La radioterapia nel trattamento multimodale delle metastasi ossee e cerebrali

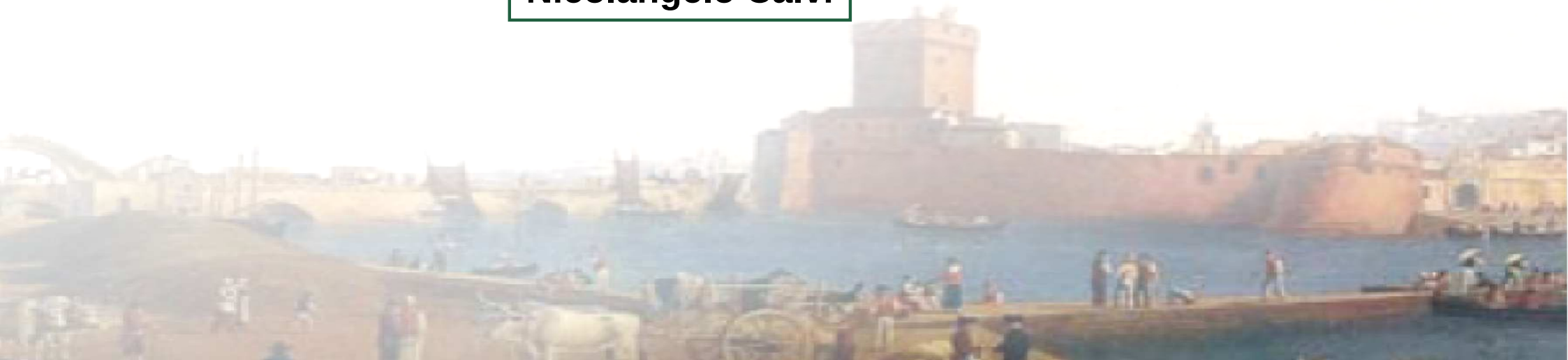
Taranto – 16 Marzo 2007

OncologiaMedica
Osp. "V. Fazzi" - LECCE
direttore: V Lorusso

Metastasi Ossee

La chemioterapia

Nicolangelo Calvi



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metàstasi — *gr.* METÀSTASIS *trasposizione, cambiamento*, comp. di METÀ *al di là, ra* e STÀSIS *stato, posizione*, da I-STÈ-MI *ui fermo, mi colloco* (v. *Stare*).

Term. di medic. Il cambiamento di sede di una malattia, ovvero Trasporto di una materia morbosa dalla parte che essa occupava verso di un'altra.

Deriv. *Metastàtico.*

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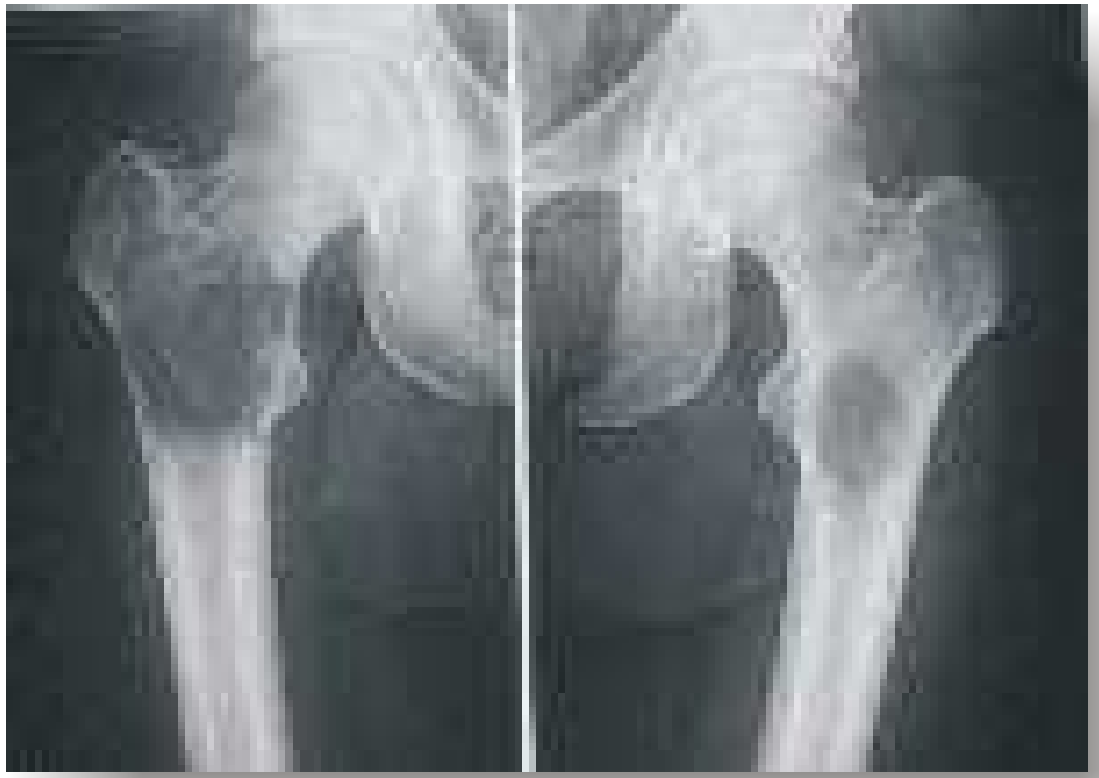

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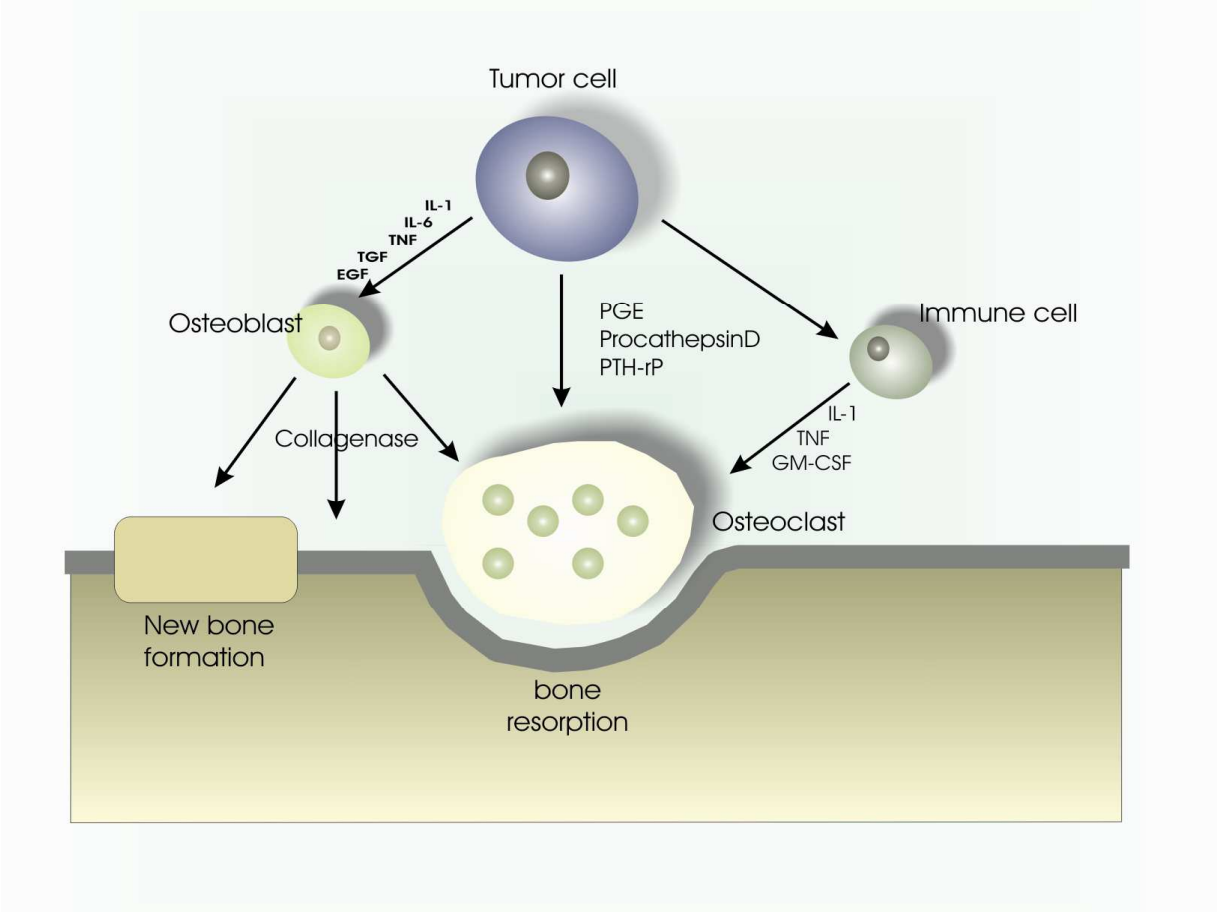

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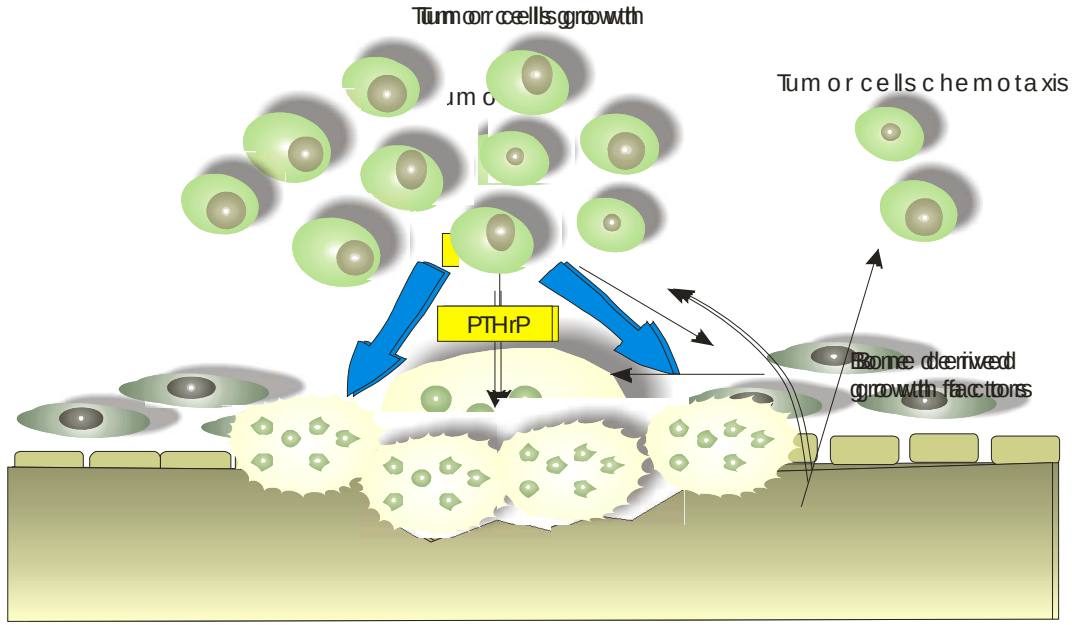

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Primary Tumor Site	No. Of Studies	Incidence % of Bone Metastases	
		Median	Range
Breast	5	73	47-85
Prostate	6	68	33-85
Thyroid	4	42	28-60
Kidney	3	35	33-40
Bronchus	4	36	30-55
Esophagus	3	6	5-7
Gastrointestinal	4	5	3-11
Rectum	3	11	8-13

CYTOTOXIC DRUGS as first treatment in bone metastases

- Not hormonoresponsive tumors
- Lymphangitic pulmonary metastases
- Liver metastases compromised hepatic function
- Need of a rapid response

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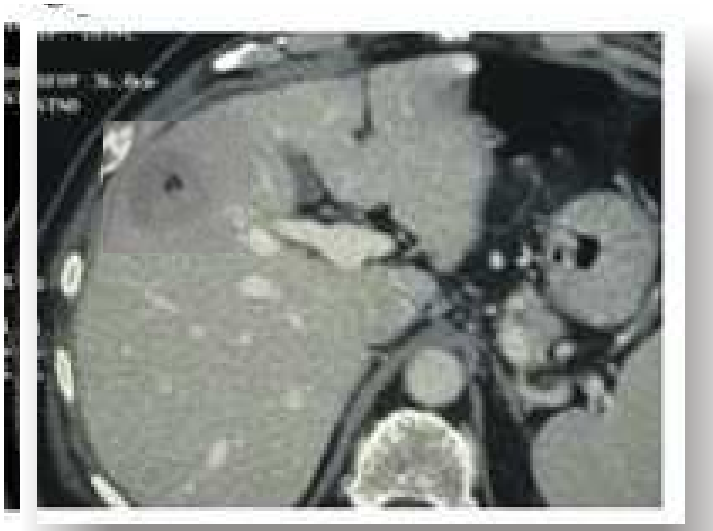

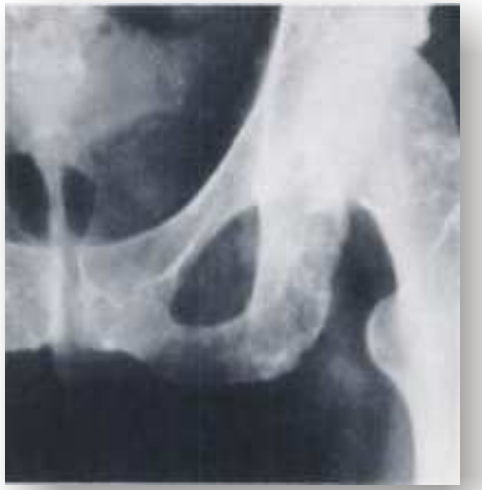

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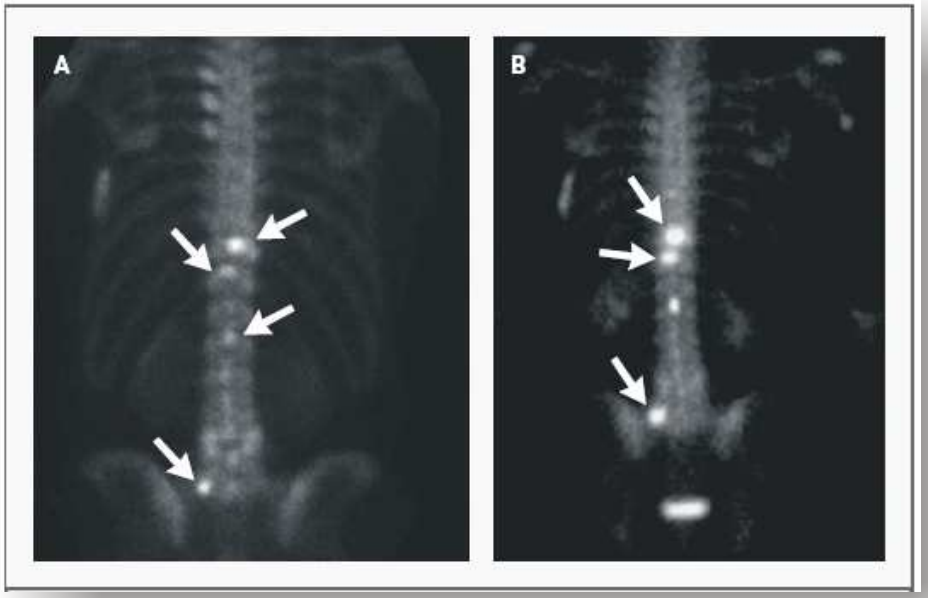

Reduction of bone metastases related pain as a new marker of tumor response

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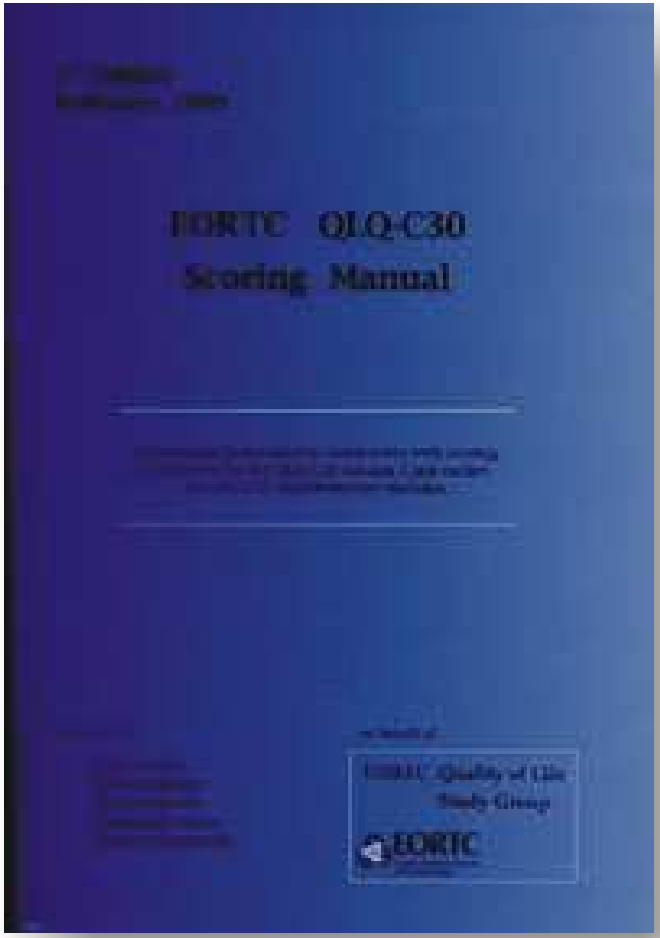

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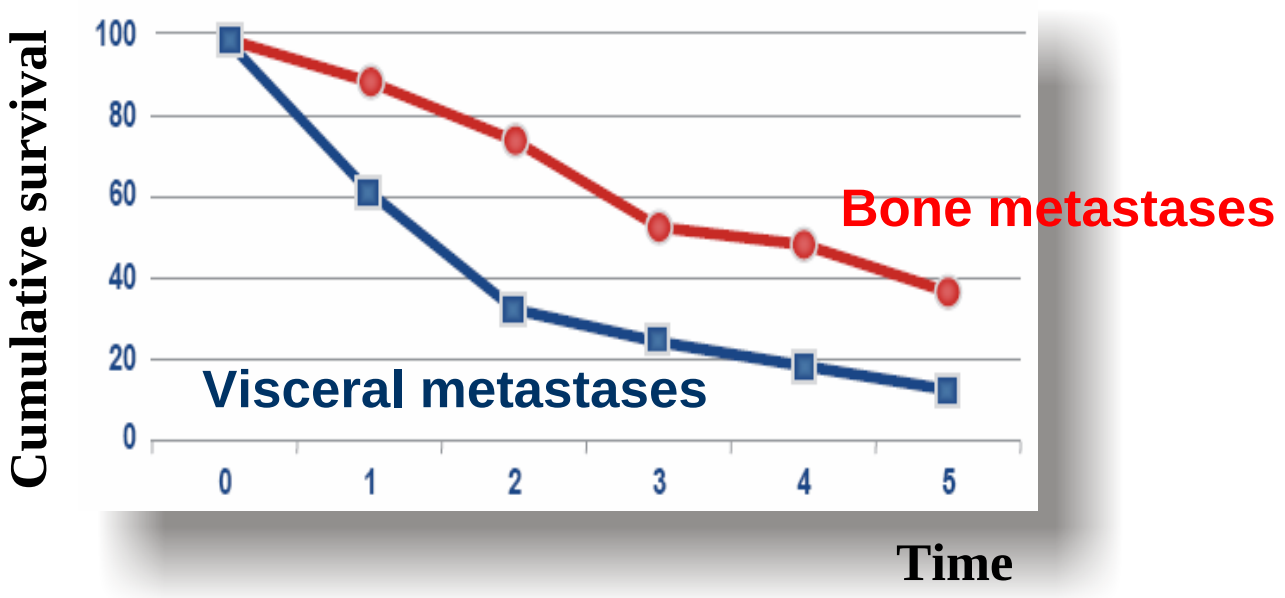

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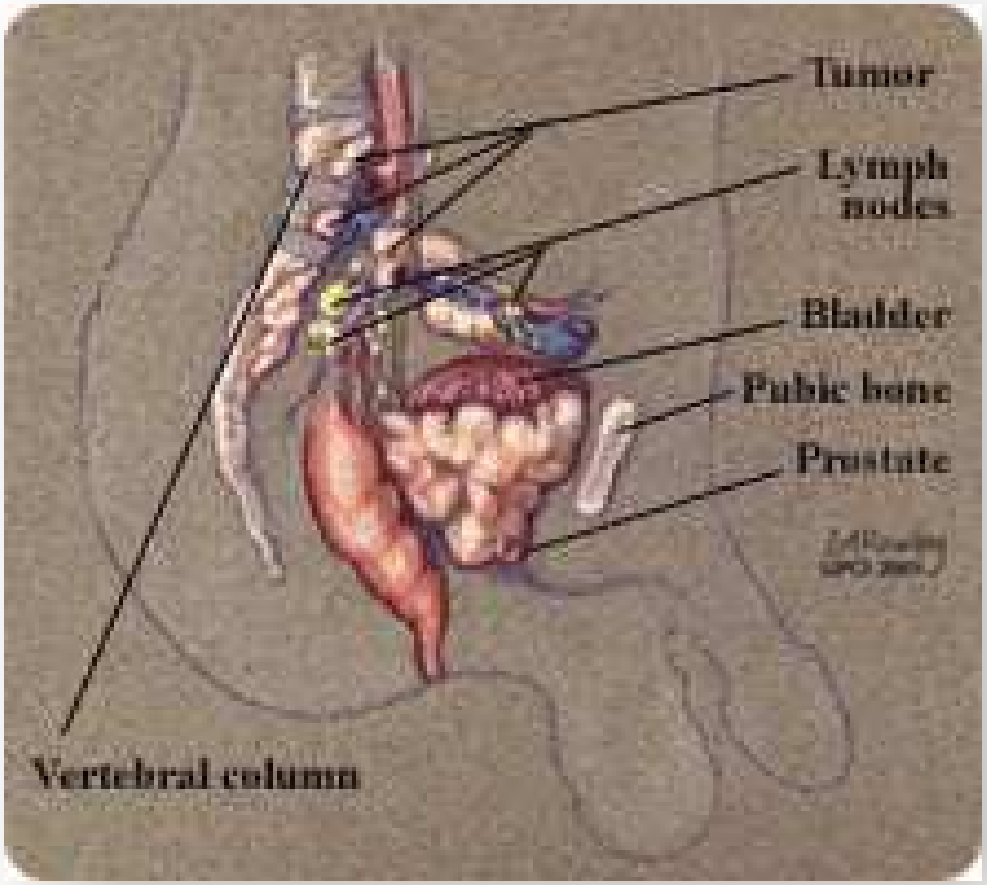

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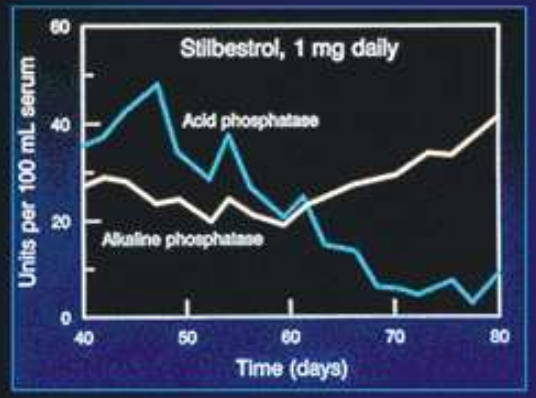
Charles Huggins and Hormonal Treatment of Prostate Cancer



Historical Article

PROSTATE CANCER: A BRIEF HISTORY AND THE DISCOVERY OF HORMONAL ABLATION TREATMENT

BERNARD LYTTON

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Classics in Oncology

Charles Brenton Huggins
(1901-)

relationship between hormones and cancer of the prostate. Huggins and Hodges showed that prostatic cancer was dramatically affected by castration or administration of estrogens, treatment which reduced the levels of acid phosphatase. Huggins' observation that the synthetic estrogen diethylstilbestrol caused regression in disseminated prostatic cancer initiated the era of cancer chemotherapy.

The following reprinted paper was the

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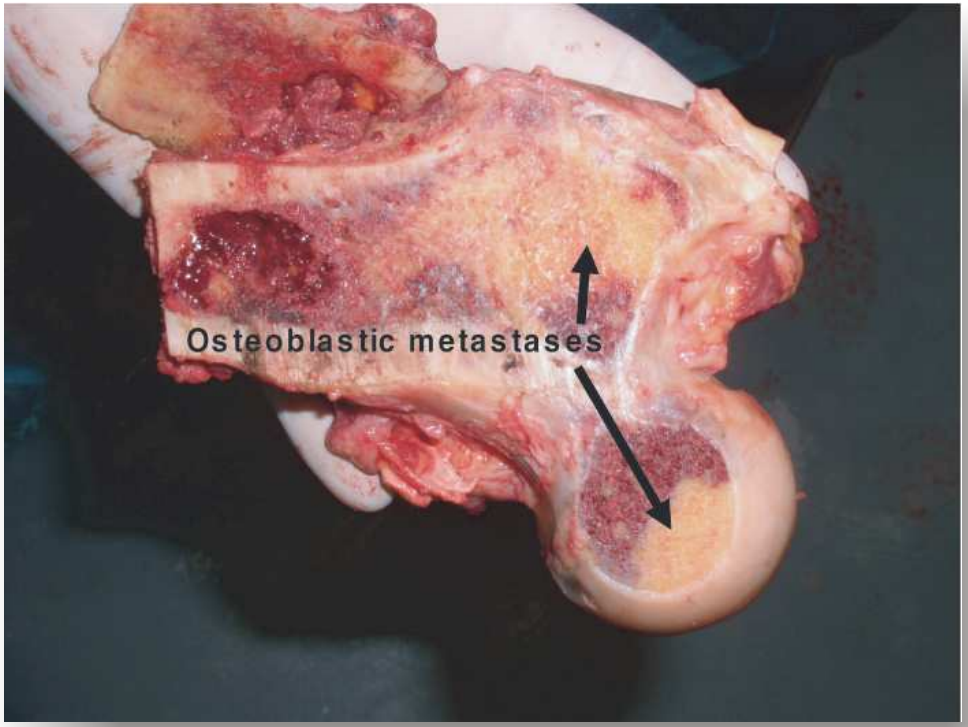

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Cytotoxic chemotherapy for
ADVANCED hormone-resistant
PROSTATE CANCER

Yagoda A, PetrylaK D

hormone-refractory prostate cancer unresponsive to cytotoxic agents.

documentation of response complicated by a lack of established criteria to judge activity in a disease in which few patients had measurable soft tissue lesions

Cancer, 1993 Feb 1; 71(3 Suppl.): 1098-109

SWOG9916 and TAX327

Comparison of Baseline Caracteristics of Patients Randomly assigned to the Trails

Study	SWOG 9916	TAX 327
Therapy	Docetaxel + estramustine v M/P	Docetaxel + prednisone v M/P
Author	Petrylak[4]	Tannock[3]
No. of patients	770	1,006
Median age, year	70	68
PSA, median	84	112
Bone metastases, %	88	91
Visceral metastases, %	6	23
Opiate analgesic use, %	36	45
Survival superior arm, months	17.5	18.9
Inferior arm(s), months	15.6	17.4
		16.5

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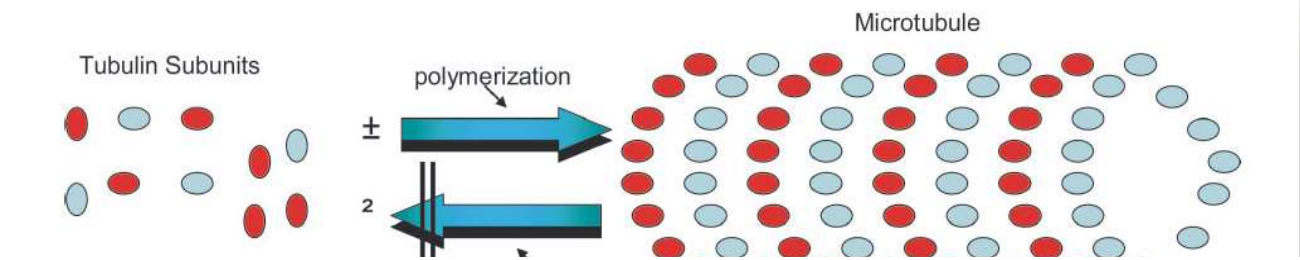

Trial	Docetaxel	Combination	Patients with ≥ 50% Decline in Prostate-Specific Antigen Level (%)	Patients with a Soft Tissue Response (%)	Overall Survival
Picus and Schultz[36] (1999)	75 mg/m^2 every 21 days	Not available	46	24	27 months
Friedland, et al.[37] (1999)	75 mg/m^2 every 21 days	Not available	38	29	67% at 15 months
Berry, et al.[38] (2001)	36 mg/m^2 weekly for 6 of 8 weeks	Not available	41	33 (complete response: 17)	9.4 months
Beer, et al.[39] (2001)	36 mg/m^2 weekly for 6 of 8 weeks	Not available	46	40	39 weeks
Gravis, et al.[40] (2003)	35 mg/m^2 weekly for 6 of 8 weeks	Not available	48	28 (stable disease)	20 months
Petrylak, et al.[41] (2000)	70 mg/m^2 every 21 days	Estramustine 280 mg three times a day for days 1–5	68	55	77% at 1 year
Sinibaldi, et al.[42] (2002)	70 mg/m^2 every 21 days	Estramustine 280 mg every 6 hours × 5 doses; coumadin 2 mg daily	45	20	13.5 months
Savarese, et al.[43] (2001), CALGB 9780	70 mg/m^2 every 21 days	Estramustine 10 mg/kg/day in three daily doses for days 1–5; hydrocortisone 30 mg every morning and 10 mg every afternoon daily	68	50 (partial response: 38; complete response: 13)	20 months
Petrylak, et al.[44] (2004), SWOG*/ Intergroup (Phase III)	60 mg/m^2 every 21 days	Estramustine 280 mg three times a day for days 1–5	50	17	18 months
Tannock, et al.[45] (2004), TAX-327 (Phase III)	75 mg/m^2 every 21 days	Prednisone 5 mg twice daily	45	12	18.9 months
	30 mg/m^2 weekly for 5 of 6 weeks	Prednisone 5 mg twice daily	48	8	17.3 months

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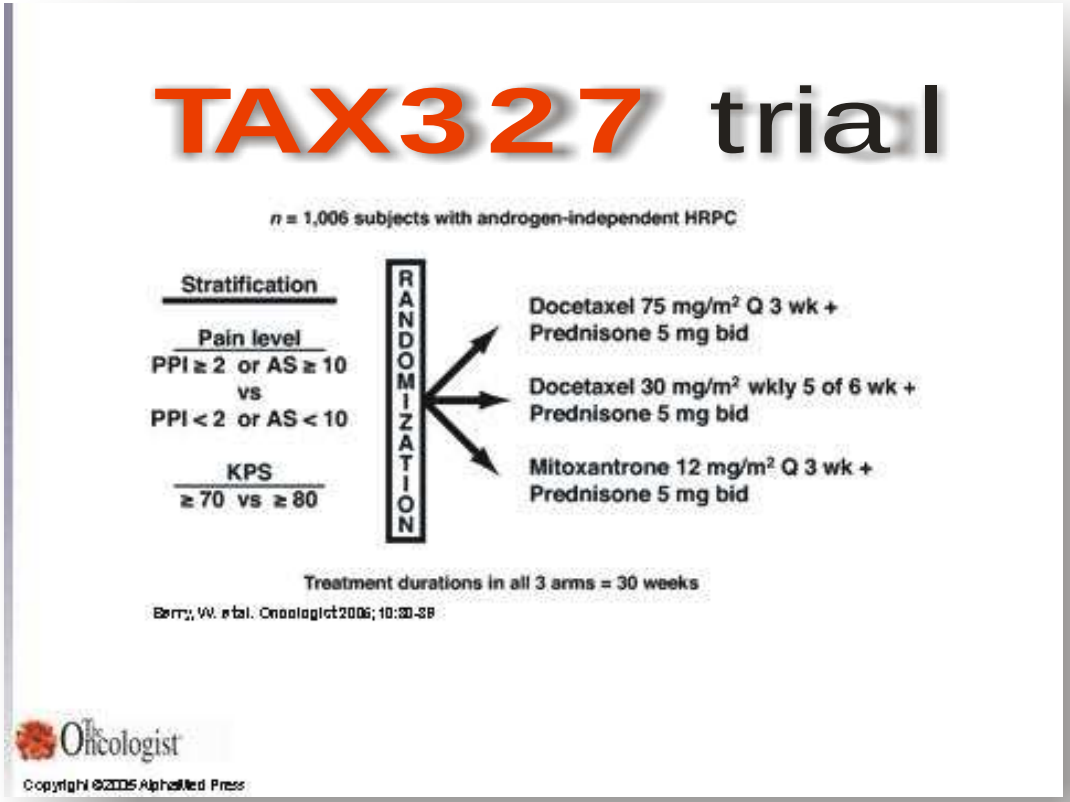

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Efficacy outcomes from the TAX 327 trial

	Q3W Docetaxel (n = 335)	Weekly docetaxel (n = 334)	Mitoxantrone (n = 337)
Median survival (months)	18.9 $p = .009$	17.4 $p = .36$	16.5
Secondary end points			
≥50% decline in serum PSA	45% (131/291) $p < .001$	48% (135/282) $p < .001$	32% (96/300)
Pain response rate	35% (54/153) $p = .01$	31% (48/154) $p = .08$	22% (35/157)
Tumor response rate	12% (17/141) $p = .11$	8% (11/134) $p = .59$	7% (10/137)
Quality of life response rate	22% (61/278) $p = .009$	23% (62/270) $p = .005$	13% (35/267)

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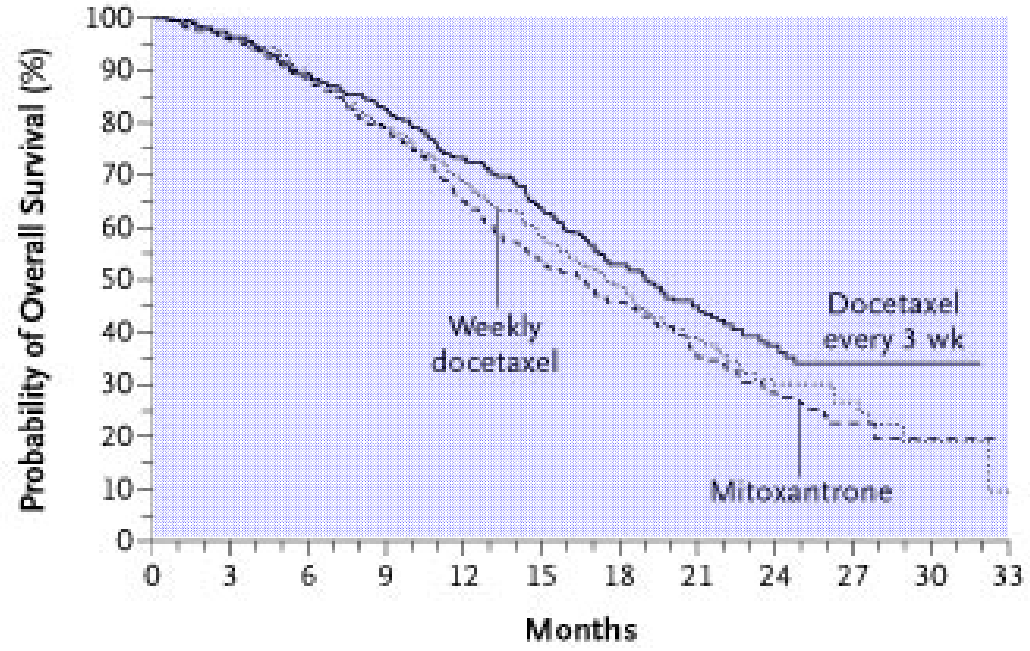
Kaplan-Meier Estimates of the Probability of Overall Survival in the Three Groups



No. at Risk						
Docetaxel every 3 wk	335	296	217	104	37	5
Weekly docetaxel	334	297	200	105	29	4
Mitoxantrone	337	297	192	95	29	3

Tannock I et al. N Engl J Med 2004;351:1502-1512

The NEW ENGLAND JOURNAL of MEDICINE

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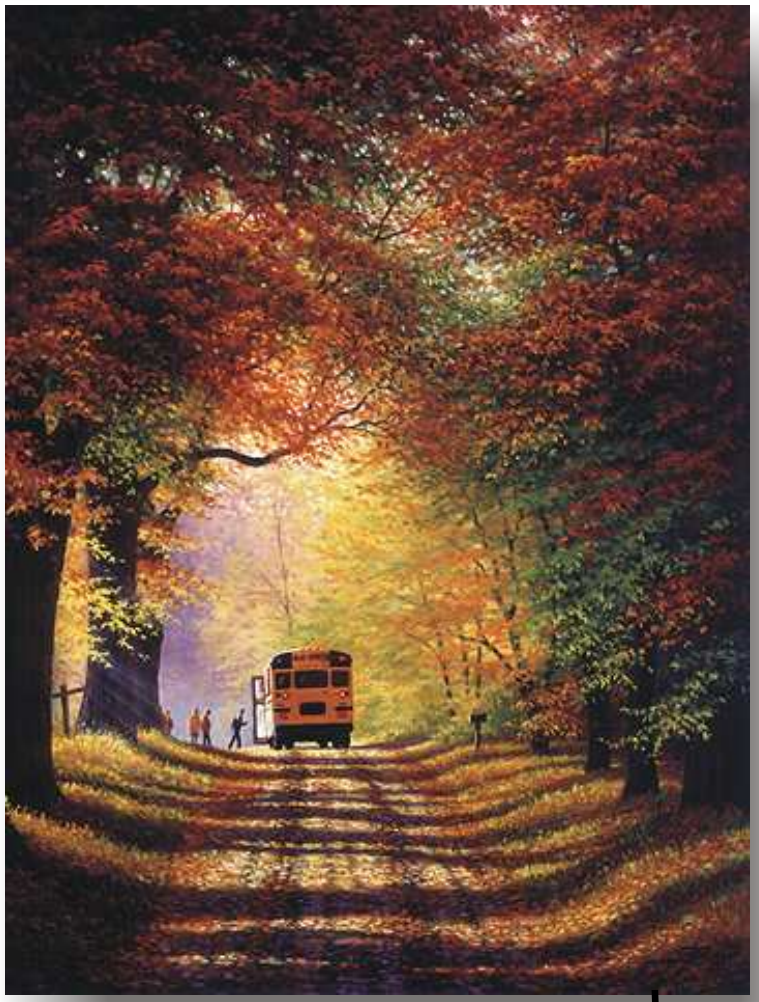
Future for the Treatment of Prostate Cancer with BONE METASTASES

Classic cytotoxic agents

Vaccines

Radiolabeled mAb

Targeted agents



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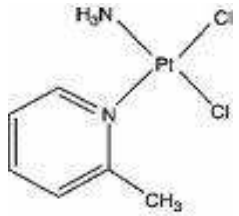
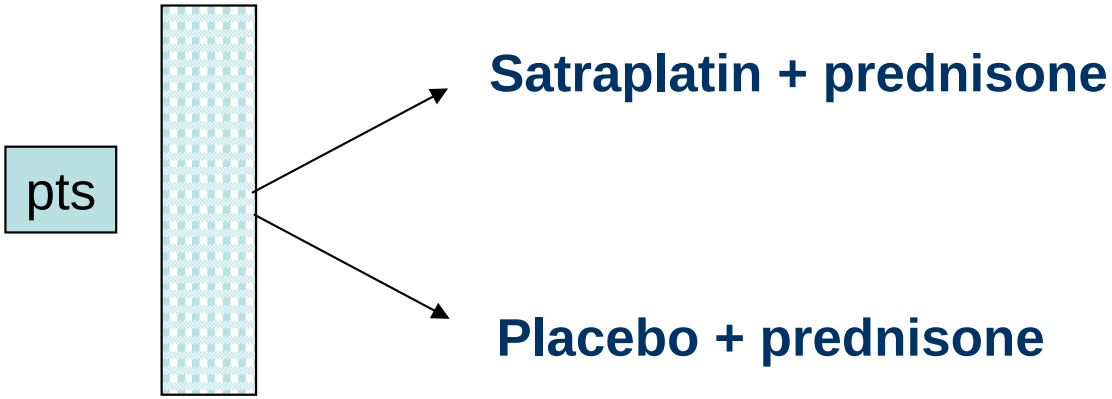


Satraplatin

SPARC trial



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Atrasentan

Endothelin-A receptor (ETAR) antagonist

Endothelin-1 (ET-1) is implicated in the development of the osteoblastic bone lesions that characterize metastatic disease.

SWOG S0421 trial, a randomized, placebo-controlled phase III trial designed to compare docetaxel, prednisone, and atrasentan with docetaxel plus prednisone alone in men with advanced HRPC.

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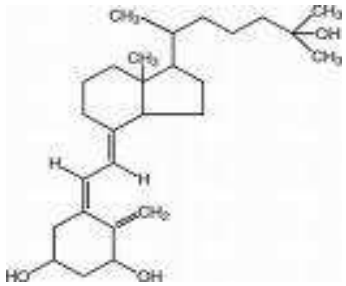

Calcitriol

Antiproliferative and proapoptotic effects in prostate cancer

ASCENT trial

randomized, double-blinded, placebo-controlled trial evaluating the combination of docetaxel with the proprietary high-dose calcitriol formulation DN-101

Thalidomide
Bevacizumab

Thalidomide is a putative angiogenesis inhibitor. It inhibits angiogenesis and reduces VEGF levels

Bevacizumab, a humanized monoclonal antibody that targets VEGF

The National Cancer Institute is currently conducting a phase II study of a four-drug combination consisting of docetaxel, prednisone, thalidomide, and bevacizumab in men with chemotherapy-naive progressive HRPC, and the CALGB is coordinating a phase III, double-blinded, placebo-controlled trial of docetaxel plus prednisone with or without bevacizumab

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Gleevec

Inhibitor of PDGF-receptor signalling pathway implicated in tumor angiogenesis and bone formation.

Administered with zolendronic acid and paclitaxel in an experimental model of bone metastases of human prostate cancer

Combination with docetaxel

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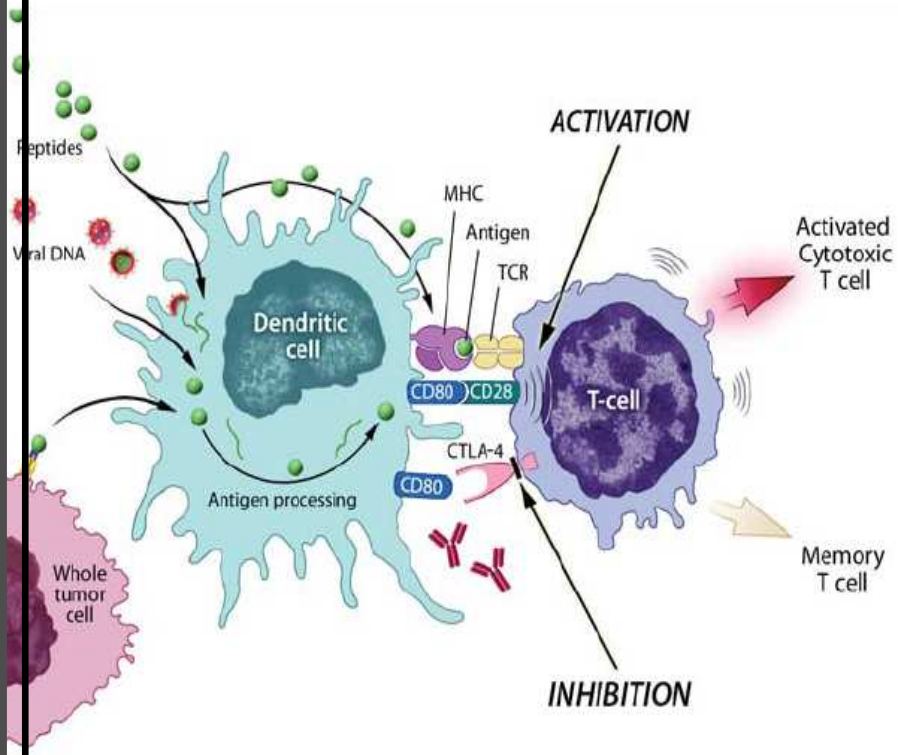
The Oncologist®

Therapeutic Vaccines for Prostate Cancer

CHRISTOPHER P. TARASSOFF, PHILIP M. ARLEN, JAMES L. GULLEY

Laboratory of Tumor Immunology and Biology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland, USA



PSA, prostatic acid phosphatase, and prostate membrane antigens have been used as targets for developing immunotherapy.

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Phase II Study of APC8015F in Patients With Progressive Metastatic Prostate Cancer and Disease-Related Pain

Alternate Title

APC8015F in Treating Patients With Progressive Metastatic Prostate Cancer and Disease-Related Pain

Basic Trial Information

Phase	Type	Status	Age	Sponsor	Protocol IDs
Phase II	Treatment	Active	18 and over	NCI, Pharmaceutical / Industry	**UCLA-0307122-01** DEN-PB01, NCT00170066

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Synergistic action of CYTOTOXIC DRUGS and BISPHOSPHONATES

Author (year)	Cancer cell line	Type of drug	Type of effect	Synergistic/ additive
Neville-Webbe *et al.* (2005)[48] Woodward *et al.* (2005)[50]	Breast and prostate cancer cell lines	Doxorubicin	Induction of apoptosis Inhibition of invasion	Synergistic, timing-dependent and schedule-dependent
Neville-Webbe *et al.* (2005)[48,49]	Breast and prostate cancer cell lines	Paclitaxel	Induction of apoptosis	Synergistic, timing-dependent and schedule-dependent
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Jagdev *et al.* (2001)[52]	Breast cancer cell lines MCF-7 and MDA-MB-231	Paclitaxel	Induction of apoptosis	Synergistic
Vogt *et al.* (2004)[51]	Breast cancer cell line	Epirubicin/ cyclophosphamide/ docetaxel/paclitaxel	Growth inhibition	Synergistic

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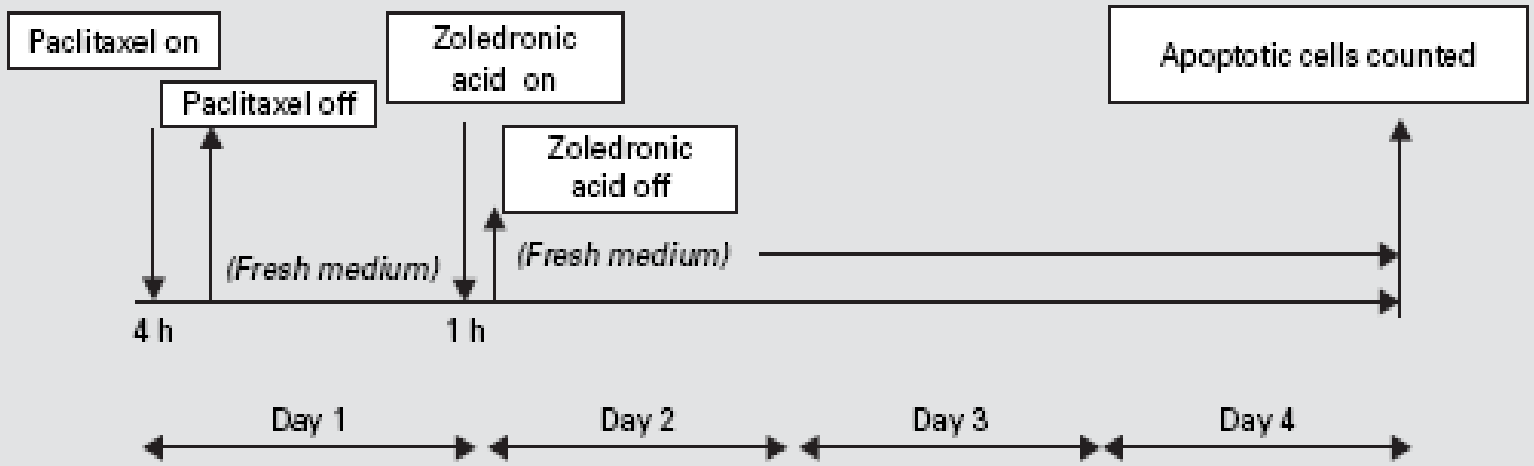
Synergistic action of CYTOTOXIC DRUGS and BISPHOSPHONATES

Paclitaxel then Zolendronic acid



Neville-Webbe HL *et al.* (2006)*Tumor Biol* **27:**92–103

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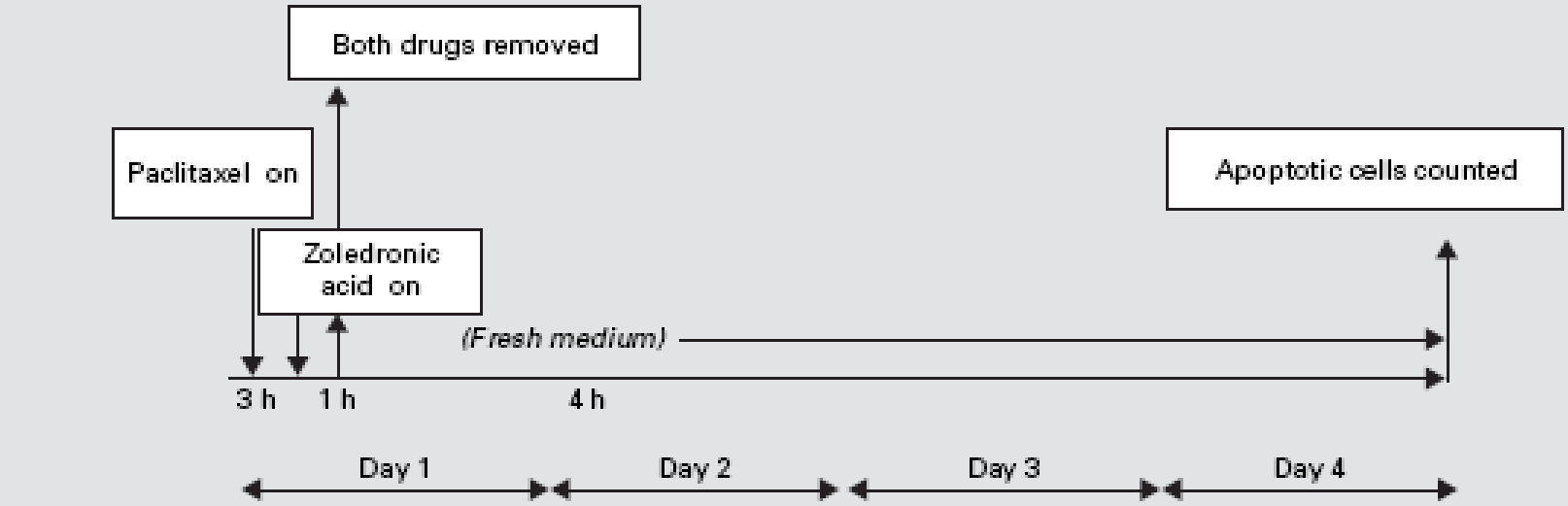
Synergistic action of CYTOTOXIC DRUGS and BISPHOSPHONATES

Paclitaxel and Zolendronic acid



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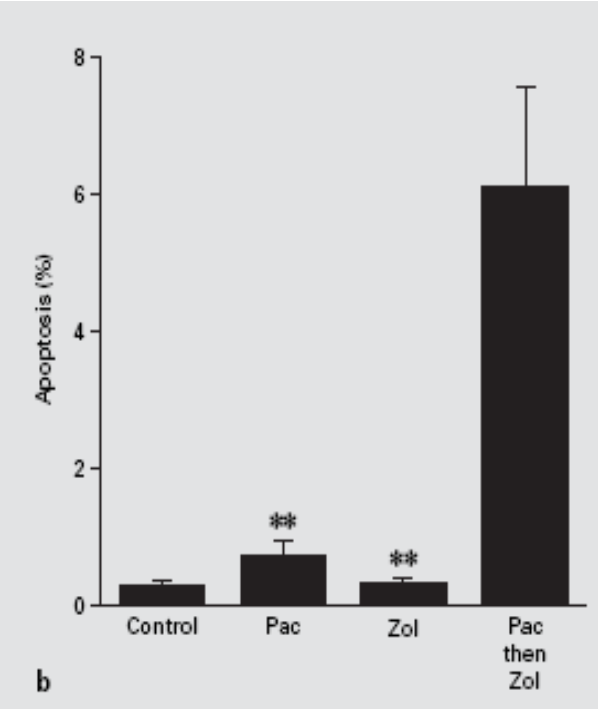

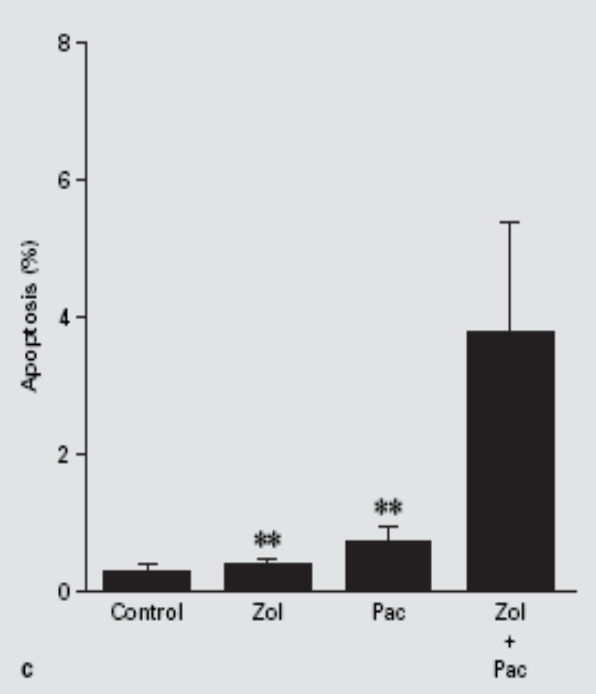

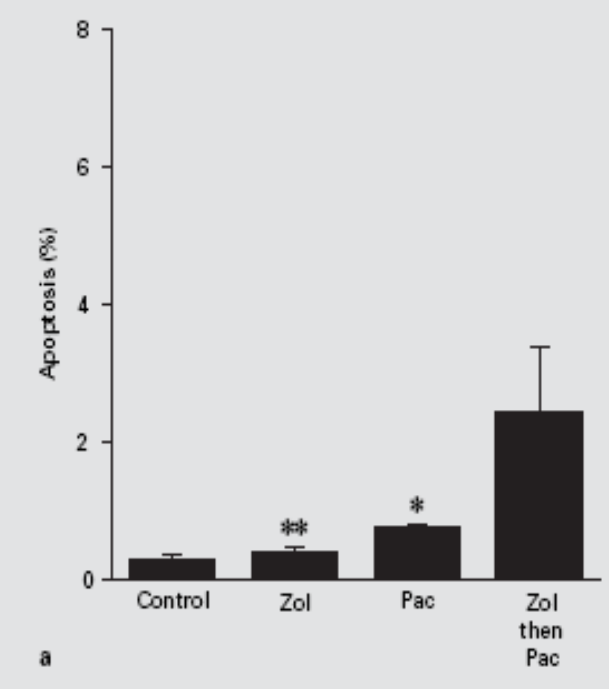

Neville-Webbe HL *et al.* (2006)*Tumor Biol* **27:**92–103

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La chemioterapia

Synergistic action of CYTOTOXIC DRUGS and BISPHOSPHONATES

Author (year)	Cancer cell line	Type of drug	Type of effect	Synergistic/ additive
Matsumoto *et al.* (2005)[56]	SCLC cell line	Paclitaxel/etoposide/ cisplatin/irinotecan	Induction of apoptosis	Synergistic
Trojan *et al.* (2005)[58]	Gastric cancer cell line	Gemcitabine, oxaliplatin	Induction of apoptosis	Synergistic
Ullen *et al.* (2003)[61]	Hormone-refractory prostate cancer cell lines	Gemcitabine	Induction of cytotoxicity	Additive/synergistic

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conclusions

In the clinic, chemotherapy and bisphosphonates are not given in any particular sequence, and tratment intervals vary; preclinical data indicate that to achieve maximum effects from the combination of treatments, the sequence and the timing of drug administration have an important role and could determine the efficacy of the therapy, both in advanced disease and in the adjuvant setting.