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Review paper

Combining 5-fluorouracil with interferon-α in the treatment of advanced colorectal cancer: optimism followed by disappointment

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Pre-clinical data have demonstrated synergy between 5-fluorouracil (5-FU) and interferon (IFN)-α in colon cancer cell lines. In 1989 the first small single-institution phase II study with this combination in advanced colorectal cancer showed a response of 81% with substantial toxicity, whereas IFN-α alone was virtually inactive. Ten published phase II studies including 175 evaluable patients have demonstrated a response rate of 2.3%. 5-FU alone has been used extensively and is moderately active with response rates of 10–11% in 1148 patients evaluated by the Advanced Colorectal Cancer Meta-analysis Project in 1992 and 1994. Eleven subsequent phase II studies with 5-FU + IFN-α published over the period of 1990–1994 on 548 patients showed a response rate of 28% with 2% toxic deaths. Recently, nine phase III clinical trials including 1727 randomized patients have compared 5-FU + IFN-α to some standard therapies, most often treatment regimens based on 5-FU + leucovorin. Except for one study involving 105 patients, the rest of the phase III studies have demonstrated either no difference (six studies) or significantly worse results (two studies showing substantial toxicity with IFN-α + 5-FU). Several studies are ongoing, but results are not likely to change. In conclusion, after a period of high hopes, the combination of 5-FU + IFN-α does not seem to fulfill the original expectations. It is costly, it is toxic and it is not effective. New treatment strategies must be developed if progress is to be obtained.

Key words: Advanced colorectal cancer, 5-fluorouracil, interferon.

Introduction

The treatment of advanced colorectal cancer with chemotherapy has been a frustrating experience over the last 30 years. Minimal response rates and no effect on survival have been 'the standard' conclusion in most reports.[1,2] It was therefore of interest that Scott Wadler *et al.* at the 1989 ASCO meeting reported a 81% response rate [mainly partial remissions (PRs)] in 16 earlier untreated colon cancer patients[3] using a combination of 5-fluorouracil (5-FU) and interferon (IFN)-α. A full length report of the study was published later in 1989.[4] The report was greeted with considerable enthusiasm and studies were initiated over the world. The results of subsequent phase II and recently several phase III studies are now available—although a number of them still in abstract form. This paper reviews the results to date.

Activity of single agent IFN-α in advanced colorectal cancer

Following the original publication in 1955 by Isaacs and Lindemann,[5] some reports were published on the activity of IFN-α in solid tumors. However, these data were scattered, mainly due to lack of supply of IFN-α, and lack of knowledge concerning doses and schedules of the drug. With the introduction of the recombinant IFNs in the early 1980s, sufficient quantities of standardized preparations became available for large-scale clinical testing. Various phase I studies were performed.[6,7] A few responses were seen in patients with advanced colorectal cancer. This led to several phase II studies with different doses and schedules in advanced colorectal cancer, published mainly in the period 1983–1987. Available data from 10 published reports[8–17] are shown in Table 1. A total of 175 evaluable patients, of which about 131 were previously untreated cases, was included in the studies. The IFN-α doses given ranged from 3×10^6 to 50×10^6 U/m^2. Four PRs, corresponding to a response rate of 2.3%, were recorded in the collected series, indicating minimal or no activity and virtually no clinical effect. Toxicity

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was substantial, especially at the higher doses. Two phase II studies with IFN-β and one with IFN-γ have been published, also showing very limited activity.[18–20]

On the basis of these data it was concluded that the IFNs by any dose or schedule as single agents are virtually without any demonstrable activity in patients with advanced colorectal cancer.

Table 1. Phase II studies of IFN-α as a single-agent in advanced colorectal cancer

Reference	Investigator year	IFN dose (U) $\times 10^6$	Type of IFN	No. of patients/no. of patients evaluable	Response rates			Prior treatment for advanced patients		No. of toxic	Remarks
					CR	PR	CR+PR	Yes	No		
8	Figlin *et al.* 1983	3/m^2/day i.m. × 5/w	IFN-α (Le)	19/18	0	0	0	17	1	0	
9	Chaplinski *et al.* 1983	3/m^2 t.i.w. for 6 w i.m. 3/m^2 × 1/w	IFN-α N1	19/18	0	0	0	7	11	0	at 6 weeks randomized to maintenance or no further treatment
10	Neefe *et al.* 1984	50/m^2 t.i.w. i.m. de-escalation	IFN-α-2a	21/19	0	1	5	0	21	0	
11	Silgals *et al.* 1984	30–50/m^2 × 5/3 w i.v. de-escalation	IFN-α-2b	21/15	0	0	0	8	13	0	
12	Lundell *et al.* 1984	(1) 20/m^2 s.c. t.i.w. (2) 50/m^2 × 5 i.v./4 w	IFN-α-2b	18/18	0	0	0	0	18	2*	randomized study * relation to IFN therapy not excluded
13	Eggermont *et al.* 1985	20/m^2 b.i.w. i.m. for 12 w	IFN-α-2a	10/10	0	1	10	0	10	0	
14	Flodgren *et al.* 1985	7.5/m^2 t.i.w. i.m.	IFN-α-2a	16/15	0	0	0	NA	NA	0	H2 block in NC + PD patients
15	Eggermont *et al.* 1986	(1) 20/m^2 i.m. b.i.w. (2) 20/m^2 i.m. × 8/4 w	IFN-α2a	20/20	0	1	5	0	20	0	non-randomized study schedule, one poorly tolerated
16	Clark *et al.* 1987	(1) 50/m^2 i.v. × 5/w/4 w (2) 20/m^2 s.c. t.i.w.	IFN-α-2b	36/30	0	0	0	14	22	0	one of two randomized studies, in the second study patients received IFN + 5-FU. (data presented in Table 2).
17	Krown *et al.* 1987	15/m^2 i.m. t.i.w.	IFN-α-N1	22/22	0	1	5	17	5	0	

LV, Leucovorin; HU, Hydroxyurea; NA, not available; * $p < 0.05$; CIV, continuous i.v. infusion; PIV, protracted i.v. infusion; TTP, time to progression.
Natural IFNs: leukocyte IFN, IFN-α (Le); lymphoblastoid IFN, IFN-α-N1 (Burroughs Wellcome).
Recombinant IFNs: α-2, IFN-α-2b (Schering); α-A, IFN-α-2a (Roche); α-2arg, IFN-α-2c (Boehringer Ingelheim).

Activity of single agent 5-FU in advanced colorectal cancer

Numerous studies and reviews have dealt with the therapeutic activity of 5-FU in colorectal cancer. It is not the intention in this review to go through this literature in any detail. A few important points will be sufficient. Carter and Friedman have reviewed literature up to 1974, comprising data on more than 2000 patients participating in phase I–II trials.[21] Response rates in individual studies varied from 5 to 70% with a median of 21% and no solid evidence of life prolongation. In their 1992 and 1994 meta-analyses of all randomized trials in patients with advanced disease comparing single-agent 5-FU to 5-FU + leucovorin (nine trials, 1381 patients[22]) and 5-FU to 5-FU + methotrexate (eight trials, 1178 patients[23]) the Advanced Colorectal Cancer Meta-analysis Project found response rates to 5-FU of 11% (64/578 patients)[22] and 10% (58/570 patients),[23] respectively, and median survivals of approximately 10 months.

In recent years, more attention has been focused on dose intensity of chemotherapy. Continuous infusion schedules for 5-FU has been developed, allowing the delivery of a higher dose intensity than by i.v. bolus injection.[24] Response rates have varied from 15 to 59% (average 36%) in phase II studies with no evidence of a survival benefit in randomized trials versus i.v. bolus injection.[24]

In summary, 5-FU definitely has some, but overall a very modest, activity in advanced colorectal cancer irrespective of dose or schedule, with response rates of the order of 10–15% and no solid evidence of life prolongation. Nevertheless, treatment with 5-FU has been accepted as the standard therapy in this disease all over the world. It is difficult to understand this, but presumably both oncologists and patients want to have some kind of therapy even if it does not work.

The rationale for combining 5-FU and IFN-α

The mechanisms of action of the IFNs on malignant cells are largely unknown, but presumably diverse.[25] The mechanism of action of 5-FU is quite well elucidated.[26] Two main mechanisms have been described for the interaction between 5-FU and IFN-α when administered together:

(1) A modulatory effect at the cellular level. In preclinical models IFN-α is able to synergise with 5-FU in a methabolic way related to the inhibition of thymidine kinase and an increased accumulation of FdUMP.[27] Thus, the IFN-α and 5-FU interaction has been described as yet another example of biochemical modulation, a mechanism known to be active with a variety of drugs, leucovorin being the most predominant example.

(2) A pharmacokinetic effect. Several studies have shown a highly significant increase in plasma levels of 5-FU and decrease of total clearance when using the combination compared with a control group.[27,28] This has, however, not been a uniform finding.[29]

The relative importance to the modulating activity of cellular effects versus the pharmacokinetic or other effects remains to be determined. Also, other mechanisms may be operating as well.

Phase II studies of 5-FU + IFN-α

As mentioned earlier, in 1989 Wadler and colleagues published a study in patients with advanced colorectal cancer treated with 5-FU + IFN-α.[3,4] A phase I study was published in 1990.[30] In the original series, 30 evaluable patients were included, 17 previously untreated and 13 previously treated with chemotherapy; 13 of the 17 previously untreated patients achieved a response (1 CR + 16 PRs), giving a response rate of 76%. None of the 13 previously treated patients responded to the therapy. Toxicity was predominant and one toxic death was reported. In the clinical update series from 1990[31] from the same institution, 32 previously untreated patients were included with 20 PRs, corresponding to a response rate of 63%. Three toxic deaths occurred in the series. The combination therapy with 5-FU and IFN-α, as originally designed, consisted of 5-FU 750 mg/m^2 i.v. continuous infusion daily for 5 days, followed by 1 week rest, then weekly bolus therapy at 750 mg/m^2; IFN 9 MU was administered subcutaneously three times weekly starting on day 1. The doses and schedules of the two agents were derived imperically and a rationale for this particular way of giving the therapy is not substantiated in any published reports. However, because of the initially very impressive results, the combination has been used largely unaltered in most subsequent studies.

During the following years a number of phase II studies were conducted trying to substantiate the response rates obtained by Wadler *et al.*[31] The results are summarized in Table 2. Twelve studies have been published over the period 1990–1994 on

548 patients (509 patients evaluable); 142 responses were recorded, corresponding to a response rate of 28% with 15 reported CRs, approximately 11%.[31–42]. Eight toxic deaths were reported in the collected series (2%).

Conclusion of phase II studies

It is evident from the data presented that the subsequent phase II studies performed over the period 1990–1994 were not able to confirm the impressive activity of this treatment schedule originally reported by Wadler *et al.* Thus 28% response rate, substantial toxicity with 2% toxic deaths is not significantly different from what can be obtained with 5-FU + leucovorin and is definitely more toxic.

Phase III studies of 5-FU + IFN-α

At the time of the initial presentation of the Wadler data (1990/1991), the interest from the medical community and pharmaceutical companies was

Table 2. Phase II studies of 5-FU + IFN-α in advanced colorectal cancer

Reference	Investigator/ year	IFN dose (U) × 10^6	Type of IFN	5-FU dose (mg/m^2)	No. of patients/ no. of patients evaluable	Response rates			Prior treatment		No. of toxic deaths	Remarks
						CR	PR	CR + PR	Yes	No		
32	Wrighley *et al.* 1984	5–20 t.i.w.	IFN-α-2b	250–500 i.v. × 5/4/w	20/14	0	2	14	5	9	0	early study
31	Wadler *et al.* 1990	9 t.i.w.	IFN-α-2a	750 × 5 CIV 750 × 1/w	32/32	0	20	63	0	32	3	leucopenia, diarrhea, sepsis
33	Pazdur *et al.* 1990	9 t.i.w.	IFN-α-2a	750 × 5 CIV 750 × 1/w	52/45	1	15	36	0	36	1	
34	Kemeny *et al.* 1990	9 t.i.w.	IFN-α-2a	750 × CIV 750 × 1/w	38/35	0	9	26	0	35	0	
35	Fornasiero *et al.* 1990	6–18 t.i.w.	NA	1000/w fixed dose	21/21	4	5	43	0	21	0	
36	Huberman *et al.* 1991	9 t.i.w.	IFN-α-2a	750 × 5 CIV 750 × 1/w	42/33	0	13	39	0	33	0	
37	Wadler *et al.* ECOG 1990	9 t.i.w.	IFN-α-2a	750 × 5 CIV 750 × 1/w	38/36	1	14	42	0	36	0	
38	Weh *et al.* 1992	9 t.i.w.	IFN-α-2b	750 × 5 CIV 750 × 1/w	59/55	0	17	31	0	55	2	
40	Diaz Rubio *et al.* 1992	9 t.i.w.	NA	750 × 5 CIV 750 × 1/w	35/33	3	5	24	0	35	2	progressive renal failure
39	Pazdur *et al.* 1993	9 t.i.w.	IFN-α-2a	750 × 5 CIV/ repeat 2/w	39/39	1	11	31	0	39	0	
41	John *et al.* 1993	(1) 10 t.i.w.	IFN-α-2a	750 × 5 CIV 750 × 1/w	18/18	1	5	33	0	18	0	significantly greater toxicity for CIV
		(2) 9 t.i.w.	IFN-α-2a	250–300 CIV/d								
42	Findlay *et al.* 1994	5 t.i.w.	IFN-α	300 CIV/d	124/118	0	5	8	72	52	0	IFN added at PD on 5-FU

See footnote to Table I.

Table 3. Phase III studies of 5-FU + IFN-α versus a comparative schedule in advanced colorectal cancer

Reference	Investigator/year	5-FU + IFN dose schedule mg/m^2 (U) × 10^6	Comparative schedule (mg/m^2)	No. of patients evaluable	Response rates (%)		Median survival (months)		Remarks
					5-FU + IFN	comparative	5-FU + IFN	comparative	
44	CORFU-A 1995	(A) 750 CIV × 5 750 × 1/w 9 t.i.w.	(B)5-FU 370 i.v. d 1–5/ 4/w + LV 200 d 1–5/4w	(A) 243 (B) 238	21	19	11	11	toxic deaths: (A) 5 (2%) (B) 4 (1.6%)
43	York *et al* 1993	(A) 750 CIV × 5 750 × 1/w 9 t.i.w.	(B) 5-FU 750 CIV × 5 750 × 1/w	(A) 121 (B) 124	31	19	NA	NA	no difference
45	Köhne *et al.* 1995	(A) 2600 24 h 3 t.i.w.	(B) 5-FU 2600 i.v. 24 h LV 500 i.v. 2 h (C) 5-FU 2600 i.v. 24 h LV 500 i.v. 2 h IFN 3 × 10^6 t.i.w.	(A) 68 (B) 69 (C) 42	(A) 19	(B) 39 (C) 31	TTP 3.7	TTP 7.8*	* significant for TTP, 10% toxic deaths in (C), closed
46	Dufour *et al.* 1994	(A) 750 CIV × 5 750 × 1/w 9 t.i.w.	(B) 5-FU 750 CIV × 5 750 × 1/w	(A) 56 (B) 49	27	10*	12.3	10.1*	* more toxicity in (A)
47	Kreuser *et al.* 1995	(A) 600i.v. 2 h/w 5 t.i.w.	(B) 5-FU 600 i.v. 2 h/w LV 200 i.v./w	142	TTP 74 d	TTP 108 d	189 d	308 d	* significant for survival in (B), toxicity worse for (A)
48	DiConstanzo *et al* 1995	(A) 600 i.v./w 3 t.i.w. HU 3000 mg p.o./w	(B) 5-FU 600 i.v./w LV 500 i.v. 2 h/w HU 3000 p.o./w	(A) 92 (B) 87	9	29	NA	NA	two toxic deaths, one in each arm
49	Seymour *et al.* 1994	(A) 400 i.v. 400 CIV 12/w LV 200 i.v. 2 h 6 q 4/w cont.	(B) 5-FU 400 i.v. 400 CIV d 1 + 2 12/w LV 200 i.v. 2 h	(A) 83 (B) 82	30	30	10.0	10.8	significant toxicity with IFN
50	Hill *et al.* 1994	(A) 300 PIV/d 10/w repeated 5 t.i.w.	(B) 5-FU 300 PIV/d 10/w repeated	(A) 63 (B) 62	31	24	11	11	significant toxicity with IFN
51	Hill *et al.* 1995	(A) 750 CIV × 5 750 × 1/w 10 t.i.w.	(B) 5-FU 750 CIV × 5 750 × 1/w	(A) 52 (B) 54	19	30	8	8	significant toxicity with IFN, four toxic deaths in (A)

See footnote to Table 1.

substantial. A number of large or semi-large phase III studies was started trying to confirm the results of Wadler,[4] and especially to investigate the impact on survival.

The two earliest studies were initiated in 1990 and results were first published at the ASCO 1993 meeting.[43,44] A further six studies were published at the 1994 ESMO meeting in Lisbon, at the 1995 ASCO

meeting in Los Angeles[45–50] and in *The Journal of Clinical Oncology* in 1995.[51] The available data are summarized in Table 3. The comparative arms in the studies differ, 5-FU alone, 5-FU + leucovorin, etc., but the basic comparison in all studies is an IFN-containing schedule versus a 'standard therapy'. Four studies use the original Wadler schedule in the IFN arm.[43,44,46,51] Two studies use a modified dose of 5-FU and/or IFN.[45,47] One study combines 5-FU and IFN with hydroxyurea (HU).[48] One study uses protracted i.v. 5-FU infusion (10 weeks),[50] and one double-modulation with both leucovorin and IFN.[49] A total of 1727 patients have been included in the phase III studies. Only the study by Dufour *et al.*,[46] with 105 randomized patients (56 in the IFN group), describes significance for response with IFN compared with 5-FU alone, 27 versus 10%, and survival 12.3 versus 10.1 months employing the Wadler schedule. The rest of the studies show either no difference from the comparative arm[43,44,48–51] or even a significant difference in favor of the comparator.[45,47]. The reported median survivals in all series are around 10–11 months. Most studies report significant increases in toxicities in the IFN-containing groups.

Summarizing the results of the phase III studies—although some of them still in progress—there is no indication that the addition of a IFN-α to 5-FU has any advantage in terms of response rate or survival compared with the 'standard therapy'.

Conclusion

The concept of biochemical modulation of 5-FU was introduced almost 30 years ago combining 5-FU and leucovorin.[52] Since then, multiple drugs have been investigated for their modulatory capacity in both experimental and clinical settings.[53] Overall, the clinical results have been disappointing, with no convincing benefit of modulation either in terms of response rates or survival. IFN is the latest of the modulating family introduced on the basis of a series of rather promising pre-clinical results.[27] Except for the first small single-institution phase II study reporting a response rate of 76%,[4] the mean response rate in the 11 subsequent phase II studies was 122 out of 477 evaluable patients (23.5%). In the largest of the phase III studies, response rates in the 5-FU + IFN arms were 19%, i.e. no different from the comparative arms 5-FU alone or 5-FU + leucovorin.[43,44] The median survival was approximately 10 months in all groups, a figure comparable to that reported for 5-FU alone, 5-FU + leucovorin, etc., over the years. Moreover, the toxicity of the IFN-containing regimens has been significantly more pronounced than the toxicity in the comparative arms. These include abdominal pain, constipation, diarrhea, fatigue, fever, influenza-like symptoms, nausea/vomiting, shivering, somnolense and stomatitis.[44] A total of approximately 2% toxic deaths have been reported in the treated groups in all published reports taken together. Focus has especially been on a toxicity syndrome characterized by watery diarrhea followed by life-threatening sepsis.[53]

In summary, enough clinical evidence has accumulated on the use of 5-FU + IFN in advanced colorectal cancer to justify the conclusion that the combination does not work, is toxic, costly and therefore is useless. The declining response rates from those in the original series in 1989 to the available results of the prospective randomized studies are disappointing and unexplainable.

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