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.

Table 1. *Strengths and weaknesses of evidence-based approaches*

Zulian	Ludwig and Fritz
Strengths	Strengths
Bases arguments on published research with emphasis on randomised trials	Bases arguments on published research with emphasis on randomised trials
Literature search terms, database (MEDLINE) specified	Attempts to pool results using valid methods
Addresses issue of publication bias through search for unpublished data (although abstracts ignored)	Understands and addresses issues of publication bias through inclusion of abstracts
Awareness of the issues of data combinability in pooled analysis based on homogeneity	Eligibility criteria for inclusion of studies well defined
Includes Nordic quality of life citation [13]	Provides original data on patient interviews about their preferences
Reference citations are up to date	
Weaknesses	Weaknesses
Explicitly reveals bias at the outset based on his assignment, alluding to 'selected' references to bolster argument	Most up to date citations not used (i.e. cites abstracts of studies that are available in fully published format)
Rejects quantitative pooling of data on flimsy grounds (clinical heterogeneity) without exploring this analytically, yet uses 'voting'* method as arbiter of evidence	In pooled analysis chooses to highlight, in figure, questionably relevant clinical outcome (response) on which to base conclusions
Key citations (e.g. Mandelli [16]) are missing, despite laudable efforts to locate unpublished evidence (e.g. from pharmaceutical company files)	Search terms and data sources for literature search not described
Does not discuss decisions about including/excluding abstracts	No presentation of analytical method for pooled analysis
Selective reference to one study (not an RCT†) in describing toxicity and tendency to put equal weight on studies of different design quality	

*Voting refers to a technique by which conclusions are drawn by simply counting the number of 'positive' and 'negative' studies, but ignores the difference in their quality and the amount of information they contribute individually through the size of the population studied [17]. †RCT, randomised controlled trial. Some of the obvious 'weaknesses' were corrected by the authors in their final draft in response to this contribution. However, it is useful to retain these items for the interest of readers. Omission by both authors of any reference to the Myeloma Trialists' Collaboration as a source of pending evidence has been removed as an item from the lists of 'weaknesses', but is an important feature of the evidence-based approach which values some unpublished work.

(the outcome chosen) is a useful marker for the biological anti-tumour activity of an agent, it is less relevant to the clinical decision about whether it ought to be recommended for the purposes of improving survival or quality of life especially where the relation between response and these other clinical outcomes has not been evaluated.

In spite of these different approaches, based on the published evidence, the authors come to the same conclusions on efficacy: (1) RCTs do not seem to demonstrate a clinically meaningful survival benefit in favour of interferon during either induction or maintenance in myeloma; (2) RCTs clearly demonstrate a benefit with respect to the duration of progression-free survival among those receiving maintenance interferon after response to induction chemotherapy, (3) the clinical importance of the magnitude of benefit in progression-free survival is open to interpretation; and (4) formal quality of life data are insufficient to guide practice. (A forthcoming meta-analysis by the Myeloma Trialists' Collaborative Group will shed more light on some of these issues.) Finally, Ludwig and Fritz provide additional original data from survey studies of patients' preferences that are a useful adjunct to the evidence for clinical decision making [2].

Circumstances

Evidence from health care research is only one factor, albeit a crucial one, for informing a clinical decision or recommendation about treatment. Particular individual circumstances and system constraints, such as the availability of expertise and resources, also need to be considered. Often, the weight placed on these factors depends on the magnitude of benefit of a particular intervention and the trade-offs to be expected when using the intervention, compared to the alternative(s). Zulian does an admirable job in pointing out the dubiously beneficial trade-off between the expected gains from the use of maintenance interferon in myeloma and the associated toxicity and inconvenience of administering the treatment [1]. On these grounds, he strongly argues against interferon as a treatment standard. The best study of this issue, which measured quality of life prospectively using validated instruments [13], tends to support the notion that prolonged progression-free survival does not compensate for early, moderate reductions in quality of life associated with interferon; conversely, quality of life reductions do not seem to extend beyond the treatment period.

Zulian goes on to raise the issues of societal costs and uses this argument to conclude that the potential marginal benefits associated with interferon therapy are not worth the costs incurred [1]. He goes further by providing actual monetary costs and concludes that the cost-effectiveness of interferon does not warrant its recommendation as a standard. However, only information on costs is provided and there is no formal comparative analysis of the cost-effectiveness of interferon treatment compared with an alternative, which would be a more appropriate basis for considering the worthiness of treatment from an economic perspective. Nevertheless, the arguments indicate a respect for a variety of inputs into the decision-making process.

Values

The arguments by Zulian conclude with a 'bottom line' suggesting that experts, after weighing the evidence on efficacy, toxicity/quality of life and costs should advise against

the use of interferon as standard practice in myeloma. Ludwig and Fritz come to the same conclusion, that interferon ought not to be recommended for *use* as a treatment standard, but they do advocate that it be *offered* as a treatment option to a well-informed patient. This is supported by new data from the authors about potential patient preferences in this clinical circumstance.

The basis for the recommendations of the two authors clearly displays differences in values. Although appropriate in his own medical and societal setting, Zulian appears to take the policy perspective, which could be labelled by detractors as 'paternalistic'. On the other hand, Ludwig and Fritz adopt a 'patient-centred' approach, which could be labelled as an impractical solution for health care systems with limited resources where difficult decisions need to be made to preserve the overall quality of care for interventions known to be effective.

CONCLUSION

Clinical decisions and, therefore, recommendations, should be guided by high-quality evidence that pays attention to the results of health care research. All patients should be provided with the opportunity to benefit from such research. Where evidence is conflicting, methods need to be employed to help clinicians determine the conclusions. Tools such as evidence-based practice guidelines can help clinicians make judicious decisions and a methodology for guideline development which tries to take into account values and circumstances, has been published [14]. However, until guidelines become more available and more reliable as an information source, clinicians will have to learn the skills necessary to become better evaluators of research, although clinicians already have a difficult enough time keeping up in their disciplinary field of expertise and cannot also be expected to be skilled consumers of methodological research. However, as such crucial methods become incorporated into undergraduate and postgraduate health professional curricula and training experiences, their clinical applications should improve.

Evidence is only one factor to consider in a clinical decision. It is a necessary component of such decisions, but not the final arbiter. Both clinical and life circumstances, as well as patient and provider values, will influence decisions. Therefore, the key aspect of a clinical decision or recommendation is to be explicit about how the various pieces of information are used.

The papers by Zulian and by Ludwig and Fritz highlight the interplay amongst evidence, circumstances and values. In the end, their fundamental conclusions based on the evidence are the same, that interferon ought not to be recommended as a *standard* or routine treatment in myeloma. Where they differ is with respect to the values as represented by their choice of perspective. Zulian chooses the population perspective to present compelling arguments against the use of interferon for a society which needs to make choices about how it spends its health care resources; and Ludwig and Fritz take a patient-centred approach that examines the same evidence through a different aspect of the same prism.

By their very nature, values are not absolutes and, therefore, different values are neither right nor wrong (within legal and conventional limits); they are only different. Thus, the conclusions of both authors are correct from their different perspectives and would apply depending on the particular health care setting and who is responsible for making the decision. This raises what is perhaps the most important characteristic of EBM, the requirement for explicitness in how decisions are made [15]. As a clinician, I favour the patient-centred approach, but understand the need for policy makers to make different kinds of choices. By framing the issues in this explicit way, we can unearth hidden and unrecognized assumptions to help resolve apparent conflicts between people who are forced through their different decision-making roles to take different perspectives in order to behave responsibly on behalf of their constituents.

1. Zulian GB. Should alpha-interferon be included as standard treatment of multiple myeloma: contra. *Eur J Cancer* 1998, **34**, 18–22.
2. Ludwig H, Fritz E. Should alpha-interferon be included as standard treatment of multiple myeloma: pro. *Eur J Cancer* 1998, **34**, 12–17.
3. Evidence-based medicine working group. A new approach to teaching the practice of medicine. *JAMA* 1992, **268**, 2420–2425.
4. Costa A, Hubbard SM. Evidence based medicine, a new challenge. *Eur J Cancer* 1997, **33**, 987–988.
5. Sackett DL, Rosenberg WMC, Gray JAM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *Br Med J* 1996, **312**, 71–72.
6. Smith BH, Taylor RJ. Medicine—a healing or a dying art? *Br J Gen Prac* 1996, **46**, 249–251.
7. Grahame-Smith D. Evidence based medicine: Socratic dissent. *Br Med J* 1995, **310**, 1126–1127.
8. Naylor CD. Grey zones of clinical practice: some limits to evidence-based medicine. *Lancet* 1995, **345**, 840–842.
9. Maynard A. Evidence-based medicine: an incomplete method for informing treatment choices. *Lancet* 1997, **349**, 126–128.
10. Haynes RB, Hayward RSA, Lomas J. Bridges between health care research evidence and clinical practice. *JAMA* 1995, **2**, 342–350.
11. Mulrow CD, Cook DJ, Davidoff F. Systematic reviews: critical links in the great chain of evidence. *Ann Intern Med* 1997, **126**, 389–391.
12. Mulrow CD. The medical review article: state of the science. *Ann Intern Med* 1987, **106**, 485–488.
13. 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.
14. Browman GP, Levine MN, Mohide EA, *et al.* The practice guideline development cycle: a conceptual tool for practice guidelines development and implementation. *J Clin Oncol* 1995, **13**, 502–512.
15. Eddy RM. Guidelines for policy statements: the explicit approach. *JAMA* 1990, **263**, 2239–2243.
16. Mandelli F, Avvisati G, Amadori S, *et al.* Maintenance treatment with recombinant interferon alpha-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med* 1990, **322**, 1430–1434.
17. Eddy DM. Combining evidence. In *A Manual for Assessing Health Practices and Designing Practice Policies. The Explicit Approach.* Philadelphia, American College of Physicians, 1992, 50–61.