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Dr. Henry G. Kaplan
Institutional Review Board Chairman
c/o FHCRC Mailstop I725

Dear Hank:

Dr. Day has forwarded to me the letter which you wrote to him on December 17, 1984 concerning protocol #159, Autologous marrow transplantation for treatment of malignant lymphoma. The major criticism which you have raised is that there is no prospectively defined control group to use to determine whether the monoclonals are effective in reducing the relapse rate of lymphoma following marrow transplantation. This criticism would be justified if we were trying to evaluate the ability of monoclonals to reduce the relapse rate following autololgous marrow transplantation but that is not one of the goals of the study. If you refer to page 4 of the protocol, under objectives, we clearly state that we are testing the feasibility of restoring hematologic function after cytoxan and TBI with autologous marrow manipulated in vitro to remove tumor cells. Thus this is a toxicity study of the use of monoclonal antibodies and we are not in any sense trying to make a judgement about the utility of the antibodies in removing tumor from marrow. The study has been structured in this way for several reasons. First, prior to starting a comparative study of the efficacy of a regimen, it is important to first determine the toxicities of that regimen. Since there is little toxicity data of the use of in vitro treated marrow, we felt that this was the first important step to take. Second, there is little point in doing a controlled study unless there is a likelihood that one could discern an effect of the treatment. In reviewing our own data and that of the rest of the world, it is apparent that autologous marrow transplantation for malignant lymphoma in relapse using untreated autologous remission marrow results in a long-term cure rate of approximately 15-25%. A review of the data obtained so far using allogeneic marrow (marrow which we know cannot be contaminated with tumor cells) reveals similar long-term survival in a similar patient population. More importantly, the actuarial relapse rates following the use of autologous untreated marrow and allogeneic marrow are identical. In both situations approximately 65-70% of patients would be expected to relapse. Therefore, even if treatment of marrow in vitro were 100% successful in removing every last lymphoma cell, it would be virtually impossible to detect an impact of this removal on relapse rates because of the relative inability of current preparative regimens to eradicate tumor in the patient. Therefore we can find no reason to proceed in a difficult and costly comparative study

which has virtually no chance of being able to detect an impact of in vitro marrow incubation. Should one then stop doing all marrow incubation procedures? We are not in favor of this approach. It is our hope that improved preparative regimens may in the future decrease the relapse rate from tumor remaining in the patient. If this were accomplished, it may then allow us to detect a difference between autologous untreated marrow and allogeneic marrow. If such a difference could be discerned, then prospective studies measuring the utility of in vitro incubation would be warranted. Therefore we feel it reasonable to proceed with the toxicity studies of marrow incubation with the hope that these techniques will be applicable in the future.

Finally, you mention that the Board is "concerned about authorizing protocols in which the apparent successful use of an agent could be potentially beneficial financially to many of the investigators listed on the study". I would like to respond to this concern in several ways. First, I am the principal investigator in the study and the collection, evaluation and interpretation of the data ultimately rests with me. I have absolutely no financial interaction with Oncogene or any other company that might be producing monoclonals used in the study. Second, the records of every patient treated on the study are available to other members of the division and are reviewed at staff conferences thus making it difficult to alter the data. Third, a similar concern could be leveled at virtually any protocol run by any institution within the United States. If suddenly no patients came to the Fred Hutchinson Cancer Research Center or the University of Washington, those of us who are involved in clinical medicine would probably lose our jobs which would have a financial impact on us. Patients come for treatment to cancer research centers, in part, because of the center's academic reputation which is on the ability of these research centers to carry out and publish innovative clinical research. Therefore, for every one of us, whether we are involved with a company or not, the success of our research endeavors ultimately has a financial impact on us. Thus, the Institutional Review Board has two choices: either they can express more concern for the research carried out using virtually every modality whether there are links to a company or not, or the review board can accept the fact that those of us in cancer research are intrinsically honest individuals who are trying our best to develop therapies which will be beneficial to our patients and further, all of us are also aware of the fact that any positive clinical studies will be repeated by other investigators and there is probably nothing as damaging to one's academic career as publishing results which cannot be reproduced. I hope these thoughts help to answer some of your concerns over protocol #159.

Sincerely,

Frederick R. Appelbaum, M.D.
Associate Professor of Medicine
Division of Oncology

FRA:lr
cc: Sue Charrier
Robert Day, M.D.
E. Donnall Thomas, M.D.
Members, Institutional Review Board