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Comments and Critique

Aggressive Non-Hodgkin's Lymphoma in Elderly Patients: Where to Go From Here?

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ELDERLY PATIENTS with aggressive non-Hodgkin's lymphoma (NHL) represent an ever larger fraction of our patients, and will become even more important if the present demographic trends of the western population continue. Since the early 1980s, outcome and tolerance of chemotherapies in these patients have been repeatedly analysed [1–3]. The conclusions drawn have often been contradictory, but nevertheless some points have emerged. Firstly, we cannot extrapolate the information obtained in trials with age limits to the elderly population. Therefore, trials should be carried out without age limits at all or specific trials must be developed for this age group [4]. Secondly, elderly patients may have relatively poor haematological tolerance so dose reductions or adapted regimens may, therefore, be necessary [5]. Thirdly, such reductions in dose (and probably dose intensity) lead to worse outcomes in elderly patients, as in younger patients [2, 6].

It is, therefore, timely and welcome that effective drug combinations with possibly better tolerance are tested on an unselected elderly population. Such a trial is reported by Bessel and colleagues in this issue (pp. 1337–1341). They included all patients older than 70 years from their geographical region, and tried to avoid all possible selection biases due to the inclusion/exclusion criteria of a prospective study. The combination used included mitoxantrone [6–10 mg/m^2 intravenous (i.v.) day 1], cyclophosphamide (500–600 mg/m^2 i.v. day 1), vicristine (1.4 mg/m^2, maximum 2 mg i.v. day 1) and prednisolene (40 mg/day, orally 5 days) (MCOP). Their conclusion is that this regimen "can be used in the majority of patients aged >70 years and older with intermediate- and high-grade NHL. Dose reductions during the course of chemotherapy are usually not necessary. The toxicity is acceptable, with no treatment-related deaths. . .". However, only 46 of 74 patients received chemotherapy according to the protocol, 20 were treated by radiotherapy only (3 with stage IV disease) and 6 were considered unfit for therapy. The remission rates were an acceptable 63%, but medium-term results were dismal, with a 3-year cause-specific survival of only 29% for the treated population. This corresponds to 17.5% of the original population of 74 patients. Nobody would accept this as an efficient therapy of a potentially curable disease. In addition, the authors fell into the trap which they set out to avoid. Patient selection for therapy was based on clinical decisions (and certainly with the best intentions), but without clearly stated criteria that can be successfully reproduced by others.

What then is the difference to clinical trials where these criteria are detailed? They claim that patients included in prospective trials "tend to be fitter patients, who could tolerate the chemotherapy regimens of the trial without dose reduction". This may well be true, as shown by two recent communications. In the December issue of the *Journal of Clinical Oncology*, an Italian group published a prospective study of P-VABEC in patients >60 years old [7]. Contrary to the present study, these patients were completely staged. 9 patients were excluded for defined reasons (hepatopathy, cardiopathy, low performance status, diabetes, second malignancy). Not surprisingly, the results in this younger population were much better. Seventy-five per cent of the patients achieved complete remission, with 55% event-free after 2 years (<30% in the Bessel study). Is this due to the different selection, i.e. the younger patient population, the compete staging, the selection inherent in a population at a referral centre, or is it the different regime? My bias is for a considerable influence of patient selection. Fortunately, these patients were included based on clear criteria, so anybody may apply the same therapy to an identically-defined population if they so wish.

At this year's American Society of Clinical Oncology (ASCO) meeting, an analysis of the elderly patient population (>60 years) in SWOG-8516 (Int 0067) was presented [8]. This study compared CHOP, m-BACOD, ProMACE-CytaBOM and MACOP-B in a prospective, randomised clinical trial. The results had been published in the *New England Journal of Medicine* [9] for all age groups. In the present analysis, a significant difference in overall survival was found between the older and younger age groups. However, in the CHOP arm, no differences in severe toxicity between younger and older patients existed (fatal toxicity 1.5 versus 1.4%), with a similar proportion of patients receiving all eight courses of CHOP (67 versus 68%). Overall, there was also no significant difference in CR rates (39 versus 40%) and disease-free survival. If the most toxic regime (MACOP-B) is excluded, no significant overall survival difference remains. Even though this is a retrospective analysis of subgroups within the trial, and the results will need confirmation in a prospective study, for these trial-included patients, CHOP seems as well tolerated and as effective as in younger age groups. Is it, therefore, really better to select patients by the subjective criteria of the treating oncologist for fitness, in a procedure that

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cannot be reproduced by others? And can we afford to undertreat elderly patients on the pretext of using well-tolerated regimens? Should we not treat all patients satisfying similar criteria with an effective regimen, e.g. CHOP? If I were such a patient, my answer would be very clear!

But what about the non-qualifying patients? Many of these may still benefit from chemotherapy, even though less aggressive, but how should these patients be selected, and by what criteria should they be declared unfit? Evidently, this is not easy and non-measurable clinical factors, including the patient's and his/her relatives' willingness, as well as the doctor's bias in favour or against such therapy, may play important roles [10]. Nevertheless, we should not accept these unclear factors, but strive to define more exactly which criteria need be fulfilled for less aggressive, palliative treatment, and which criteria for no treatment. Anything else is an unsatisfactory solution, and will not help future generations of patients and doctors forced to take treatment decisions.

Finally, recent developments point out that even so-called well-tolerated regimens may have side-effects comparable to CHOP. In the Dutch CNOP versus CHOP study, similar toxicities and a better complete response rate and overall survival was found in the CHOP arm in 145 evaluable patients older than 60 years (Sonneveld, personal communication). Finally, the EORTC 20872 trial, comparing VMP to CHOP in elderly patients, was prematurely closed for ethical reasons at the recent Paris meeting of the EORTC lymphoma group because of unexpected imbalances in efficacy and tolerance of the two arms (Tirelli, personal communication). Of course, we have to wait for the published full reports to know exactly how to interpret this information. Nevertheless, for the time being, it seems clear that all patients fulfilling entry criteria such as required for a prospective study should receive CHOP or an equivalent regime, without dose reduction. Those that do not fulfil the criteria should be included in trials that try to better define objective reasons for not treating these patients at all, or for treating them with a tolerable and efficient therapy adapted to their situation.

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Renal Cell Cancer: is There Long-term Survival Advantage From Cytokine Treatment?

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INTRODUCTION

IN THE U.K. financial restrictions have limited widespread use of interleukin (IL)-2 and interferon (IFN-α). Elsewhere in the world, there is disbelief that there is a need for a randomised trial in metastatic renal cell cancer patients, comparing IFN-α and placebo, namely medroxyprogesterone acetate (MPA)[1]. The U.K. MRC trial has now recruited 107 cases and has successfully passed its first review by a data monitoring committee, suggesting that there is, as yet, no significant gain from the use of IFN-α.

This situation, taken with the previously published small Scandinavian randomised trial involving 60 patients who showed no gain [2], gives added encouragement for continued recruitment into this trial. The retrospective prognostic factor analysis, comparing patients receiving either chemotherapy or IFN-α, reported by Fossa and colleagues in this issue, (pp. 1310–1314) provides added support. Though they claim significant gain with IFN compared to chemotherapy, it is only seen in the minority of patients who survive for more than 12 months and who have good risk factors, as defined by low erythrocyte sedimentation

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