormone analogue; NSAA, nonsteroidal

The clinical significance of survival benefit with a new treatment is also influenced by associated adverse events. Nonsteroidal antiandrogens have a mild-to-moderate adverse-event profile, while new cytotoxic therapies approved for other common cancers are associated with WHO grade 3 and 4 toxicities. Finally, when one compares the cost and toxicity associated with radical nephrectomy prior to systemic immunotherapy for metastatic renal cancer,[35,36] CAB for prostate cancer appears less toxic.

Our findings must be tempered due to some significant methodologic limitations. This study is not a complete assessment of all direct and indirect costs that comprise a formal cost-benefit analysis. It is possible that some treatments in some cancers result in significant palliative benefits which improve quality of life and therefore result in less overall cost. We have not addressed the potential palliative benefits of each treatment and as such our study is incomplete. Nevertheless, we believe it is fair to state that the cost associated with the potential benefits of CAB in prostate cancer is comparable to that observed in other cancers.

Conclusions

CAB with nonsteroidal antiandrogens and castration may provide a modest survival benefit for patients with advanced prostate cancer, and the magnitude and cost per month of survival benefit are comparable with new accepted treatments for other common malignancies, including advanced NSCLC, metastatic colorectal cancer, and breast cancer. Clinical toxicities and potential associated indirect costs favor the mild to moderate adverse-event profile of nonsteroidal antiandrogens compared with the grade 3 and 4 toxicities associated with other new treatments. □

References

1. National Cancer Institute of Canada. Canadian cancer statistics 2001. Available at: http://66.59.133.166/stats/tables/tab1e.htm. Accessed February 4, 2002.
2. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *Cancer Res* 1941:1:293-297.
3. Debruyne FM, Dijkman GA. Advances and trends in hormonal therapy for advanced prostate cancer. *Eur Urol* 1995:28:177-188.
4. Huggins C, Scott W. Bilateral adrenalectomy in prostate cancer. *Ann Surg* 1945:122:1031-1041.
5. Bracci U, Di Silverio F. Role of cyproterone acetate in urology. In Martini L, Motta M eds, *Androgens and Antiandrogens*. New York: Raven Press, 1977:333-339.
6. Labrie F, Dupont A, Belanger A, et al. New hormonal therapy in prostatic carcinoma: combined treatment with an LHRH agonist and an antiandrogen. *Clin Invest Med* 1982:5:267-275.
7. Mahler C, Verhelst J, Denis L. Clinical pharmacokinetics of the antiandrogens and their efficacy in prostate cancer. *Clin Pharmacokinet* 1998:34:405-417.
8. van Tinteren H, Dalesio O. Systematic overview (metaanalysis) of all randomized trials of treatment of prostate cancer. *Cancer* 1993:72(suppl 12):3847-3850.
9. Tyrrell CJ. Controversies in the management of advanced prostate cancer. *Br J Cancer* 1999:79:146-155.
10. Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000:355:1491-1498.

11. PPS Pharma Publication. January 2001 ed. Moncton: Total Pricing Systems Inc.; 2001. p. 88, 117, 118, 229, 241, 324.
12. Compendium of Pharmaceuticals and Specialties. 36th ed. Ottawa: Canadian Pharmacists Association; 2001.
13. Sarosdy MF. Which is the optimal antiandrogen for use in combined androgen blockade of advanced prostate cancer? The transition from a first- to second-generation antiandrogen. *Anti-Cancer Drugs* 1999:10:791-796.
14. Schellhammer PF, Sharifi R, Block NL, et al. Clinical benefits of bicalutamide compared with flutamide in combined androgen blockade for patients with advanced prostatic carcinoma: final report of a double-blind, randomized, multicenter trial. Casodex Combination Study Group. *Urology* 1997:50:330-336.
15. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. *N Engl J Med* 1998:339:1036-1042.
16. Crawford ED, Eisenberger MA, McLeod DG, *et al*. A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N Engl J Med* 1989:321:419-424.
17. Tyrrell CJ, Altwein JE, Klippel F, et al. Comparison of an LH-RH analogue (goserelin acetate, 'Zoladex') with combined androgen blockade in advanced prostate cancer: final survival results of an international multicentre randomized-trial. International Prostate Cancer Study Group. *Eur Urol* 2000:37:205-211.
18. Boccardo F, Pace M, Rubagotti A, et al. Goserelin acetate with or without flutamide in the treatment of patients with locally advanced or metastatic prostate cancer. Italian Prostatic Cancer Project (PONCAP) Study Group. *Eur J Cancer* 1993:29A:1088-1093.
19. Denis LJ, Keuppens F, Smith PH, et al. Maxaimal androgen blockade: final analysis of EORTC phase III trial 30853. European Organization for Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Cooperative Group and the EORTC Data Center. *Eur Urol* 1998:33:144-151.
20. Dijkman GA, Janknegt RA, De Reijke TM, et al. Long-term efficacy and safety of nilutamide plus castration in advanced prostate cancer, and the significance of early prostate specific antigen normalization. International Anandron Study Group. *J Urol* 1997:158:160-163.
21. de Voogt HJ, Studer U, Schröder FH, et al. Maximum androgen blockade using LHRH agonist buserelin in combination with short-term (two weeks) or long-term (continuous) cyproterone acetate is not superior to standard androgen deprivation in the treatment of advanced prostate cancer. Final analysis of EORTC GU Group trial 30843. European Organization for the Research and Treatment of Cancer (EORTC) Genito-Urinary Tract Cancer Cooperative Group. *Eur Urol* 1998:33:152-158.
22. Di Silverio F, Serio M, D'Eramo G, et al. Zoladex vs. Zoladex plus cyproterone acetate in the treatment of advanced prostatic cancer: a multicenter Italian study. *Eur Urol* 1990:18(suppl 3):54-61.
23. Tyrrell CJ, Altwein JE, Klippel F, et al. A multicenter randomized trial comparing the luteinizing hormone-releasing hormone analogue goserelin acetate alone and with flutamide in the treatment of advanced prostate cancer. International Prostate Cancer Study Group. *J Urol* 1991:146:1321-1326.
24. Caubet J-F, Tosteson TD, Dong EW, et al. Maximum androgen blockade in advanced prostate cancer: a meta-analysis of published randomized controlled trials using nonsteroidal antiandrogens. *Urology* 1997:49:71-78.
25. Bennett CL, Tosteson TD, Schmitt B, et al. Maximum androgen-blockade with medical or surgical castration in advanced prostate cancer: a meta-analysis of nine published randomized controlled trials and 4128 patients using flutamide. *Prostate Cancer Prostatic Dis* 1999:2:4-8.
26. Bertagna C, De Géry A, Hucher M, et al. Efficacy of the combination of nilutamide plus orchidectomy in patients with metastatic prostatic cancer. A meta-analysis of seven randomized double-blind trials (1056 patients). *Br J Urol* 1994:73:396-402.
27. Wozniak AJ, Crowley JJ, Balcerzak SP, et al. Randomized trial comparing cisplatin with cisplatin plus vinorelbine in the treatment of advanced non-small-cell lung cancer: a Southwest Oncology Group Study. *J Clin Oncol* 1998:16:2459-2465.
28. Figueredo A, Moore M, Germond C, et al. Use of irinotecan in second-line treatment of metastatic colorectal carcinoma. Gastrointestinal Cancer Disease Site Group. *Curr Oncol* 2000:7:29-36.
29. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet* 2000: 355:1041-1047.
30. Saltz LB, Cox JV, Blanke C, et al. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. Irinotecan Study Group. *N Engl J Med* 2000:343:905-914.
31. Buzdar AU, Jonat W, Howell A, et al. Anastrozole versus megestrol acetate in the treatment of postmenopausal women with advanced breast carcinoma: results of a survival update based on a combined analysis of data from two mature phase III trials. Arimidex Study Group. *Cancer* 1998:83:1142-1152.
32. Kaufmann M, Bajetta E, Dirix LY, et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: Results of a phase III randomized double-blind trial. *J Clin Oncol* 2000:18:1399-1411.
33. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001: 344:783-792.
34. Blackledge G, Kolvenbag G, Nash A. Bicalutamide: a new antiandrogen for use in combination with castration for patients with advanced prostate cancer. *Anti-Cancer Drugs* 1996:7:27-34.
35. Mickisch GH, Garin A, van Poppel H, et al. Radical nephrectomy plus interferon-alfa-based immunotherapy compared with interferon alfa alone in metastatic renal-cell carcinoma: a randomized trial. *Lancet* 2001:358:966-970.
36. Flanigan RC, Salmon SE, Blumenstein BA, et al. Nephrectomy followed by interferon alfa-2b compared with interferon alfa-2b alone for metastatic renal-cell cancer. *N Engl J Med* 2001:345:1655-1659.