Temas de Revisão

Controversies Involving the Systemic Treatment for Metastatic Prostatic Cancer

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Introduction

In the United States, 1987 estimates of cancer incidence by site indicate that prostatic cancer is equal to lung cancer as the first in incidence in adult males[1]. Over 90,000 new cases are diagnosed and between 25-30,000 patients die of this disease each year. While early prostatic cancer is a surgically curable disease, the majority of patients present with widely metastatic cancer, where the main objective of treatment is palliation.

For many years prostatic cancer has been shown to be androgen dependent for its growth. The major circulating androgen in adult males is testosterone (T). Approximately 95% of T in adult males is of gonadal (testicular) origin and only about 5% originate from the adrenal glands in the form of two precursors (androstenedione and dehydroepiandrosterone) both of which are readily converted to T. T enters the prostatic cell passively and is subsequently converted to dihydrotestosterone (DHT) by the enzyme 5-alpha-reductase, which reacts with specific cytosolic receptors. DHT-receptor complexes are incorporated into the cell nucleus thereby promoting cell growth and differentiation. The synthesis and release of gonadal T is controlled by pituitary gonadotropins (LH and FSH). LH and FSH synthesis and release in turn are modulated by a hypothalamic hormone, known as Gonadotropin-Hormone-Releasing-Hormone (GnRH or LHRH). Interventions at any step of the hypothalamic-pituitary-gonadal axis produce the necessary deprivation of androgens which results in one of the most effective systemic palliations for solid tumors in man.

Extensive experience indicates that this androgenic control of tumor growth is only temporary and that effective resistance to this modality of treatment almost always predictably occurs with time. Resistance to endocrine manipulations in prostatic cancer may be a result of an expansion of previously existing endocrine insensitive cell clones, the development of somatic mutations in previously androgen dependent cells or both. Virtually all non hormonal cytotoxic agents currently available in clinical practice have been systematically tested and applied in patients with disseminated prostatic cancer. In this review we will address the past and current experience with both endocrine treatment and non-hormonal cytotoxic chemotherapy and discuss the future perspectives involving systemic treatment for this disease.

Endocrine Manipulations for Prostatic Cancer

For many years, the main stay for treatment has been the administration of pharmacological doses of estrogens and surgical castration. Both modalities produce objective and subjective improvements in patients with disseminated disease[2]. Much has been learned from the series of prospective randomized trials conducted by the Veterans Administration Cooperative Urological Research Group (VACURG) conducted from 1960 to 1975[3,4]. On the VACURG study 1, patients with stage III and IV (C and D) were randomly allocated to receive either a placebo initially, daily oral 5.0mg of diethylstilbestrol (DES), orchiectomy plus placebo or orchiectomy plus 5.0mg of DES. The main objective was to determine whether combined treatment with orchiectomy plus DES was superior to either treatment alone. Patients randomized to receive placebo initially were subsequently crossed over at the time of progression to one of the other 3 arms and the choice of treatment was left at the discretion of the investigators. The main endpoint for study was survival. Also as part of study 1, patients with stages I and II (A & B) were randomly allocated to prostatectomy and placebo or prostatectomy + 5mg of DES daily.

The most important observation on both studies was that 5.0mg of DES was associated with an increased risk of death from cardiovascular disease. Among the complications associated with DES treatment were: deep vein thrombosis/thrombophlebitis, angina pectoris, acute myocardial infarction, congestive heart failure, pulmonary embolus and cerebral-vascular accidents. The final results on both segments of study 1 indicated no survival differences

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in favor of any treatment, thus suggesting that: (1) For patients with early disease (stages I and II), the addition of 5.0mg of DES to local surgical treatment does not provide additional benefits and in fact may adversely affect long term prognosis because of a high incidence of severe, life-threatening, cardiovascular complications; (2) The addition of 5.0mg of DES to surgical castration in patients with stages III and IV disease was not superior to either modality alone and this could at least partly be due to an increase in potentially lethal toxicity. The impact of treatment related morbidity and mortality was more apparent on the stage III group; (3) Patients randomized to the placebo arm and subsequently treated on one of the other treatment arms at the time of their symptomatic or objective progression had the same survival of those receiving these treatments at the time of randomization. Thus, it was interpreted that early treatment for asymptomatic prostatic cancer patients provides no survival advantage over treatment at the symptomatic stage only. This assessment of VACURG Study 1 has been subject of significant criticism, particularly with regard to the optimal timing for initiation of endocrine treatment. Is it appropriate to assume, based on these data, that early treatment offers no advantages over delayed initiation of treatment ¼ The VACURG Study 1 was *not* designed to test the concept of early versus delayed treatment, and the appropriate design of a study to test this important question requires very specific definitions of endpoints to be assessed prospectively and not retrospectively as done on VACURG Study 1. Since the decision of "progression" was not uniformly defined "a priori" it remains possible, and likely, that the cross over to an alternate treatment in actuality occurred at different biological times. Similarly, the choice of cross over treatment was left at the discretion of the treating physicians, thus resulting in different therapeutic approaches following progression, which incorporates additional complexity for final analysis. Another important aspect is the recognition of several independent prognostic elements in prostatic cancer, which is clearly a heterogeneous disease. It becomes specially difficult to assess therapeutic benefits in these various subgroups, and an imbalance on the distribution of elements with established prognostic significance between the various treatment arms may by itself heavily influence the outcome of a study[5]. Furthermore, a substantial proportion of the patients included on study 1 died of either treatment related toxicity or other intercurrent complications, thus preventing reliable assessments of survival in relation to prostatic cancer.

Data in various pre-clinical models strongly suggest that early initiation of treatment may be important to minimize the emergence of mutant resistant cell clones and that at early stages, therapeutic benefits may be more achievable because of a smaller burden of pre-existing resistant tumor cells[6-8]. Extensive clinical data available in a number of neoplasms in man, would support the pre-clinical hypothesis that early treatment may in fact provide better chances for more effective palliation. While in stage D_2 prostatic cancer treatment is frequently reserved for symptomatic patients, partly because of the VACURG study results, it is this author's opinion that the answer to this question needs to be appropriately addressed before standards of care could be defined in a more definitive manner. An important biological effect observed on VACURG Study 1 which may support early treatment in the context of the above discussion is that the progression from stage III to IV was significantly delayed in patients receiving immediate endocrine treatment.

In VACURG Study 2, patients with stage III and IV disease were randomized to receive placebo, 0.2mg of DES, 1.0mg of DES and 5.0mg of DES. This study was stopped early, once the increased risk of cardiovascular complications with 5.0mg of DES emerged. The final results showed that both 1.0 and 5.0mg doses of DES had better survival than placebo and 0.2mg of DES (both of which were quite similar in outcome) and that 1.0mg was equal to 5.0mg of DES in terms of prostatic cancer deaths but with less cardiovascular complications particularly in stage III patients. Unfortunately, Study 2 ended with insufficient numbers of patients in each arm to allow for a reliable assessment of early *versus* delayed treatment, although the trend of survival curves was in favor of the most effective doses (1mg and 5.0mg)[4].

A group of drugs, known as antiandrogens, interfere with androgen effects at the cellular level, by competitive binding with DHT cytosolic receptors. They are classified as steroidal and non-steroidal compounds. Among the steroidal antiandrogens are cyproterone acetate and megestrol acetate (megace). Steroidal antiandrogens also produce a suppression of gonadotropins and gonadal T, thus in a sense reflect a "combined" therapeutic approach. Non-steroidal or "pure" antiandrogens act primarily at the target cell by competing with DHT receptors only, without directly affecting androgen synthesis and release. Uncontrolled studies suggest that both steroidal and non-steroidal antiandrogens may be as effective as estrogens and orchiectomy and their advantages over estrogens are primarily reflected on their lower incidence of side effects, such as cardiovascular, mammotropic complications and less impotence and loss of libido[9-23]. More data regarding their relative efficacy compared to standard treatment are needed, however, it remains possible that antiandrogens may in the future emerge as one of

the best choices for the first line endocrine treatment for this disease.

Another drug in more preliminary stages of development is ketoconazole, an antifungal drug that produces a dose dependent inhibition of gonadal (90%) and adrenal sex steroids (70%), thus producing response in patients with stage D_2 disease and no prior treatment. Because of its unsettled safety, ketoconazole requires further testing until it becomes more clearly indicated for the treatment of prostatic cancer[30, 31].

More recently, the identification, structural characterization and synthesis of the naturally occurring gonadotropin hormone releasing hormone by Schally et al[24-26] resulted in a new therapeutic approach for prostatic cancer. The demonstration that LH and FSH synthesis and release could be modulated by exogenous GnRH provided the rationale for the therapeutic application of this hormone. Substitutions on the 6th and 10th positions of the decapeptide resulted in analogs several times more potent than the parent compound[27-29]. Frequent administration of low doses of GnRH activates gonadotropins secretion whereas chronic administration of superagonistic analogs produces a paradoxical inhibition of LH, FSH and consequently of T of gonadal origin. This observation provides the basis for the oncological use of these drugs[30-31].

Table 1 illustrates GnRh analogs available in the United States. The mechanisms underlying their biochemical and physiological effects are essentially identical and the only differences between these various compounds and the naturally occurring GnRH relate to their relative potency and route of administration. They are available for daily subcutaneous administration, intranasal use, and as long acting (depot) forms which allow for a monthly administration. GnRH analogs have established activity against prostatic cancer and their biological effects are consistent with a chemical castration virtually indistinguishable from an orchiectomy. Their choice over surgical castration is primarily dependent on patients' choice, however from a cost/effectiveness point of view it is clear that the surgical approach has its advantages, primarily in view of its relative simplicity, low morbidity and much lower overall cost than a long term administration of GnRH analogs. The availability of intranasal and long acting preparations will certainly enhance their attractiveness for clinical use.

The preference of GnRH analogs over pharmacological doses of estrogens, deserves careful discussion. While these compounds have been shown to have a better therapeutic index than 3mg of DES (i.e., are as effective but less toxic)[32] their advantage over lower doses of established activity in prostatic cancer, such as 1 mg/day, remain unclear. The VACURG Study 2 indicated that the dose of 1mg/day was not associated with an increased hazard for cardiovascular complications in patients without important risk factors such as age under 75 years and/or no history of active cardiovascular disease. Extensive data thus far accumulated with 1mg of DES/day indicate significant clinical benefits comparable to other standard approaches. Preliminary results of a recently completed randomized study in patients with advanced disease conducted by the EORTC (European Organization for Research and Treatment of Cancer) suggest that doses of 1mg/DES daily may be as effective as orchiectomy or orchiectomy plus cyproterone acetate[33].

This brings up another important issue involving endocrine treatment for this disease. The selection of treatments is frequently based upon their ability to suppress T to the castrate range. In animals, there is a clear thereshold for tumor growth stimulation and this appears to be within a range usually achieved with various endocrine manipulations including surgical castration[34], however the extrapolation of data between species in such situations should be cautiously interpreted. In humans 1mg/day of DES does not produce a sustained suppression of T to the castrate range in a proportion of patients[35], yet it appears to be as effective as other forms of treatment which result in T suppression to levels of detectability. **Klotz** et al[36] studied a selected group of patients who received intermittent DES treatment, administered until their symptoms related to the disease were controlled and then stopped. Treatment was only restarted when patients became symptomatic. Their results demonstrated that satisfactory palliation can be achieved by intermittent treatment and that survival figures are comparable to continuous treatment. This observation may suggest that a continuous and sustained suppression of T may not be necessary in all patients with this disease. Another example involves the use of pure antiandrogens (Flutamide®) which may be as effective as pharmacological doses of estrogens without reducing gonadal testosterone levels. While the optimal levels of T suppression necessary to optimize therapeutic benefits for prostatic carcinoma remain unestablished at the present time the selection of treatments continues to be heavily influenced by this concept.

More recently, **Labrie** et al[37] introduced a new concept of *"maximal androgen blockade"* by suggesting that prostatic cancer is variably, but always, dependent on androgens and that the development of resistance is primarily a result of inappropriate androgen suppression. This concept, while not supported by many other laboratory and clinical observations, has generated major interest in urological on-

Table 1 — GnRH agonists currently in clinical trials

	Structure										Relative Potency	Route of Administration
LH-RH	1	2	3	4	5	6	7	8	9	10	1	—
	p-GLU	His	Trp	Ser	Tyr	Gly	Leu	Arg	Pro	Gly-NH_2		
Buserelin (Hoechst)	.....				D-Ser(TBU)	.....				Ethylamide	100	SC,IN
Nafarelin (Syntex)	.....	.....	.....	.....	D-(2-Na1)	.....	.....	.....	.....	.....	100	SC,IN
Leuprolide (Abbott-Takeda)	.....	.....	.....	.....	D-Leu	.....	.....	.....	.....	Ethylamide	50	SC
Lutrelin (Wyeth)	.....	.....	.....	.....	D-Trp-7-N-Me-Leu	.....	.....	.....	.....	Ethylamide	100	
ICI-113630	.....	.....	.....	.....	D-Ser(TBU)	.....	.....	.....	.....	Az-Gly-NH_2	50	SC,IM (DEPO)
Histrelin (Ortho)	.....	.....	.....	.....	D-His(Bzl)	.....	.....	.....	.....	Ethylamide	100(?)	
Decapeptyl[t] (Triptorelin) (Debiopharm) (Lederle-American Cyanamid) (Ferring) (Ipsen-Beaufour Int.)	.....	.....	.....	.....	D-Trp	.....	.....	.....	.....	.....	100	Microcapsules*

** Once a month, i.m. (SC, subcutaneous; IN, intranasal; IM, intramuscular)*
[t] D-Trp-6-LH-RH Ethylamide (Generic) is also used by some groups

Table 2 — Objective parameters most commonly used to assess responses in patients with endocrine resistant prostatic cancer

Method	Limitations
Bone Radiographs	Lesions are predominantly blastic and usually will not change with treatment
Bone Scans	Quantitative assessments of positive areas are difficult in either direction. More useful to document progression
Serum Acid Phosphatase	Valuable only in rare occasions when very high values return to normal. Significant variations may be observed independent of treatment.
Serum Alkaline Phosphatase	Usually does not correlate with response or progression after treatment
Measurement of Prostatic Size	Measurements are frequently unidimensional (digital exam). The use of transrectal ultrasound and prostatic CAT scan or magnetic ressonance imaging are still controversial for monitoring response to treatment.

Table 3 — Single agent phase II trials in hormone-resistant prostatic carcinoma

Drug/Study (Ref)	Total number of responders reported/evaluable	CR + PR	SD	Improvement[1] (subjective)	Response[2] criteria
Doxorubicin					
O'Bryan et al (64)	2/9	2	0	0	B
O'Bryan et al (65)	5/15	5	0	0	B
Torti et al (88)*	21/25	4	17	0	C
Blum (7)[2]	7/51	NR[3]	NR	NR	A
Scher et al (74)	6/39	2	1	3 (5)	D
BCNU					
Carter et al (14)[4]	2/15	NR	NR	NR	A
CCNU					
Carter et al (14)[4]	2/19	NR	NR	NR	A
Cyclophosphamide					
Carter et al (14)[4]	8/57	NR	NR	NR	A
Cisplatin					
Yagoda et al (96)	4/25	3	1	0 (8)	D
Merrin (50)	24/54	17	7	0 (20)	A
Rossof et al (72)	4/21	4	0	0	B
Qazi et al (71)	0/17	0	0	0	E
Estracyt					
Mittleman et al (52)	9/44	9	0	0 (7)	C
Fossa et al (25)	6/17	NR	NR	6 (3)	A
Jonsson et al (37)	28/91	NR	NR	28 (24)	A
Kuss et al (42)	3/15	3	0	0 (2)	A
Leistenschneider et al (43)	8/23	NR	NR	8 (10)	A
Edsmyr et al (24)	19/90[5]	NR	NR	NR (40)	A
Nilsson et al (62)	28/91	NR	NR	NR (24)	A
Veronesi et al (92)	20/27	3	17	0	C

Table 3 (Cont)

Drug/Study (Ref)	Total number of responders reported/evaluable	CR + PR	SD	Improvement[1] (subjective)	Response[2] criteria
5-Fluorouracil					
Moore et al (54)	7/7	4	3	0	B
Ansfield et al (3)	1/7	0	0	NR	B
Weiss et al (34)	1/4	NR	NR	NR	B
Hall et al (27)	3/6	NR	NR	NR (3)	B
Hydroxyurea					
Lerner et al (44)	19/30	15	4	0	A
Mithramycin					
Kofman et al (41)	2/6	NR	NR	NR	B
Carter et al (14)[4]	2/36	NR	NR	NR	A
Mitomycin-C					
Humphrey et al (32)	4/4	0	0	0 (4)	B
Melphalan					
Houghton et al (29)	1/15	0	0	1 (1)	A
Nitrogen Mustard					
Karnofsky et al (38)	0/3	0	0	0 (2)	B
Carter et al (14)[4]	12/31	NR	NR	NR	A
Prednimustine					
Catane et al (15)	5/23	0	0	5 (8)	A
Vincristine					
Carter et al (14)[4]	2/22	NR	NR	NR	A
m-AMSA					
Drelichman et al (21)	10/21	0	10	0	C
Natale et al (59)	0/19	0	0	0	D
Aziridinylbenzoquinone					
Nichols et al (61)	16/36	0	13	3	B
Dihydroxyanthracenedione					
Drelichman et al (22)	7/35	2	5	0	A
Hexamethylmelamine					
Drelichman et al (20)	0/14	0	0	0	C
MGBG					
Scher et al (73)	6/29	6	0	0 (3)	D
Neocarzinostatin					
Natale et al (60)	0/14	0	0	0	D
Vindesine					
Jones et al (36)	16/27	5	11	0	E
VP-16-213					
Nissen et al (63)	2/5	1	0	1	B
Wlather et al (93)	1/23	1	4	0	E

[1]*Improvement — "Objective" evidence of response, but less than a PR*
[2]*A Not specified or unclear*
B Broad phase II (no specific criteria listed, or unclear)
C National Prostatic Cancer Project Response Criteria (NPCP) (81)
D Memorial Sloan-Kettering Response Criteria (96)
E Standard response criteria for solid tumors, including a decrease in markers
[3]*NR — Not reported (Responses reported but not quantitatively classified as CR, PR, SD or improvement)*
[4]*Review of multiple doses/schedules*
[5]*Included 26/90 patients with no prior hormonal treatment. Actual results for hormone-resistant patients are unclear*
**412 (CR + PR) in patients with bidimensionally measurable disease.*

cology. These investigators have combined GnRH analogs or surgical castration with antiandrogens (Flutamide®) and according to their data in various tumor models, this results in a more profound depletion of intracellular DHT compared to either approach alone and was associated with further retardation of androgen dependent tumor growth. While their preliminary clinical observations with the combined treatment in an uncontrolled setting are quite encouraging and provocative, the final conclusions regarding the relative efficacy of this treatment compared to standard approaches can only be determined in carefully conducted randomized studies. Currently, there are several randomized trials designed to study various combined endocrine treatments, and their results are still pending. In the United States, the National Cancer Institute sponsored a multi-institutional study comparing Leuprolide® + Flutamide® *versus* Leuprolide® + placebo in a randomized, double blind fashion. If combined treatment is proven superior to conventional approaches, the current availability of various treatments acting at different levels in the pathway of androgenic control of tumor growth provides ample opportunity for a logical selection of combinations, however until the results of the various clinical trials become available, routine use of such approaches should be confined to an investigational setting.

Non-Hormonal Cytotoxic Chemotherapy

Virtually all drugs available in the clinics have been applied or systematically tested in patients with endocrine resistant prostatic cancer. Despite extensive testing, the role of this treatment modality for prostatic cancer has yet to be determined[38].

Chemotherapy studies in prostatic cancer are difficult to conduct and assess. One of the major problems relates to the disease itself. Prostatic cancer usually involves bone and this is manifested radiographically by osteoblastic lesions which are difficult if not impossible to quantify prospectively in a reproducible fashion. The presentation of soft tissue and visceral involvement that allows for more reliable measurements both clinically and radiographically is rare and similarly, serum markers frequently lack specificity relative to the disease status and response to treatment. *Table 2* describes the usual methods applied for the assessment of treatment in patients with disseminated disease.

Table 3 describes the experience with various single agents developed in uncontrolled studies and *Table 4* illustrates the same with combinations and in both tables we specify the response criteria used in all studies[38].

Table 4 — Phase II trials with combination chemotherapy

Drug/Study (Ref)	Total number of responders reported/evaluable	CR + PR	SD	Improvement[1] (subjective)	Response[2] criteria
CTX + Doxorubicin					
Izbicki et al (91)	8/20	3	5	(8)	E
Ihde et al (34)	11/22	7	4		F
Merrin et al (51)	5/19	0	5	(8)	A
Lloyd (45)	2/11	2	0		B
Soloway et al (85)	12/21	0	12	(7)	C
CTX + 5-FU					
Merrin et al (51)	2/13	1	1	0 (7)	A
Estramustine Phosphate + 5-FU					
Kennealy et al (40)	3/25	0	0	3 (8)	A
Chlorambucil + Prednisolone					
Beckley et al (4)	2/11	0	2	0	C
BCNU + CTX + Doxorubicin					
Presant et al (70)	11/27	7	4	2	E
Doxorubicin + DDP					
Citrin et al (18)	10/21	NR	NR	NR	G
Perloff et al (68)	9/17	9	0	(2)	A
CTX + Prednisolone					
Anderson et al (2)	7/83	NR	NR	7 (55)	A
CTX + Doxorubicin + DDP					
Ihde et al (35)	12/17	7	5	0	F
CTX + DDP + Prednisone					
Berry et al (6)	10/22	0	10	0	C

Table 4 (Cont.)

Drug/Study (Ref)	Total number of responders reported/evaluable	CR + PR	SD	Improvement[1] (subjective)	Response[2] criteria
Doxorubicin + 5-FU + Mito-C					
Logothetis et al (48)	30/62[3]	NR	NR	NR	H
Kasimis et al (39)	7/16	0	7	0 (9)	C
Hsu et al (31)	9/14	1	8	0 (10)	C
Melphalan + MTX + 5-FU + VCR + Prednisone					
Paulson et al (67)	51/84[4a]	3[4b]	0	NR (40)	I
CTX + MTX + 5-FU + VCR + Prednisone					
Buell et al (10)	6/16	5	1	(11)	E

Abbreviations: CTX = Cyclophosphamide; 5-FU = 5-Fluorouracil; DDP = Cisplatin
[1]Improvement — "Objective" evidence of response, but less than a PR
[2]A Not specified or unclear
B Broad phase II (no specific criteria listed, or unclear)
C National Prostatic Cancer Project Response Criteria (NPCP) (81)
D Memorial Sloan-Kettering Response Criteria (96)
E Standard response criteria for solid tumors, including a decrease in markers
F NCI-VAH criteria (34)
G Citrin et al (17)
H Logothetis et al, M.D. Anderson Hospital and Tumor Institute (48)
I Paulson et al (67)
[3]Responses were seen in 18/41 patients with bone metastasis only and 12/21 with bone and visceral sites (8 in the lung).
[4a] Twenty-four patients had at least 50 percent decrease in acid phosphatase (A.P.),
13 had normalization and 11 had 50 percent reduction without normalization.
Twenty-seven patients had improvement in performance status correlated with improved survival.
[4b] Three of seven patients with bidimensionally measurable disease had CR + PR.

The results of clinical studies in this disease depend heavily on the response criteria used to establish therapeutic efficacy. A response criteria commonly used for clinical trials in prostatic cancer was introduced by the National Prostatic Cancer Project (NPCP), which incorporates the category of stabilization of disease (SD) as evidence of response to treatment[39]. SD as defined by NPCP reflects the evidence of "no progression" at 3 months and this was supported by the observation that patients demonstrating "no progression" (at 3 months) lived significantly longer than those demonstrating failure during that time interval. What remains unproven, however, is whether this stabilization is due to treatment. It is only logical to assume that patients with more indolent disease live longer than those with a more aggressive biology. It remains possible that stabilization of disease and the survival differences aluded to above are most likely secondaray to biological factors inherent of the disease rather than therapeutic effects. Because of this, the use of SD to support for therapeutic benefits remains questionable at best, and may bias the results by falsely inflating response rates.

Despite the short commings appreciated with most response criteria in this disease, investigators still report therapeutic benefits by using "response rates", however in situations where tumor response cannot provide reliable estimates of therapeutic efficacy, the use of survival may be beneficial. Because of this we have assessed the survival results in all prospective randomized studies and this is illustrated on *Tables 5* and *6*. Two important studies conducted by NPCP compared various single agents to a no chemotherapy control arm ("standard treatment") (studies 100 and 200, Table 8)[38]. In both studies patients randomized to one of the chemotherapy arms were subsequently crossed over at the time of progression to receive the other cytotoxic drug, while those randomly allocated to receive the standard treatment were maintained on this approach until death. The response rates on the chemotherapy arms were better than standard treatment on both studies. Despite this, both studies showed virtually identical median survival figures for all treatment arms. Furthermore, a more careful examination of the responses reported, indicate that the overwhelming majority were included on the SD category. *Table 8* shows that complete and partial responses (CRF + PR) are uncommon in this disease, and *Figure 1* illustrates a composite of all survival figures observed in randomized studies containing at least 20 patients/arm, which demonstrates their close similarities.

Table 5 — National prostatic cancer project: randomized trials in prostatic carcinoma

Treatment (Ref)	Number evaluable/ entered	CR + PR	SD	Median survival (wks)
NPCP Study 100 (78,80)				
CTX	41	4	20	47
5-FU	33	4	14	44
Standard (A)	36	0	7	38
NPCP Study 200 (56,80)				
Estramustine Phosphate	46/54	3	11	26
Streptozotocin	38/46	0	12	25
Standard (A)	21/25	0	4	24
NPCP Study 300 (76)				
CTX	35/39	0	9	27
DTIC	55/68	2	13	40
Procarbazine	39/58	0	5	31
NPCP Study 400 (57)				Mean:
Estramustine Phosphate + Prednimustine	54	1	6	37
Prednimustine	62	0	8	36
NPCP Study 700 (47)				
CTX	43/47	3	12	41
MeCCNU	27/38	1	7	22
Hydroxyurea	28/40	2	2	19
NPCP Study 800 (84)				
Estramustine Phosphate	27/38	1	6	26
Vincristine	29/42	1	4	22
a + b	34/41	0	7	32
NPCP Study 1100 (46)				
Estramustine Phosphate	50/63	1	16	43
MTX	58/67	3	21	37
DDP	50/59	2	16	33
NPCP Study 1200 (83)				
Estramustine Phosphate	40/50	0	7	38
DDP	42/51	0	9	28
a + b	42/48	0	14	40

(A) Radiation therapy, prednisone, TACE, dexamethasone, testosterone, DES, stilphostrol, Aldactone, cryosurgery, dicorvin, estinyl.

The above data support the view that cytotoxic chemotherapy seldom produces significant palliation in this disease and its use most likely does not affect survival in endocrine resistant patients. Routine use of this modality in such patients should be reserved for situations where other less costly and toxic palliative modalities can no longer be used. Major efforts should be made to study chemotherapy in this disease, focusing on the search for new agents and, at the same time, for methods to provide more reliable assessment of response.

Table 6 — Other randomized trials in prostatic carcinoma

Treatment (Ref)	Number evaluable/ entered	CR + PR	SD	Improvement[1]	Median Survival	Response[2] criteria
Smalley et al (82)						
5-FU	32/49	2	5	—	34 wks	A
CTX + Doxorubicin + 5-FU	39/52	2	4	—	25 wks	
Eagan et al (23)						
Adriamycin	19	—	—	5	NR	B
CTX + 5-FU	18	—	—	2	NR	
Chlebowski et al (16)						
CTX	15	0	8	—	7,2 mos	C
CTX + Doxorubicin + 5-FU	12	0	6	—	8,9 mos	
Muss et al (58)						
CTX	17	0	9	—	8 mos	C
CTX + MTX + 5-FU	15	1	7	—	5 mos	
Herr et al (28)						
CTX + MTX + 5-FU	20	3	4	—	26 wks	D
CCNU	20	0	6	—	24 wks	
Tejada et al (87)						
5-FU	8	2	1	—	NR	D
CCNU	10	4	2	—	NR	
Pavone-Malacuso et al (66)						
Doxorubicin	11/22	0	3	—	NR	C
Procarbazine	14/24	1	0	—	NR	
DeWys et al (19)						
Doxorubicin	96/112	15/61*	0	—	29 wks	D
5-FU	51/54	3/42*	0	—	24 wks	
Stephens et al (86)						
CTX + Doxorubicin	68	6/19*	18	—	27 wks	D
Hydroxyurea	69	1/24*	9	—	28 wks	
Torti et al (90)						
Doxorubicin	20	1/13**	8	**	48 wks	E**
Doxorubicin + Cisplatin	17	2/10**	9	**	43 wks	

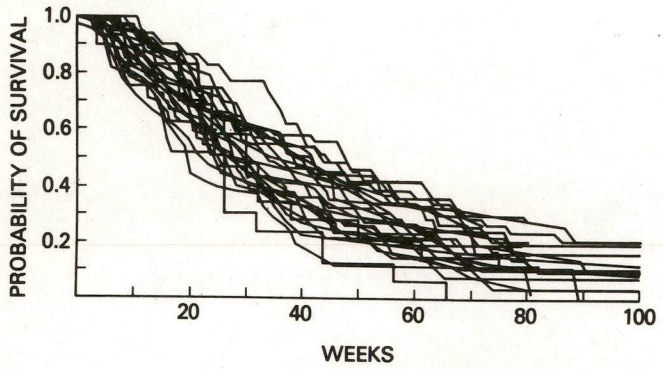
[1]Improvement reported but not quantitated, or some evidence regarded as treatment benefit (decrease in marker values, decrease in prostatic size)
[2]A Southeastern Cancer Study Group Criteria (82)
B Ancillary Scoring System.(23) (including crossed-over patients)
C National Prostatic Cancer Project Criteria (81)
D Usual criteria for solid tumors, including a decrease in acid phosphatase
*Patients with "measurable disease" only (including bidimensionally measurable disease, elevated markers or presence of "evaluable" bony (lesions). Figures include crossed-over patients
*Northern California Oncology Group criteria for response (90). Objective Responses are recorded separately according to their category of measurable *versus* evaluable. Ancillary responses included on the improvement section do not allow for a determination of an actual denominator.
NR Not reported

Table 7 — Summary of overall responses in uncontrolled studies*

Total number of evaluable pts.	Responses (%)	CR + PR (%)	SD (%)	Other** (%)
1683	526 (31%)	131 (8%)	156 (9%)	239 (14%)

*Extrapolated from Tables 2 and 3
**Include those responses not specified as CR, PR, SD (NR)

Figure 1 — Composite of survival curves in randomized studies (20 or more patients/arm).



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