Chemotherapy for Advanced Renal-Cell Carcinoma: 1983-1993

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RENAL-CELL CANCER (RCC), as documented in prior (1967,[1] 1975,[2] 1977[3] and 1983[4]) reviews has been a hormonally and cytotoxic chemotherapeutically resistant tumor: It remains so today.

Since the present review spans 11 years, January 1983 through December 1993, it is of interest to examine changes in cancer incidence and death rates of 1983[5] and 1993.[6] While the incidence increased for all and for renal malignancies by 41.3% and 51.7%, respectively, the percent of RCCs remained rather constant at 2.1% and 2.3%, respectively (Table 1). There was no change in males (each 2.7% and only a +0.2% in females (1.6% and 1.8%, respectively).

The enormous increase in the number of prostate cases from 75,000 to 200,000 dramatically impacted on the incidence of genitourinary tumors (renal, renal pelvis, ureter, bladder, prostate, urethra, testis, and others) resulting in increase of 109.7% for such cancers; +120.4% for men compared with +37.3% for women. The percentage of kidney tumors within the genitourinary group actually decreased by −3.7% to 9.6% in 1993 from 13.3% in 1983 (Table 1), with a decrease in males by −1.8%, and an increase in females by +5.2%.

Overall cancer mortality increased from 440,000 cases in 1983 to 538,000 in 1994, a +22.3% change, yet the percentage dying from renal tumors remained about the same for all (1.9% and 2.1%, respectively) males and females (Table 1). The change in the RCC death rate between 1983 and 1993 in relationship to all cancers increased, +32.9%, (8,500 to 11,300 cases) and although all genitourinary malignancies had almost a similar increase, +36.5%, (44,290 to 60.475 cases), the change was only +1.1% for the percent of genitourinary to all cancers. The estimated death rate for patients with RCC within the genitourinary group decreased slightly from 19.2% in 1983 to 18.7% in 1993; for men it was 11.7% to 11.2%, respectively, and for females, it was 7.5% to 7.2%, respectively. There was no definitive evidence that therapy has favorably affected survival of patients with advanced local and distant disease, and any marginal improvement in survival, in fact, might simply be due to patient selection factors—"stage migration"—because of more patients being diagnosed with lower stage disease that was treated successfully by surgery alone.

MATERIALS AND METHODS

To assure consistency in reporting results, ground rules were set when reviewing the large number of published studies. Differences in defining the categories minor response (MR) and stabilization of disease (STAB) (ie, a decrease of $<50\%$ or $<25\%$ with an increase of $>25\%$ or $>50\%$ in either all or selected parameters), coupled with varied patient selection (good risk factors[7]), extent of restaging used, tightening of criteria for patient entry (ie, bidimensional parameters, absence of prior systemic therapy, better performance status, exclusion of certain metastatic sites, etc), and introduction of new diagnostic tests (ie, computed tomographic (CT) scans, ultrasound), have led to more accurate documentation of the extent of tumor regression. Such refinements probably have resulted in decreasing the number of complete (CR) and partial (PR) remissions while increasing the MR/STAB group. Without more accurate immunological or biological markers for this disease, attainment of MR/STAB may be due more to the eye of the observer, the absence of consistent restaging procedures, or the biological variation of tumor growth and cell death (so-called, "natural history").[7] It remains unclear whether STAB represents a true biological effect of therapy on tumor growth, a lead-time bias, and/or intermittent periods of cell division-apoptosis. In older trials, many investigators frequently recognized STAB as evidence of an "objective response" and thus, reported moderate to significant remission rates; others dismissed this category altogether, failed to mention MR/STAB at all, or automatically placed it into the nonresponding/progression (PROG) category. The latter view is now being questioned again because of

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Table 1. Incidence and Mortality Rates in 1983 and 1994

Cancers	1983 Total	1983 Males	1983 Females	1994 Total	Change Between 1983 and 1993 Males	Change Between 1983 and 1993 Females	Change Between 1983 and 1993 Total	Males (%)	Females (%)
Incidence									
All:									
Number	855,000	422,500	432,500	1,208,000	632,000	576,000	+41.3	+49.6	+33.2
Male:Female	—	49.4%	50.6%	—	52.3%	47.7%	—	+2.9	−2.9
Genito-urinary:									
Number	137,350	119,800	17,550	287,200	263,100	24,100	+109.7	+120.4	+37.3
Male:Female	—	87.2%	12.8%	—	91.6%	8.4%	—	+4.4	−4.4
Of *All*	16.1%	28.4%	4.1%	23.8%	41.6%	4.2%	+7.7	+13.3	+0.1
Renal:									
Number	18,200	11,400	6,800	27,600	17,000	10,600	+51.7	+49.1	+55.1
Male:Female	—	62.6%	37.4%	—	61.6%	28.4%	—	−0.1	+1.0
Of *All*	2.1%	2.7%	1.6%	2.3%	2.7%	1.8%	+0.2	0.0	+0.2
Of *Genito-urinary*	13.3%	8.3%	38.8%	9.6%	6.5%	44.0%	−3.7	−1.8	+5.2
Mortality									
All:									
Number	440,000	238,500	201,500	538,000	283,000	255,000	+22.3	+18.7	+26.6
Male:Female	—	54.2%	45.8%	—	52.6%	47.4%	—	+0.4	+1.6
Genito-urinary:									
Number	44,290	37,550	6,740	60,475	52,325	8,150	+36.5	+39.4	+20.9
Male:Female,	—	84.8%	15.2%	—	86.5%	13.5%	—	+1.7	−1.7
Of *All*	10.1%	15.7%	3.4%	11.2%	18.5%	3.2%	+1.1	+2.8	−0.2
Renal:									
Number	8,500	5,200	3,300	11,300	6,800	4,500	+32.9	+30.9	+36.4
Male:Female	—	61.2%	38.8%	—	60.2%	39.8%	—	−1.0	+1.0
Of *All*	1.9%	2.2%	1.6%	2.1%	2.4%	1.8%	+0.2	+0.2	+0.2
Of *Genito-urinary*	19.2%	11.7%	7.5%	18.7%	11.2%	7.4%	−0.5	−0.5	−0.1

recent prospective randomized trials, particularly with immunological agents, describing modest CR + PR rates (about 18%) yet a statistically significant increases in survival (about 2.5 times controls) for CR + PR + STAB.[8] In the present review (Table 2), MR/STAB, although listed, are excluded from the final response rate which denotes attainment only of CR + PR. Response durations also were not reported because definitions varied (most lasted < 3 to 9 months) but mixed responses always were included in the PROG category.

Many phase II trials used different initial and/or escalated dosages, as well as schedule adjustments, sometimes based on so-called "good-risk" and "poor-risk" factors usually defined by prior treatment with irradiation, immunotherapy or chemotherapy, poor performance status, renal dysfunction, anemia, metastatic sites, single versus multiple organ involvement, etc.[7] To simplify the multitude of changes, only the initial highest planned plus the highest escalated doses (in parenthesis) were recorded in Table 2.

Particular attention was given to trace final publications of abstracts presented before 1990; in fact, some investigators were contacted concerning manuscript status. Numerous studies, which were presented as an abstract or preliminary report initially, sometimes were summarized as part of a review of multiple drug- or disease-oriented trials within a cooperative group or institution. Except where otherwise indicated by a double reference, only the last and/or updated study result was reported.

Data are from phase II disease-oriented (not phase II drug-oriented) trials and almost all phase I pharmacokinetics/dose-finding studies were excluded because doses and schedules varied and, of more importance, response rates were absent.[9] However, drugs evaluated in the time frame of this review that also had trials published before 1983

Table 2. Chemotherapy Trials From January 1983 to December 1993

Reference(s)	No. Entered	No. Inadequate	No. Adequate	No. Unpretreated	No. CR	No. PR	Percent of Adequate CR + PR (95% CI)	MR/ STAB	Initial (highest) Dose
Acivicin, CI	35		27	22	0	1	4 (0-19)		
Elson et al[10]	35	8	27	22	0	1	4	*/*	20 mg/m² d 1-3 Q3W.
Aclarubicin (aclacinomycin-A)	16		15	6	0	0	0 (0-18)		
Decker et al[11]	16	1	15	6	0	0	0	0/12	65 mg/m² weekly for 4 weeks Q6W.
Alanosine	37		36	29	1	0	3 (0-15)		
Elson et al[10]	37	1	36	29	1	0	3	*/*	160 mg/m² d 1-5 QM.
Ametantrone	25		25	18	0	2	8 (1-26)		
Hansen et al[12]	25	0	25	18	0	2	8	0/5	135 (162) mg/m² Q2W.
Aminothiadazole	46		46	30	0	1	2 (0-12)		
Elson et al[10]	46	0	46	30	0	1	2	*/*	125 mg/m² QW + Allopurinol 300 mg QD.
Amonafide	29		24	24	0	0	0 (0-12)		
Higano et al[13]	29	5	24	24	0	0	0	0/6	300 (450) mg/m² d 1-5 Q3W.
Ampligen	31		31	*	1	1	7 (1-21)		
Strayer et al[14]	31	0	31	*	1	1	7	*/*	10 (120) mg BIW, or 200 (500) mg BIW.
Amsacrine	145		140	63*	0	2	1 (0-5)		
Schneider et al[15]	21	0	21	17	0	0	0	0/0	120 (180) mg/m² Q3W.
VanEcho et al[16]	16	0	16	14	0	0	0	0/5	same (150).
Amrein et al[17]	42	0	42	11*	0	1	2	0/7	same (160).
Earhart et al[18]	66	5	61	21*	0	1	2	*/*	120 mg/m² QM.
5-Aza-2'Deoxycitidine	15		12	12	0	0	0 (0-22)		
Abele et al[19]	15	3	12	12	0	0	0	0/2	75 mg/m² Q8H on d 1 Q5W.
Bisantrene	140		126	94*	1	5	5 (2-10)		
Scher et al[20]	27	1	26	16	0	0	0	0/2	260 (300) mg/m² Q3W.
Myers et al[21]	42	5	37	33*	0	2	5	0/12	same (280).
Evans et al[22]	24	4	20	15*	0	1	5	0/4	180 mg/m² weekly for three weeks Q6W.
Spicer et al[23]	14	0	14	11	0	0	0	0/6	150 (175) mg/m² QW.
Elson et al[24]	33	4	29	19	1	2	10	*/*	260 mg/m² QM.
Carboplatin	42		37	37*	0	0	0 (0-8)		
Tait et al[25]	22	3	19	19*	0	0	0	0/5	450 mg/m² QM.
Trump et al[26]	20	2	18	18	0	0	0	*/*	400 (440) mg/m² QM.
Cimetidine	42		38	38	2	0	5 (1-18)		
Inhorn et al[27]	42	4	38	38	2	0	5	0/4	600 mg QID.
Cimetidine + coumarin	202		198	172*	5	19	12 (8-17)		
Marshall et al[28]	45	3	42	40	3	11	33 (20-50)	0/12	300 mg Q6H daily starting d 15 + Coumarin 100 mg QD.
Glynne-Jones et al[29]	12	1	11	11	0	0	0 (0-24)	0/2	same.
Vennok et al[30]	25	0	25	16*	0	0	0 (0-11)	0/5	same.
Hermann et al[31]	31	0	31	31	0	2	7 (1-21)	0/5	same, except Cimetidine 400 mg Q8H.
Dexeus et al[32]	50	0	50	40	0	3	6 (1-17)	2/5	same (400 mg), or with Cimetidine 900 mg QD (8 cases).
Kokron et al[33]	39	0	39	34	2	3	13 (4-27)	4/6	400 mg QD + Coumarin 100 mg QD starting d 7.
Cimetidine + interferon	20		20	20	3	3	30 (12-54)		
Kotake et al[34]	20	0	20	20	3	3	30	0/9	200 mg QID + Interferon 5 mU IM twice in week 1, three times in week 2, then QD.
Cyclophosphamide + misonidazole	38		31	27	0	1	3 (0-17)		

Table 2. (*continued*)

Reference(s)	No. Entered	No. Inadequate	No. Adequate	No. Unpretreated	No. CR	No. PR	Percent of Adequate CR + PR (95% CI)	MR/ STAB	Initial (highest) Dose
Glover et al[35]	38	7	31	27	0	1	3	0/1	1.2 g/m² + Misonidazole 5 g/m² Q3W.
10-Deaza-aminopterin	14		12	10	0	0	0 (0-22)		
Scher et al[36]	14	2	12	10	0	0	0	0/0	37.5 mg/m² QW.
Deoxycorformycin	49		43	43	0	0	0 (0-7)		
Venner et al[37]	20	2	18	18	0	0	0	0/4	4 mg/m² weekly for three weeks, then Q2W.
Witte et al[38]	29	4	25	25	0	0	0	*/*	4 (8) mg/m² Q2W.
Diaziquone	132		119	88	0	2	2 (0-6)		
Nichols et al[39]	20	0	20	18	0	0	0	3/7	27.5 mg/m² QM.
Hansen et al[40]	33	4	29	25	0	1	4	0/2	27 mg/m² QM.
Decker et al[41]	22	7	15	15	0	0	0	0/8	20 mg/m² weekly for four weeks Q6W.
Stephens et al[42]	57	2	55	30	0	1	2	*/*	40 mg/m² Q3W.
Didemnin-B	50		43	43	0	1	2 (0-12)		
Motzer et al[43]	23	2	21	21	0	1	5	0/0	4.2 (4.8) mg/m² QM.
Taylor et al[44]	27	5	22	22	0	0	0	*/*	3.47 mg/m² QM.
Echinomycin	49		47	47	0	1	2 (0-11)		
Marshall et al[45]	49	2	47	47	0	1	2	*/*	1.25 mg/m² QM.
Elliptinium	70		60	46*	1	7	13 (6-25)		
Sternberg et al[46]	14	6	8	4*	0	0	0 (0-31)	0/0	100 mg/m² weekly for four weeks, then QOW.
Caille et al[47]; Droz et al[48]	40	2	38	28*	1	7	21 (10-37)	0/18	100 mg/m² QW.
Droz et al[48]	16	2	14	14*	0	0	0 (0-19)	*/*	80 mg/m² d 1-3 Q3W.
Epirubicin	41		39	24*	0	0	0 (0-7)		
Fossa et al[49]	21	1	20	12*	0	0	0	0/2	75 mg/m² Q3W.
Benedetto et al[50]	20	1	19	12	0	0	0	0/0	85 (110) mg/m² Q3W.
Esorubicin	107		97	92*	1	2	3 (1-9)		
Carlson et al[51]	25	1	24	24	0	0	0	*/*	30 mg/m² Q3W.
VanOstrom et al[52]	33	6	27	27	0	0	0	0/12	same.
Kish et al[53]	15	0	15	15	0	1	7	0/8	same.
Braich et al[54]	13	1	12	7*	0	0	0	1/0	same (32.5).
Hurteloup et al[55]	21	2	19	19	1	1	11	0/9	35 mg/m² Q3W.
Floxuridine, CI	363		330	273*	12	36	15 (11-19)		
CIRCADIAN INFUSION	290		265	227*	10	30	15 (11-20)		
Hrushusky et al[56]	61	5	56	47*	4	9	23 (13-36)	4/28	0.15 (0.325) mg/kg IV d 1-14, or 0.25 mg/kg via hepatic artery d 1-14 QM at 68% of the dose between 1500-2100 hours + 15% between 2100-0300 hours + 2% between 0300-0900 hours + 15% between 0900-1500 hours (51 cases IV + 5 IA).
Damascelli et al[57]	45	3	42	42	3	3	14 (5-29)	0/18	same (0.20).
Dexeus et al[58]	42	2	40	33	0	4	10 (3-24)	4/7	same (0.25).
Huben et al[59]	24	3	21	21*	3	6	43 (22-66)	0/2	same.
Clark et al[60]	6	0	6	5	0	0	0 (0-39)	0/3	same (0.225).
Budd et al[61]	26	0	26	26	0	2	8 (1-25)	*/*	same (20 cases), or with minor modification (6 cases).

Table 2. (*continued*)

Reference(s)	No. Entered	No. Inadequate	No. Adequate	No. Unpretreated	No. CR	No. PR	Percent of Adequate CR + PR (95% CI)	MR/STAB	Initial (highest) Dose
DeMarsh et al[62]	7	2	5	4*	0	1	20 (1-72)	0/4	same, except minor modification by 2%.
Merrouche et al[63]	20	6	14	14	0	0	0 (0-19)	0/5	same, except modified sinusoidal peak at 1800 hours.
Wilkinson et al[64]	12	0	12	12*	0	0	0 (0-22)	0/0	same (0.4)
Conroy et al[65]	30	2	28	8	0	4	14 (4-33)	3/5	same (0.4), except modified with 33% between 2300-1100 hours + 66% between 1100-1100 hours.
Poorter et al[66]	17	2	15	15*	0	1	7 (0-32)	0/10	0.15 (0.35) mg/kg IV d 1-14 with 70% between 2000-0200 hours + 30% between 0200-2000 hours.
CONSTANT INFUSION	73		65	46*	2	6	12 (6-23)		
Hrushusky et al[56]	7	0	7	7*	1	1	29 (4-71)	0/0	0.15 (0.325) mg/kg d 1-14 QM (5 cases IV + 2 IA).
Richards et al[67]	37	8	29	29	0	0	0 (0-10)	0/13	0.15 (0.20) mg/kg d 1-5 QM.
Wilkinson et al[64]	29	0	29	10*	1	5	21 (8-40)	0/12	0.075 (0.275) mg/kg d 1-14 QM.
Floxuridine + interferon	47		39	35*	1	8	23 (11-39)		
Falcone et al[68]	16	1	15	11	1	4	33 (12-62)	1/6	0.075 (0.200) mg/kg d 1-14 CI QM + Interferon 10 mU IM TIW.
Dimopoulous et al[69]	13	0	13	13*	0	4	31 (9-61)	3/0	0.125 mg/kg circadian CI d 1-14 QM + Interferon 1-2 mU/m² QD.
Soori et al[70]	18	7	11	11*	0	0	0 (0-24)	0/7	0.15 mg/kg CI d 1-14 + Interferon 3 mU/m² SQ TIW QM.
Floxuridine + Leucovorin	23		23	17*	0	0	0 (0-12)		
Raminski et al[71]	15	0	15	15*	0	0	0	*/*	100-2000 mg/m² d 1-5 given between 1800-2100 hours + Leucovorin 200 mg/m² IV day 1-5 between 1900-2100 hours QM.
Vokes et al[72]	8	0	8	2	0	0	0	1/2	0.1 (0.375) mg/kg CI d 1-5 hours Q3W + Leucovorin 100 mg PO QH for four doses, then Q4H d1-5 Q3W.
Floxuridine + Leucovorin + Interferon	25		20	19	0	0	0 (0-14)		
Stadler et al[73]	25	5	20	19	0	0	0	0/0	0.1 mg/m2 CI d 1-5 + Leucovorin 100 mg PO every four hours for 36 doses + Interferon 30xmU/m² SC d 1-6.
Floxuridine + Vinblastine	14		11	11	0	2	18 (2-52)		
Small et al[74]	14	3	11	11	0	2	18	0/4	0.075 (0.125) mg/kg CI d 1-14 + Vinblastine 0.7 (0.8) mg/m² CI d 15-28 QM.
Fludarabine	54		45	45	0	0	0 (0-6)		

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