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Dear Christopher,

STA Fludarabine for the treatment of lymphocytic leukaemia

It has been apparent for 10 years that fludarabine is an effective drug in CLL. At that time the standard treatment for CLL was an alkylating agent, usually chlorambucil but in patients who were intolerant to this drug cyclophosphamide was substituted.

When oncologists find two drugs that are effective in the treatment of a malignant disease, then their natural instinct is to combine them. The CALGB trial published in the New England Journal in 2000 (Rai et al) included the fludarabine + chlorambucil combination, but this was considered too toxic. Subsequently the combination of fludarabine + cyclophosphamide has been demonstrated in 3 randomised clinical trials to be superior to fludarabine alone in the following respects: it produces more overall responses and more complete responses, it produces longer remissions, and it is cheaper. Moreover, the toxicity of the combination is tolerable and does not add significant extra costs.

In one randomised clinical trial (LRF CLL4) it is also superior to chlorambucil in overall remissions, complete remissions, and length of remission. It is of course more expensive than chlorambucil.

Because CLL is a chronic disease and because during the course of the disease the patient may have three, four, five or even six rounds of treatment which may be of the same or different drugs, it will never be possible demonstrate an overall survival advantage for a particular type of treatment given as first line, unless that treatment cures the disease. Nor is it likely that trials will be able to demonstrate that a particular sequence of treatment is preferable. We must work within the limitations of what data are available.

I am aware that the FC combination has not been commented on because there is no marketing authorisation fro the combination. This seems to me to be a mistake, especially so, as we know the evaluation has been done and the decision is likely to be favourable. The fact is that virtually all cytotoxic drugs are given in combinations, and it

would be perfectly reasonable for NICE to recommend that fludarabine should ordinarily be given in combination with cyclophosphamide. For many years the standard therapy for acute myeloid leukaemia employed Daunorubicin in combination, an unlicensed indication. It seems to me that the reputation of NICE depends on it making recommendations that relate to real life rather than to some paper world that exists only in the minds of those who don't treat patients.

I think I am well known as someone who believes that the rest of the world has discarded chlorambucil in the treatment of CLL far too easily. Nevertheless, to recommend that the FC combination not be used as first line treatment for some cases of CLL in NHS hospitals is such a distortion of the evidence as to make those making the recommendation a laughing stock in the eyes of patients and doctors alike. I realise that NICE is not saying that, but to fail to make a recommendation in favour of the combination comes to the same thing. People will undoubtedly say that NICE is hiding behind a technicality.

I fully understand why NICE is not making a recommendation on the combination, but it will reflect very badly on the reputation of NICE if it does not do so. Some method of surmounting this difficulty must be found.

Yours sincerely,

University of Southampton

On behalf of LRF