Cancer Chemother Pharmacol (1984) 13:153–156

Cancer Chemotherapy and Pharmacology

Editorial

Perusing the ASCO abstracts with a focus on interferons in malignant melanoma and renal cell carcinoma

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The ASCO-AACR meetings are the major event of the year for oncologists in the United States. The meetings are eagerly awaited as a chance to hear about the new advances that may have occurred in both clinical and preclinical trials. One of the most eagerly awaited aspects of the meetings is the receipt of the abstract books which grow in size with each advancing volume. These books of abstracts are pored over in great detail and provide a common ground for discussion among clinical investigators and their counterparts or collaborators in clinical practice.

Table 1. Interferon in malignant melanoma in the Proceedings of ASCO (1984)

Investigators	Type of interferon	Dosage schedule	No. of patients treated	No. of patients evaluable	No. CR+PR	No. MR+stable	% Response	
							No. CR+PR / No. entered	No. CR+PR+MR+stable / No. evaluable
Thomson, McLeod C-180	Recombinant leukocytic A (RO-22-8181)	10×10^6 U/m^2 IM Twice weekly for 12 weeks	12	12	1	2	7	14
Goldberg, Silgals, Ayoub et al. C-189	Lympho-blastoid	15×10^6 U/m^2 days 1,3,5,8,10,12 or 0.5×10^6 U/m^2 weekly × 12 or $0{,}5 \times 10^6$ U/m^2 daily, all IM	30	24	2	4	6	25
Hawkins, McCune, Speyer et al. C-195	Recombinant alpha-2 (SCH 30500)	30×10^6 U IV daily 1–5 Q21 days	29	23	1	3	3	17
Slater, Krown, Pinsky et al. C-210	Human leukocyte alpha-2	3×10^6 U IM 5 days/weekly + cimetidime	25	23	2	3	8	22
Robinson, Kirkwood, Harvey et al. C-234	Human alpha-2	30×10^6 U/m^2 IV daily × 5 Q21 days	31	31	2	0	6	6
		or 10×10^6 U/m^2 SC 3 × weekly	32	32	6	0	19	19
Ernstoff, Davis, Kirkwood C-242	Human leukocyte	$5–40 \times 10^6$ U/day 1 × 5 Q21 days	16	14	1	2	6	21
		Total	175	159	15	14	8	18

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The abstract books have two facets which are worth emphasizing. The first is that the abstracts are considered acceptable references for use in published papers by all the major journals. The second is that the books contain some abstracts referring to papers which have not been accepted for either oral presentation or poster sessions. These two facets tend to give these abstracts an importance beyond those of any other meeting. It enables authors to 'publish' data in a way that has no equivalent counterpart in the oncologic community. It obviously encourages the submission of abstracts with small prospect of 'acceptance' for presentation.

The great difficulty with the use of abstracts as published referenceable data is that the amount of information given is so scanty that a meaningful evaluation is extremely difficult. The authors can make claims that cannot be analyzed with so detailed a scrutiny as they would get in a full paper where more details are available.

An example of a differing perspective in abstract reporting and analysis can be seen in this year's (Volume 3, 1984) Proceedings of ASCO concerning interferons in malignant melanoma and renal cell carcinoma. Table 1 details all the abstracts on phase 2 trials of interferons in malignant melanoma, while Table 2 does the same for abstracts describing drug trials in the same disease. Tables 3 and 4 look at the interferons and chemotherapy, respectively, in phase 2 studies against renal cell carcinoma.

Tables 1–4 show the response rates calculated in two ways, as allowable by the abstracts. The first is a conservative technique in which the denominator is the number of patients entered and the numerator is the number of patients achieving either complete or partial response. The assumption is that complete and partial responses are being evaluated in a standard and acceptable manner since the abstracts do not contain any information on the exact criteria used. The second way to calculate the response rate is a liberal approach in which the denominator is the number of patients 'evaluable' or 'adequately treated', while the numerator now adds 'minor responses' and 'stable disease' to the complete and partial responses.

In Table 1, the response rates for interferons in melanoma utilizing the conservative approach range from 3% to 19%, exceeding 10% with only one schedule in one abstract. The cumulative response rate for all six studies is 8%. The liberal approach changes the range from 6% to 25%, now exceeding 10%, with all but one schedule in one abstract. The cumulative liberal response rate is 18%. Despite this un-

Table 2. Chemotherapy trials in malignant melanoma in the Proceedings of ASCO (1984)

Investigators	Drug regimen	No. of patients entered	No. of patients evaluable	No. CR	No. PR	No. MR+stable	% Response	
							No. CR+PR	No. CR+PR+ MR+stable
							No. entered	No. evaluable
Retsas et al. C-998	Sequential vinblastine + cisplatin + bleomycin followed by DTIC + vincristine	64	63	3	15	–	28	30
Carmo-pereira et al. C-1000	Vindesine + CCNU + procarbazine or	14	14	1	3	–	28	28
	DTIC + CCNU + procarbazine	14	14	3	4	–	50	50
Samson et al. C-1001	DTIC + dibromodulcitol + actinomycin D	37	37	2	9	–	30	30
Shah et al. C-1007	High-dose DTIC	50	50	2	7	–	18	18
Kuperminc et al. C-1022	Methyl-GAG or	–	41	0	1	–	–	2
	Methyl-CCNU	–	38	1	3	–	–	13
Morton et al. C-1023	BCNU + 6-thioguanine	28	21	0	2	5	7	33
Koller et al. C-1024	Weekly methyl-CCNU	10	9	0	1	1	10	22
Schneider et al. C-0211	4-demethoxy-daunorubicin	16	13	0	0	0	0	0
Gale et al. C-1028	Alpha-methyl para-tyrosine (DEMSER)	36	33	1	2	0	7	9

impressive data set, the conclusions given in the abstracts tend toward the side of optimism. Thomson et al. (C-180) conclude that 'the response rate is low but the different toxicity warrants further studies using interferon in combination with cytotoxics and other biological modifiers.' Goldberg et al. (C-189) conclude that 'it is required to give interferon at doses near the maximum tolerated dose for several months' after projecting a response rate of 14%. Hawkins et al. (C-195) state in their last line that although dose reduction was rarely required, cyclic therapy with recombinant IFN-alpha may be less effective in patients with malignant melanoma than continuous treatment'. Slater et al. (C-210) make the cautious statement that interferon, with the dose and schedule used, appears to have 'marginal efficacy'. Robinson et al. (C-234) sum up: 'these studies suggest that IFN-alpha 2 has activity in malignant melanoma.' Ernstoff et al. conclude with the statement that interferon is well tolerated, and has activity against melanoma.

The nine trials with chemotherapy in Table 2 display a much less pronounced dichotomy between the conservative and liberally defined response rates (0–50%), the range being identical with both approaches.

Table 3 outlines five abstracts concerning phase 2 trials of interferon in renal cell carcinoma. The ranges of the response rates are 0–18% (conservative approach) and 0–73% (liberal approach). The cumulative response rates are 11% (conservative) or 26% (liberal). As with malignant melanoma, the conclusions tend toward the positive. Einzing et al. (C-209) conclude that 'our preliminary results confirm previous reports of antitumor activity.' Kempf et al. (C-228), despite observing only one partial response, end their abstract with the statement

Table 3. Interferon in renal cell carcinoma in the Proceedings of ASCO (1984)

Investigator	Type of interferon	Dosage schedule	No. of patients treated	No. of patients evaluable	No. CR + PR	No. MR+stable	% Response	
							No. CR+PR / No. entered	No. CR+PR+MR+stable / No. evaluable
Einzig, Krown, Oettgen C-209	Recombinant alpha	$3-36 \times 10^6$ U IM over 10 days then 36 daily for 9 weeks	31	24	2	4	6	25
Kempf, Grunberg, Daniels et al. C-228	Recombinant alpha-2	30×10^6 U/m^2 IV daily × 5 Q2-3 weeks or 2×10^6 U/m^2 SC 3 times per week	26	24	1	1	4	16
Neidhart, Gagen, Kisner et al. C-232	Human lymphoblastoid (Wellferon)	5×10^6 U/m^2 TIW for 24 weeks	33	33	5	1	16	18
		$3-5-10 \times 10^6$ U IM over 10 days then 20×10^6 U IM × 7 days Q21 days	23	23	5	0	18	18
		5 then 10×10^6 U IV days 1, 2 then 50×10 U/m^2 IV × 3 Q21 days	11	9	2	0	18	22
Vugrin, Hood, Taylor et al. C-599	Lymphoblastoid alpha	3×10^6U/m^2 IM TIW for 6 weeks	22	21	2	13	9	73
		30×10^6 U/m^2 IV daily × 3 weekly for 6 weeks with prednisone	12	5	0	0	0	0
Trump, Harris, Tuttle et al. C-600	Human lymphoblastoid (Wellferon)	30×10^6 U/m^2/day × 10 or 3–5–10 on days 1, 2, 3, then 20 on days 4–10 Q21 days	40	28	5	3	13	29
		Total	198	167	22	22	11	26

Table 4. Chemotherapy phase 2 trials in renal cell carcinoma in the Proceedings of ASCO (1984)

Investigators	Drug regimen	No. of patients entered	No. of patients evaluable	No. CR	No. PR	No. MR+stable	% Response	
							No. CR+PR	No. CR+PR+ MR+stable
							No. entered	No. evaluable
Oishi et al. C-598	VM-26	–	37	0	1	13	–	38
Weinerman et al. C-611	Lonidamine	24	15	0	1	8	4	60
Preifle et al. C-634	VM-26	34	32	0	3	0	9	10

that 'IFN-alpha 2 thus appears to be active in the treatment of renal cell carcinoma.' Neidhart et al. (C-232) are equally positive with their final line reading 'we feel this data confirms activity of HLBI in renal cell cancer.' Vugrin et al. (C-599) conclude that interferon 'has some activity against metastatic renal carcinoma, though clinically useful responses were infrequent.' Trump et al. (C-600) finalize their abstract with the statement that: 'These data confirm the activity of L-IFN in renal cell carcinoma.'

Table 4 outlines three chemotherapy phase 2 trials in renal cell cancer where there is a wide range of response rates when the liberal definition is used (10%–60%). With the conservative approach, the range is only 4%–9%.

In the phase 2 study of VM-26 reported by Oishi et al., 27 'fully and partially evaluable' patients are reported on so that the number entered is not available. The results are 1 partial response and 13 patients with 'improved or stable disease for at least 2 months.' The authors correctly state that 'VM-26 appears to have minimal activity in advanced renal cell carcinoma.' With the criteria applied to interferon trials, the 'response rate' would be 38%, and it is doubtful whether the conclusion would be so pessimistic.

The phase 2 trial of Lonidamine is another interesting example of how one could accentuate the positive if one was so inclined. With the conservative criteria of response rate determination, the figure is 4%. On the other hand, if a liberal approach is used, the 'response rate' would be 60% with 1 PR + 8 cases of stable disease in 15 evaluable patients. The authors conclude that Lonidamine 'may have some antitumor effect in renal cell carcinoma.'

What is obvious from this brief analysis is that neither interferon nor chemotherapy appears to accomplish a meaningful complete plus partial response rate in advanced malignant melanoma or renal cell carcinoma. The optimism concerning interferon in these diseases comes from the use of a very liberal way of defining the response rate, which most oncologists would not consider accetable if it were applied to more traditional therapies such as cytotoxic drugs. There appears to be a double standard when it comes to interferon responses, which may or may not be credible. If this liberal approach leads to further clinical investigations which ultimately define a meaningful rate for interferon in caring for patients, then it will be validated. If this liberal approach is being used to imply that interferon currently benefits patients to the extent that it should be widely used, then its validity is open to serious question. This issue should be something the ASCO Program Committee, the ASCO leadership, the ASCO membership, and the oncology community all ponder.