**Example of essay question with outline of model answer**

Discuss the type of evidence that could be used discover if treatment for neoplastic conditions causes leukaemia (70% of marks for question). What are the characteristics of therapy-related acute myeloid leukaemia? (30% of marks for question)

**Essay outline**

Part 1

Start by stating what you mean by ‘neoplastic conditions’. These are conventionally divided into benign and malignant neoplasms. They include acute and chronic leukaemias, lymphomas, myelodysplastic syndromes and myeloproliferative neoplasms as well as the various types of solid tumours.

Next consider what treatment might be used, e.g. surgery, chemotherapy, radiotherapy, monoclonal antibody therapy.

The evidence might be derived from a cohort study in which a group of patients treated for a neoplastic condition was followed for a number of years to establish the incidence of leukaemia of various types. The group should be as homogeneous as possible, e.g. the same type of tumour, and treatment should be by defined regimes and should be carefully documented. It would be possible to compare the patient group with an age and gender matched control population but this might not be ideal since patients who had already developed one neoplasm might have an inherited susceptibility to leukaemia. Ideally the study group should be compared with a control group with the same tumour treated in a different manner. For example a group of patients with breast cancer treated by surgery plus radiotherapy, or surgery plus chemotherapy, might be compared with a group treated by surgery alone (with the assumption being made that there is no *a priori* reason to think that surgery can cause leukaemia). In order to avoid possible bias, the control group should ideally be treated contemporaneously with the trial group. Using this type of design it would also be possible to compare different drugs with each other, to compare different doses of a given drug or different treatment duration, and to compare chemotherapy plus radiotherapy with each modality used alone. This type of investigation should be planned with the aid of a statistician to make sure that the numbers of patients to be studied was sufficient to detect a clinically relevant increase in the leukaemia incidence with an appropriate degree of statistical significance. If a study showed a significant increase in leukaemic incidence related to a particular form of therapy a follow up study might study the effects of omitting a suspect drug from the treatment regime. This could be a randomised controlled trial in which, for example, one group of patients received a three drug regime and another group received only two of the drugs. The patients would need to be fully informed and consent. It would be essential to study disease-free survival and overall survival as well as the incidence of leukaemia since omitting one drug might reduce the occurrence of leukaemia but lead to more recurrence, e.g. of breast cancer, and more deaths from the primary tumour. An alternative study design would be to omit the suspect drug and compare the trial group with a historical control group who had received all three drugs. This would be scientifically less satisfactory (as other factors might also have changed) but it might be the only ethical way to proceed if there was a very strong suspicion that a particular drug was leukaemogenic. In these sorts of studies you would be looking for:

1. An increased incidence of leukaemia related to a particular form of treatment
2. A dose or treatment duration effect
3. Any evidence of interaction, e.g. between chemotherapy and radiotherapy
4. A reduction of incidence when the drug was omitted from the regime.

An alternative method to look for evidence that a particular treatment was leukaemogenic would be to take a group of patients presenting with, for example, acute myeloid leukaemia, and determine how many of them had previously had treatment for another neoplastic condition, with the nature of that treatment also being studied. The control group could be an age and gender matched healthy population. This is a less satisfactory study design because of the possibility that an increase incidence of leukaemia could result from a genetic predisposition rather than the treatment and also because the patient’s recall of previous treatment might not be reliable and accurate records, e.g. of drugs used and their doses might not be available.

Another alternative would be to use animal experiments and administer drugs under investigation to healthy animals in a randomised controlled trial.

Yet another alternative would be to study patients receiving the same suspect drugs for a non-neoplastic condition. This type of study has been done and has shown, for example, that mitoxantrone used for treating multiple sclerosis rather than a malignant condition, increases the incidence of acute promyelocytic leukaemia; in this case the appropriate control group would be patients with multiple sclerosis not receiving the suspect drug.

Studies such as those described above could and should be carried out on patients being treated for lymphoid malignancies, such as acute lymphoblastic leukaemia, Hodgkin lymphoma and non-Hodgkin lymphoma. They could also be carried out on patients with myeloid neoplasms, such as the myeloproliferative neoplasms but bearing in mind that these conditions have a propensity to transformation to acute leukaemia; nevertheless, it is very relevant to establish whether a patient with, for example, polycythaemia vera, is less likely to develop acute transformation if given hydroxycarbamide rather than busulphan or chlorambucil or radioactive phosphorus.

Further information might be obtained by cytogenetic and molecular studies. For example, if a particular chromosomal rearrangement was found only or almost always in people who had had preceding chemotherapy it might reasonably be concluded that the chemotherapy was responsible. Similarly, with molecular studies it has been discovered that patients developing acute promyelocytic leukaemia after mitoxantrone therapy tend to have different breakpoints from patients developing *de novo* acute promyelocytic leukaemia, supporting the hypothesis that this is a genuine treatment effect.

Part 2

Therapy-related leukaemia can follow radiotherapy and chemotherapy. For chemotherapy, a dose/duration effect and a beneficial effect of omitting the most leukaemogenic drugs from treatment regimes has been shown. There are two major groups of drugs that cause therapy-related leukaemia, the alkylating agents and the topoisomerase II-interactive drugs. Their characteristics differ.

Therapy-related AML following alkylating agents tends to occur 5-10 years after treatment, usually has a preceding myelodysplastic phase, has unbalanced chromosomal abnormalities (such as -5, -7, 5q- and 7q-), and has a very poor survival.

Therapy-related AML following topoisomerase II-interactive drugs occurs after a shorter time interval, often does not have a preceding myelodysplastic phase, is more likely to have balanced chromosomal rearrangements and has a somewhat better prognosis. The balanced translocations that occur include some that also occur in *de novo* leukaemia, such as t(8;21) and t(15;17), the latter in the context of acute promyelocytic leukaemia.