This letter was referred to the authors, who respond as follows:

The comments of Dr. Baumgart and Dr. Kühnel, in our opinion, tend to load our paper [1] of a clinical relevance which, due to the laboratory nature of the investigation, can only be hypothesized. They argue that the percentages of patients with complete/incomplete plasmatic L-asparagine (L-ASN) depletion during L-asparaginase (L-ASE) treatment were miscalculated; in their opinion in fact, in the case of lacking data, patients should be considered depleted (if found depleted thereafter) or not depleted (if found previously not depleted) or with 'missing data' (if data are not interpretable). L-ASN depletion rates during induction treatment were thus recalculated according to these criteria and including the new entity of 'missing data'.

We are aware of the limitations of our study due to the lack of complete longitudinal data on a substantial subset of patients; in our opinion however the inclusion of the entity of 'missing data', suggested by Dr. Baumgart and Dr. Kühnel, makes the interpretation of the results more difficult and somehow confusing. The interpretation of missing data is always based on assumptions and considered a matter of major concern for statistical analysis; it is hard, however, to imagine that the interpretation of missing data might be the right solution for biological problems!

The real biological issue, concerning L-ASE treatment, is to define the level and duration of L-ASN depletion needed to obtain a complete antileukemic effect, which cannot be established simply on plasmatic L-ASN levels. Theoretically it may be supposed that a product with higher L-ASN depletion activity may be more effective; it is not proved, however, that the deeper is the depletion the higher is the antileukemic effect, and it is thus also possible that an enhanced effect may be useless or even counterproductive in the case of increased toxicity. It should also be considered that the clinical effect of a single drug may also depend on the polychemotherapy schedule adopted. Drawing definite conclusions on the clinical efficacy of antineoplastic agents exclusively from laboratory data is thus inappropriate and possibly even dangerous. Accordingly, the last statement of the letter of Dr. Baumgart and Dr. Kühnel cannot be applied to our laboratory-data based study.

To this regard it may be added that when the paper was accepted for publication there were no clinical data available to suggest that any Escherichia coli (E. coli) products could provide superior clinical results compared to the Erwinia chrysanthemi (E. chrysanthemi) product given at the same doses; conversely, the E. chrysanthemi product had been reported to be associated with lower risk of major side effects, suggesting that it 'should be considered as the L-asparaginase of choice in treating ALL in children' [2]. In the UKALL VIII study [3] the clinical data reported on historical comparisons between two groups of patients treated with an E. coli product (Crasnitin, Bayer) or with the E. chrysanthemi product (Erwinase, Speywood) showed in fact no difference in the Disease Free Survival (DFS). Similar results have been recently reported by our group too in a retrospective, non-randomized comparison of data on clinical efficacy and toxicity in intermediate-risk ALL children treated with BFM protocols. The four years DFS in the two groups treated with Crasnitin (Bayer) or Erwinase (Speywood) was, respectively, 85.0% and 88.2%, P = n.s., see Figure 1 [4]. It could thus be concluded that, in the context of those treatment schedules, these two products (Crasnitin and Erwinase) provided the same clinical effects.

A totally different experience has been however reported at the 38th ASH meeting (December, 1996) as mentioned by Dr. Baumgart and Dr. Kühnel in their letter; the results of the EORTC 58881 randomized clinical trial in fact showed a highly significant difference of EFS in two groups of patients treated either with an E. coli L-ASE product (obtained from a different strain in respect of Crasnitin) or with the E. chrysanthemi L-ASE (four years EFS was 75% and 62% respectively, median observation time 3.8 years, 2P < 0.0001) [5]. These results clearly indicate that L-ASE is an important component of ALL treatment and that not only the products derived from different bacteria (E. coli or E. chrysanthemi) but also those derived from different strains of the same bacteria (E. coli) may be associated with very different clinical effects. This is in keeping with the findings of laboratory studies recently reported by our group and others [1, 6], showing major differences of L-ASE activity and/or L-ASN depletion not only in patients treated with the E. chrysanthemi product or E. coli products but also among patients treated with different E. coli products. Further information on these issues is however still needed before drawing definite conclusions.

Note: We agree that the number of 23 (instead of 24) samples tested (first column of Table 3) is wrong; this was a typing error. All the calculations reported were, however, correct since they have been performed on the basis of the correct number of samples tested (i.e., 24).

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References


Book review


I very much enjoyed reading the Textbook of Medical Oncology. This volume has a stated purpose of being predominately for European physicians and it has an overwhelming predominance of European authors. For practical purposes one might consider it the textbook for the European Society for Medical Oncology (ESMO).

The significance of a European textbook on medical oncology will be missed by many Americans. In America we have blurred the borders between hematology and oncology. However, in much of the rest of the world hematology, including laboratory based activities, has been a viable specialty for many years but medical oncology is still trying to find its way. The existence of a high quality book like this written almost exclusively by European authors makes a statement about the health of medical oncology in Europe and, I believe, its bright future. Of course, leukemias and lymphomas still represent an area of considerable overlap between physicians in Europe who call themselves hematologists and those who call themselves oncologists. However, the recognition of the importance of internists especially skilled in the management of patients with cancer is important and this text takes another step in that direction.

I found the text itself to be very much as 'advertised' by the title. This book is not a comprehensive review of cancer and its management like Devita's Cancer: Principles and Practices of Oncology or Abeloff's Clinical Oncology (i.e., both over 2000 pages). Rather, this is really a textbook that would be appropriate required reading for medical students or postgraduate trainees while studying medical oncology. The book provides a description of the specialty and an accurate presentation of the capabilities of its practitioners. The book itself is well written and readable. Because of my own interests, I especially enjoyed the chapters on hematologic malignancies. In general, chapters in all areas are comprehensive without being exhaustive and, even for the experienced medical oncologist, might be a place to look for a quick review of a condition that is not regularly treated. The book is not a place to look for subtle nuances of the management of any particular kind of cancer. It is also not the place to find extensive reference lists.

In summary, I enjoyed this book and believe it will be enjoyed by anyone interested in medical oncology. The volume will be especially appropriate as a textbook for medical students or postgraduate trainees studying medical oncology. However, its most important contribution might be as a statement that medical oncology as a specialty has come of age in Europe and has an exciting future.

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