PII: S0959-8049(97)10047-8

Contra:

G.B. Zulian

Centre for Continuous Care (Cesco), CH-1245 Collonge-Bellerive and Division of Oncology, CH-1211 Geneva 14, Geneva University Hospitals, Switzerland

INTRODUCTION

MULTIPLE MYELOMA (MM) is a rare tumour whose incidence increases with increasing age from one new case per 100 000 people at the age of 50 years to 70 new cases at over 80 years of age. At the present time, there are no curative treatments and median survival time is between 3 and 4 years, although long survivals have occasionally been reported [1].

As with any other malignancy, the development of MM is a multistep process. Pesticides are a likely causative agent, with farmers at the highest risk. The diagnosis is usually made at a late stage with a high tumour burden. The M-component, i.e. the paraprotein, is detected in the serum in the presence of some 10^9 secretory plasma cells. Monoclonal gammopathy of undetermined significance (MGUS) is the recognised pre-malignant condition in approximately 50% of cases. However, MM can develop without preceding MGUS and not every MGUS will become MM. The transformation rate is approximately 2% per year, but the transition time may take a few months emphasising the need for active screening [2, 3].

Animal models of MGUS, plasmacytoma and MM have shown the key role of the cytokines, mainly interleukin-6 (IL-6), in the establishment and maintenance of these malignancies. Human studies have confirmed most of these findings and IL-6 is now a powerful prognostic factor in MM, together with the plasma cell labelling index [4–6].

Alpha interferon (IFN) inhibits both IL-6-dependent and -independent myeloma cell lines *in vitro* [7]. However, this inhibition is dose-dependent and this makes a wide application of IFN quite difficult because of unacceptable side-effects [8].

Standard cytotoxic chemotherapy with single or multiple agents and prednisone, including high-dose chemotherapy with haemopoietic stem cell support, are the ways by which MM is best treated today [9, 10]. IFN has been combined or added to chemotherapy with the aim of improving the response rate, the response duration and eventually the survival rate. Its mechanism of action is not well understood, since low-dose IFN can increase the proliferation of MM cells *in vitro* [11] whereas high-dose IFN appears directly cytotoxic [12].

In the present review, emphasis is put on many of the negative aspects of IFN therapy during both the induction chemotherapy, where IFN is administered concomitantly to conventional cytotoxic agents, and after induction chemotherapy, during the plateau phase, when IFN is administered as a maintenance of the response.

Received 22 Sep. 1997; revised/accepted 25 Sep. 1997.

METHODS

Through a MedLine™ search carried out in April 1997, 50 reports dealing with IFN and MM published as full papers between 1991 and 1996, were identified for the purpose of the ongoing argument. Abstracts were not considered suitable for analysis because of the absence of peer revision at time of publication. Free text with key words used in this search were ⟨⟨interferon and multiple myeloma⟩⟩. In addition, the local representatives of the companies Roche Pharmaceuticals (interferon alpha-2a, Roferon®) and Essex-Schering-Plough (interferon alpha-2b, Intron®) kindly provided significant information and literature extracts.

The following items were then determined for each clinical report, type of study, actual randomised number of patients or actual total number of patients, presence or absence of previous treatment, type of induction chemotherapy regimen, weekly dose of IFN during induction and/or maintenance therapy, response rate, progression-free survival, median survival time and complications of IFN therapy.

Patients receiving IFN either during induction or maintenance were eventually pooled and analysed in order to determine response rates, progression-free survival and median survival times, as well as major side-effects of IFN.

Heterogeneity of the patient population and of published data did not allow pertinent statistical studies, as would have been the case in a proper meta-analysis.

RESULTS (TABLE 1)

Twenty-three studies were identified to have included between 17 and 583 patients each. Only five of them included previously treated patients either resistant or relapsing after initial chemotherapy (CT). The other 18 studies included previously untreated patients who received CT with concomitant IFN or induction CT followed by maintenance IFN. Four pilot studies included 214 patients who all received IFN. Three comparative studies included 339 patients of which 147 received IFN. Sixteen randomised studies included 2875 patients of which 1728 received IFN.

CT regimens were usually the combination of mephalan and prednisone but regimens such as VMCP, VAD, C-VAMP, HDM, autologous and allogeneic bone marrow, were also used. This is the first illustration of treatment heterogeneity.

IFN was given during induction CT in eight studies, during maintenance in 12 studies and during both phases in four studies. Doses of IFN ranged from 1 MU three times per week to 5 MU/m^2 5 days per week for a few days up to several months, another illustration of treatment heterogeneity.

Progression-free survival ranged from 5.7 to 30 months and median survival time from 8.3 to 50.6 months. This is in accordance with previous data showing a median survival

Table 1. Overview of 23 studies using interferon alpha (IFN) in the treatment of multiple myeloma (MM)

Type of study	Number of patients	Previous treatment	Chemotherapy combination	Weekly dose of IFN during induction	Weekly dose of IFN during maintenance	PFS (months)	MST (months)	Major side-effect of IFN	Interpretation of the study	[Ref.]
Pilot	5	Yes	aBMT		3 MU	NA	NA		?	[37]
	7				6 MU	NA	NA	1 graft versus host disease	Negative	
	5				9 MU	NA	NA	4 graft versus host disease	Negative	
Pilot	156	No	MP or C or (C)-VAMP + HDM + ABMT		9 MU/m^2	NA	NA	NA	Positive	[35]
					0					
Pilot	21	Yes	Methylprednisolone	9 MU/m^2		NA	5	19% toxic deaths	?	[24]
				0						
Pilot	20	No	VAD or VMCP + HDM + TBI + ABMT		9 MU/m^2	85% at 2 years	NA	None	?	[36]
					0					
Random	72	No	VAD	9 MU	3 MU	15	22	46% G3–4 infection	Negative	[16]
	32			0	0	15	43			
Random	286	No	MP	15 MU	5 MU	21	32	30% treatment stop	Negative	[17, 18]
	297			0	0	15	29		Negative	
Random	23	Yes	VAD	9 MU/m^2		3.6	8.3	90% G3–4 toxicity	Negative	[30]
	24			0		3.6	8.3			
Random	85	No	MP		2 MU/m^2	17	44	14% treatment stop	Positive	[19]
	91				0	12	33			
Random	61	No	MP		5 MU	13.9	36	15% treatment stop	Positive	[20]
	64				0	5.7	35			
Random	52	No	CVMP/BEVD	15 MU		36	NA	32% G3–4 leucopenia	Positive (Stage III)	[21]
	51			0		18.5	32			
Random	31	No	VMCP	10 MU/m^2	2 MU/m^2	NA	53	12% G3–4 leucopenia	Positive (Stage III)	[15]
	84			0	0	NA	26			
Random	52	No	MP or VBAMdex		5 MU	13	45	25% dose reduction	Negative	[27]
	65				0	13	45			
Random	125	No	VMCP	10 MU		23.2	38.9	45% G3–4 haematotoxicity	Positive (stage I, II)	[14]
	131			0		15.8	30.2			
					6 MU	17.8	50.6	65% G1–2 haematotoxicity	Positive	
					0	8.2	34.4			
Random	42	No	C-VAMP+HDM+ABMT		9 MU/m^2	46	5 deaths	NA	Positive	[22]
	42				0	27	14 deaths			
Random	15	No	MP or VMCP or VPP	9 MU	6 MU	8	NA	> 50% influenza-like symptoms	Negative	[31]
	55			0	0	12	NA			
Random	97	No	MP or VMCP/VBAP		9 MU	12	32	10% treatment stop	Negative	[25]
	93				0	11	38			
Random	164	No	MP	35 MU/m^2	9 MU/m^2	NA	29	17% treatment stop	Positive (IgA, BJ)	[26]
	171			0	0	NA	27			
Random	17	No	Cyclophosphamide	9 MU		8	NA	> 50% influenza-like symptoms	Negative	[32]
	63			0		8.5	NA			
Random	136	No	MP	6 MU/m^2		18	36	> 50% influenza-like symptoms	Negative	[33]
	134			0		21.5	38			
Random	109	No	MP	35 MU/m^2		18	NA	10% treatment stop	Positive (stage II)	[23]
	111			0		6	NA			
Comparison	51	No	Dexamethasone	21 MU/m^2		30	NA	80% dose reduction	Negative	[28]
	46			0		30	NA			
Comparison	28	Yes	Radiation therapy		9 MU	NA	10	> 50% influenza-like symptoms	Negative	[34]
	31				0	NA	10			
Comparison	68	Yes	VAD or HDex		35 MU/m^2	NA	17	> 50% fatigue + dose reduction	Negative	[29]
	115				0	NA	15			

BEVD, carmustine, epirubicin, vincristine, dexamethasone; (C)-VAMP, (cyclophosphamide), vincristine, doxorubicin, methylprednisolone; HDex, high-dose dexamethasone; MP, melphalan, prednisone; RX, radiation therapy; VAD, vincristine, doxorubicin, dexamethasone; VBAM, vincristine, carmustine, doxorubicin, melphalan; VBAP, vincristine, carmustine, doxorubicin, prednisone; VBMCP, vincristine, carmustine, melphalan, cyclophosphamide, prednisone; VMCP, vincristine, melphalan, cyclophosphamide, prednisone; VPP, vincristine, peptichemio, prednisone; aBMT, allogeneic bone marrow transplantation; ABMT, autologous bone marrow transplantation; TBI, total body irradiation; MU, mega-unit; NA, not assessable.

time of 36–48 months for MM patients [13]. Survival was significantly better for the IFN treated group of patients in two studies [14, 15], whereas it was worse in one study [16]. Progression-free survival, however, was better in most studies for the IFN treated group of patients [14, 17–23]. In one study, as many as 19% of the patients died as a direct result of the treatment which indeed incorporated IFN [24]. Other major side-effects of IFN led to treatment interruption in six studies for 10–30% of patients [17–20, 23, 25, 26]. In addition, 25–80% of patients necessitated dose reduction in three studies [27–29]. WHO grade 3 to 4 infections or leucopenia were reported in five studies for 12–90% of patients [14–16, 21] and grade 1 to 2 in one study for 65% of patients [14]. Over 50% of influenza-like symptoms were described in four studies [31–34] whereas no significant side-effects were reported in only three studies [22, 35, 36].

Overall interpretation of the study was positive in nine studies. Three showed a benefit limited to advanced stages [15, 21, 23], one a benefit limited to early stages [14] and one a benefit limited to two paraprotein subtypes [26]. The interpretation was negative in 12 studies and not clearly stated in two others.

Among positive studies, two did not report any significant side-effects of IFN [22, 35]. Treatment was stopped in 14–17% of patients in four studies [19, 20, 23, 26] whereas 12–45% of grade 3–4 haematoxicity was reported in the three remaining positive studies [14, 15, 21]. Among negative studies, five cases of graft-versus-host disease (GVHD) occurred in a group of 17 patients treated with allogeneic bone marrow transplantation as a result of the immunosuppression caused by the increasing dose of IFN [37]. Treatment was stopped or IFN dosage reduced in five other negative studies [17, 18, 25, 27–29]. Forty-six per cent grade 3–4 infections [16], 90% grade 3–4 toxicities [30] and > 50% influenza-like symptoms [31–34] were the main side-effects observed in the remaining negative studies.

On the whole, no striking differences are apparent between positive and negative groups of studies with the notable exception of GVHD which is exclusively related to the transplanting procedure.

Quality of life questionnaires were not routinely used in the studies and therefore no interpretation or comparison of this important value can be attempted.

DISCUSSION

IFN has been administered over the past few years to thousands of patients suffering from MM. In spite of these numbers, no standard recommendation has been made for its use, since the results are still conflicting.

IFN showed no useful activity as a single agent in advanced disease and no studies have been performed at the other end of MM nebulosa, the MGUS stage. Combination of IFN with induction CT initially gave promising results with higher response rate in stages I to III disease for patients treated with CT and IFN compared with those receiving CT only. Translation of these results into a significant prolongation of the interval to relapse and/or progression, i.e. progression-free survival, was then shown by many authors only in responding patients [14, 17, 19–23]. Others could not find any significant difference [16, 25, 27, 28, 31–33]. Also, the so-called benefit never exceeds a few months, during which all sorts of unpleasant side-effects of the treatment were reported.

The balance between symptoms caused by MM and toxicity due to treatment is, therefore, difficult to find and sometimes well illustrated by patient's refusal to continue on therapy despite achievement of a good response.

An increased toxicity, mainly on the bone marrow, is reported, leading to treatment interruption, infections and dose reduction. In addition, the majority of patients suffer from influenza-like symptoms. There is, therefore, a clinically detectable price to pay for the administration of concomitant IFN. Since MM is a chronic deadly disease causing symptoms such as pain, fatigue or recurrent infections, it might be difficult to accept additional toxicities from any type of treatment for a questionable benefit. During the treatment, the quality of life is of great importance and there is no point in making a patient more ill from the treatment than from the disease if the goal is palliation and not cure.

In this respect, the assessment of remission entirely depends upon the accepted definition of MM and the criteria used for measuring this response. Those criteria may vary from one group to another, thus creating another area of possible confusion. The disappearance of a paraprotein from the serum might only mean that the tumour burden has been reduced from 10^{12} plasma cells, i.e. stage III, to perhaps 10^{9}, i.e. stage I. At this level of residual disease, the bone marrow infiltration by plasma cells is usually within normal limits at around 2–3%. In this case, according to traditional measurements, a complete remission is achieved. Nowadays, both the serum paraprotein level and the bone marrow cytological infiltration are not accurate enough in assessing response. Immunofluorescence cytology or flow cytometry, which can demonstrate persisting disease at the molecular level should, therefore, be part of any scientific clinical studies. In the years to come, genetic testing with immunoglobulin gene rearrangement analysis should help in making a complete remission biologically acceptable, as in chronic myeloid leukaemia and follicular lymphoma. In the present clinical approach of the treatment of MM, this level is unfortunately never reached. Comparison of response rate is, therefore, most of the time imprecise and should not allow any type of definitive conclusion.

Few studies have shown a survival benefit for patients taking IFN as maintenance after the achievement of a response [14, 15, 19, 21, 22, 25]. Here as well, there is a price to pay in terms of side-effects roughly comparable to the ones previously mentioned. In addition, the benefit is also rather marginal. The difference might be the result of the aggressivity and the efficacy of the chemotherapy regimen rather than the subsequent administration of IFN. In other words, the status of the disease after induction CT makes the difference, with patients in the best possible remission doing much better than others, as suggested by some authors [22]. At this point, patients are almost selecting themselves to receive the next step of treatment because their individual MM is probably less resistant to CT *ab initio*. Negative reports simply cannot show any advantage from the addition of IFN, possibly because patient selection is different. This appears quite frequently in collaborative studies when data are compared with those of a single centre.

Quality of life is another aspect of clinical research that may be controversial, since it can vary from one person to another and questionnaires may also be difficult to use. Appropriate evaluation is therefore a difficult task, but one that is so important it cannot be avoided in future trials [38, 39]. None of the studies reviewed here reported adequately on quality of life.

At the end of this millenium, any review of a medical area should now touch on economy. IFN is certainly not the most expensive agent in cancer therapy. In addition, it does not require hospitalisation and can be self-administered. IFN has many unpleasant side-effects, including life-threatening ones, and compliance is thus not easily achieved. Finally, IFN is not that active in MM.

If health has no price, it has a cost. In Switzerland, the public price of IFN is now between Swiss francs (SF) 21.25 and 26.15 per MU. According to the studies analysed in this paper, the weekly cost of maintenance IFN is thus reaching between SF 63.75 and 191.30. From our point of view, IFN does not match the cost-effectiveness requirement an active agent should have to become part of standard therapy in MM. In economical terms, low efficacy and high toxicity result in poor efficiency.

However, since there is no standard treatment for MM, IFN is only to be considered one of those. We should thus continue to design collaborative randomised studies aiming at improving the issue of such a deadly disease using all energy and every available agent for the true benefit of the patient. Then, there should be no argument left for any type of controversy.

1. Ries LAG, Hankey BF, Miler BA, *et al.* Cancer Statistics review 1973–88. NIH Publication No. 91-2789. National Cancer Institute, Bethesda, Maryland, 1991.
2. Bladé J, Lopez-Guillermo A, Rozman C, *et al.* Malignant transformation and life expectancy in monoclonal gammopathy of undetermined significance. *Br J Haematol* 1992, **81**, 391–394.
3. Kyle RA. Benign monoclonal gammopathy—after 20 to 35 years of follow-up. *Mayo Clin Proc* 1993, **68**, 26–36.
4. Bataille R, Jourdan M, Zhang XG, *et al.* Serum levels of interleukin-6, a potent myeloma cell growth factor, as a reflect of disease severity in plasma cell dyscrasias. *J Clin Invest* 1989, **84**, 2008–2011.
5. Durie BGM, Salmon SND, Finley SE, *et al.* Prognostic value of pretreatment serum β2 microglobulin in myeloma, a South-West Oncology Group study. *Blood* 1990, **75**, 823–830.
6. Greipp PR, Witzig TE, Gonchoroff NJ, *et al.* Immunofluorescence labelling indices in myeloma and related monoclonal gammopathies. *Mayo Clin Proc* 1987, **62**, 969–972.
7. Brenning G, Ahre A, Nilsson K. Correlation between *in vitro* and *in vivo* sensitivity to human leukocyte interferon in patients with multiple myeloma. *Scand J Haematol* 1985, **35**, 543–549.
8. Ahre A, Björkholm M, Österborg A, *et al.* High doses of natural alpha-interferon in the treatment of multiple myeloma—a pilot study from the Myeloma Group of Central Sweden. *Eur J Hematol* 1988, **41**, 123–130.
9. Zulian GB. Multiple myeloma, clinical evaluation of plasma cell lymphoproliferative disorders and initial management. *Sem Hematol* 1997, **34** (Suppl. 1), 29–39.
10. Kovacsovics TJ, Delaly A. Intensive treatment strategies in multiple myeloma. *Sem Hematol* 1997, **34** (Suppl. 1), 49–60.
11. Klein B, Zhang XG, Jourdan M, Bataille R. Interleukin-6 is a major myeloma cell growth factor *in vitro* and *in vivo* especially in patients with terminal disease. *Curr Topics Microbiol Immunol* 1990, **166**, 23–31.
12. Salmon SE, Durie BGM, Young L, Liu R, Trown PW, Stebbing N. Effects of cloned human leukocyte interferons in the human tumor stem cell assay. *J Clin Oncol* 1983, **1**, 217–225.
13. Gregory WM, Richards MA, Malpas JS. Combination chemotherapy versus melphalan and prednisolone in the treatment of multiple myeloma. An overview of published trials. *J Clin Oncol* 1992, **10**, 334–342.
14. Ludwig H, Cohen AM, Polliack A, *et al.* Interferon-alpha for induction and maintenance in multiple myeloma. Results of two multicenter randomized trials and summary of other studies. *Ann Oncol* 1995, **6**, 467–476.
15. Cohen AM, Meytes D, Many A, *et al.* Interferon-alpha-2b with VMCP for induction in multiple myeloma, The Israël Myeloma Cooperative group experience. *Isr J Med Sci* 1995, **31**, 604–610.
16. Abrahamson GM, Bird JM, Newland AC, *et al.* A randomized study of VAD therapy with either concurrent or maintenance interferon in patients with newly diagnosed multiple myeloma. *Br J Haematol* 1996, **94**, 659–664.
17. Hjörth M, Westin J, Dahl IMS, *et al.* Interferon-α2b added to melphalan–prednisone for initial and maintenance therapy in multiple myeloma. A randomized, controlled trial. *Ann Intern Med* 1996, **124**, 212–222.
18. Wisloff F, Hjörth M, Kaasa S, Westin J. Effect of interferon on the health-related quality of life of multiple myeloma patients, results of a nordic randomized trial comparing melphalan–prednisone to melphalan–prednisone + α-interferon. *Br J Haematol* 1996, **94**, 324–332.
19. Browman GP, Bergsagel D, Sicheri D, *et al.* Randomized trial of interferon maintenance in multiple myeloma, a study of the National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1995, **13**, 2354–2360.
20. Westin J, Rödjer S, Turesson I, Cortelezzi A, Hjorth M, Zador G. Interferon alfa-2b versus no maintenance therapy during the plateau phase in multiple myeloma. A randomized study. *Br J Haematol* 1995, **89**, 561–568.
21. Avilés A, Alatriste S, Talavera A, Delgado S, Rosas A. Alternating combination chemotherapy and interferon improves survival in poor prognosis multiple myeloma. *Clin Oncol* 1995, **7**, 97–101.
22. Powles R, Raje N, Cunningham D, *et al.* Maintenance therapy for remission in myeloma with Intron A following high-dose melphalan and either autologous bone marrow transplantation or peripheral stem cell rescue. *Stem Cells* 1995, **13** (Suppl. 2), 114–117.
23. Mellstedt H, Osterborg A, Björkholm M, *et al.* Treatment of multiple myeloma with interferon alpha, the Scandinavian experience. *Br J Haematol* 1991, **79** (Suppl. 1), 21–25.
24. Ganjoo RK, Johnson PWM, Evans ML, *et al.* Recombinant interferon-alpha 2b and high dose methyl prednisolone in relapsed and resistant multiple myeloma. *Haematol Oncol* 1993, **11**, 179–186.
25. Salmon SE, Crowley JJ, Grogan TM, Finley P, Pugh RP, Barlogie B. Combination chemotherapy, glucocorticoids, and interferon alfa in the treatment of multiple myeloma, a South-West Oncology Group study. *J Clin Oncol* 1994, **12**, 2405–2414.
26. Österborg A, Björkholm M, Björeman M, *et al.* Natural Interferon-α in combination with melphalan/prednisone versus melphalan/prednisone in the treatment of multiple myeloma stages II and III, a randomized study from the Myeloma Group of Central Sweden. *Blood* 1993, **81**, 1428–1434.
27. Peest D, Deicher H, Coldewey R, *et al.* A comparison of polychemotherapy and melphalan/prednisone for primary remission induction, and interferon-alpha for maintenance treatment, in multiple myeloma. A prospective trial of the German Myeloma Treatment Group. *Eur J Cancer* 1995, **31A**, 146–151.
28. Dimopoulos MA, Weber D, Delasalle KB, Alexanian R. Combination therapy with interferon–dexamethasone for newly diagnosed patients with multiple myeloma. *Cancer* 1993, **72**, 2589–2592.
29. Alexanian R, Barlogie B, Gutterman J. α-Interferon combination therapy of resistant myeloma. *Am J Clin Oncol* 1991, **4**, 188–192.
30. Gertz MA, Kalish LA, Kyle RA, Hahn RG, Tormey DC, Oken MM. Phase III study comparing vincristine, doxorubicin (adriamycin), and dexamethasone (VAD) chemotherapy with VAD plus recombinant interferon alfa-2 in refractory or relapsed multiple myeloma. *Am J Clin Oncol* 1995, **18**, 475–480.
31. Capnist G, Vespignani M, Spriano M, *et al.* Impact of interferon at induction chemotherapy and maintenance treatment for multiple myeloma. *Acta Oncol* 1994, **33**, 527–529.
32. Aitchison R, Williams A, Schey S, Newland AC. A randomised trial of cyclophosphamide with and without low dose alpha-interferon in the treatment of newly diagnosed myeloma. *Leukemia Lymphoma* 1993, **9**, 243–246.
33. Cooper MR, Dear K, McIntyre OR, *et al.* A randomized clinical trial comparing melphalan/prednisone with or without interferon alfa-2b in newly diagnosed patients with multiple myeloma. A Cancer and Leukemia Group B study. *J Clin Oncol* 1993, **11**, 155–160.

34. Giles FJ, McSweeney EN, Richards JDM, *et al.* Prospective randomised study of double hemibody irradiation with and without subsequent maintenance recombinant alpha 2b interferon on survival in patients with relapsed multiple myeloma. *Eur J Cancer* 1992, **28A**, 1392–1395.
35. Malpas JS, Ganjoo RK, Johnson PWM, *et al.* Myeloma during a decade, clinical experience in a single centre. *Ann Oncol* 1995, **6**, 11–18.
36. Attal M, Huguet F, Schlaifer D, *et al.* Maintenance treatment with recombinant alpha interferon after autologous bone marrow transplantation for aggressive myeloma in first remission after conventional induction chemotherapy. *Bone Marrow Transplant* 1991, **8**, 125–128.
37. Samson D, Volin L, Schanz U, Bosi A, Gahrton G for the EBMT Multiple Myeloma Study Group. Feasibility and toxicity of interferon maintenance therapy after allogeneic BMT for multiple myeloma, a pilot study of the EBMT. *Bone Marrow Transplant* 1996, **17**, 759–762.
38. Child JA. Evolving strategies for the treatment of myelomatosis. *Br J Haematol* 1994, **88**, 672–678.
39. Johnson PWM, Selby PJ. The treatment of multiple myeloma—an important MRC trial. *Br J Cancer* 1994, **70**, 781–785.

PII: S0959-8049(97)10048-X

Arbiter:

G.P. Browman

Department of Clinical Epidemiology and Biostatistics, Health Information Research Unit, McMaster University, Hamilton, Ontario, Canada

INTRODUCTION

THE CONTRIBUTIONS of Zulian [1] and Ludwig and Fritz [2] in this issue of *European Journal of Cancer* are framed as opposite views on whether alpha interferon ought to be considered a standard treatment for patients with multiple myeloma. In spite of this billing, it is clear that the respective authors agree on most things, except their conclusions. The purpose of this editorial is to place these different conclusions in context, using the principles and newer conceptualisations of an even greater area of controversy, evidence-based medicine (EBM) [3, 4].

ASSESSMENT FRAMEWORK

EBM is defined as the conscientious, judicious and explicit use of the best available evidence from healthcare research to make clinical decisions for individual patients [5]. Opponents are concerned about the apparent disregard of EBM for the opinions of experts (like the authors of these two articles), the devaluing of clinical experience and the complexity of clinical decisions, and the apparent unfeasibility of applying EBM in practice [6–9]. Opposition also represents a reaction to the apparent appropriation of the term 'evidence' as exclusively the domain of health care research, which trivialises the contributions of basic research which has informed clinical practice in the past and continues to do so.

However, the definition of EBM does acknowledge the importance of clinical judgment (*judicious use*) and simply stresses the importance of applying a careful eye to research evidence about interventions in situations where they are intended to be used. Proponents of EBM have also acknowledged the interplay of research *evidence*, clinical and personal *circumstances* (including resource constraints), as well as personal (both patient and provider) and societal *values* as determinants of a clinical decision [10]. Thus, the term 'evidence-guided' medicine may be more appropriate and acceptable.

The different arguments advanced by the authors of the two papers under consideration in support of their conclusions could reflect either differences in: (i) the evidence domain (different interpretations of the same evidence, or reference to different bodies of evidence); (ii) the interpretation of circumstances in which decisions or recommendations about alpha interferon are made; and/or (iii) the values that relate to these decisions or recommendations. In the remainder of this commentary, I will evaluate the different perspectives within this framework.

ASSESSMENT OF THE PAPERS BY ZULIAN, AND LUDWIG AND FRITZ

The papers in question are evaluated according to the use of *evidence* by the authors, the assumed *circumstances* under which the recommendations are intended to apply and the implicit *values* suggested by the recommendations.

Approach to the evidence

By concentrating their arguments on the results of randomised controlled trials (RCTs) and referring to the value of the methodology of the systematic review [11, 12], both authors clearly demonstrate respect for the approach of EBM. However, in both papers there are flaws in the approach which may reflect either inherent biases of the authors, or a lack of familiarity with certain aspects of the sophisticated methods of the systematic review. Examples of these flaws and the strengths of the papers from an evidence perspective are shown in Table 1. The most serious flaws include admission by Zulian of a selective sampling of the literature to support an a priori argument, and the use of a weak method for synthesising the evidence; and, for Ludwig and Fritz, failure to specify literature search methods and the use of a clinical outcome of questionable relevance (response to treatment) as the basis of a pooled analysis. While response to treatment

Received 22 Sep. 1997; accepted 25 Sep. 1997.