New Platinum Anti-Cancer Drugs

THE POSSIBILITIES OF IMPROVED SELECTIVITY

Work is continuing in a number of institutions to develop a second generation of anti-tumour drugs, based upon complex compounds of platinum, that will offer greater selectivity together with a reduction in toxic side-effects. During the course of a three-day meeting held in Bologna in Italy in September, the Ninth International Symposium on the Biological Characterisation of Human Tumours, a paper was presented by Dr. M. J. Cleare of the Johnson Matthey Group Research Centre. A summary of his talk is given here.

The first generation platinum drug, *cis*-dichlorodiammineplatinum(II), known either as Cisplatin or Neoplatin, is now an established member in the armamentarium of anti-neoplastic agents, and it has made a major contribution to the long term survival of patients treated for ovarian and testicular tumours. Unfortunately however, its therapeutic efficacy is somewhat compromised by the occurrence of severe side effects that limit the doses that may be given to a patient. There is therefore a great need for another platinum drug with an equivalent or improved range of activity but with less toxic side effects.

Since the discovery of Cisplatin a large number of platinum compounds has been screened for anti-tumour activity. By 1979 the United States National Cancer Institute had examined no less than 1055, and of these 185 showed at least minimal activity. Johnson Matthey, in conjunction with other researchers in the United Kingdom, have tested around 500 compounds. This U.K. collaborative group have selected eight compounds, on the basis of initial animal screening results, for more detailed toxicological and anti-tumour evaluation in order to identify the most worthwhile candidate to put forward for Phase 1 clinical trials. The general conclusion from pre-clinical studies on these eight complexes was that some of them definitely exhibited less overall toxicity than the existing platinum drug. Although there was no convincing evidence of superior anti-tumour activity one of the compounds, the 1,1-cyclobutanedicarboxylatodiammine derivative of platinum (CBDCA), showed some evidence of increased selectivity during testing. On this basis CBDCA was chosen for a Phase 1 clinical trial in the U.K.at the Royal Marsden Hospital, Sutton. Another of the compounds considered then, *cis*-dichloro-trans-dihydroxo-bis(isopropylamine)platinum(IV) (CHIP), was selected by U.S. researchers for a separate clinical trial at Buffalo, New York.

Preliminary Phase 1 Results

Some preliminary results are available for Phase 1 trials being undertaken on three different compounds; on CBDCA at the Royal Marsden Hospital, London on 4-carboxyphthalato(1,2-diaminocyclohexane)platinum(II) at the Memorial Sloan Kettering Hospital in New York, and on CHIP at the Roswell Park Memorial Hospital in Buffalo. In all three cases they appear to confirm that these three compounds are less toxic than Cisplatin, as indicated by pre-clinical trials on animals. In addition, with the first of them (CBDCA) interesting responses have been observed against several types of tumours. Thus it is likely that a second generation platinum drug will emerge at least on the grounds of diminished toxicity.

In addition to the three trials referred to above, other trials on these and other platinum compounds are known to be in preparation or under way in France, Holland and the U.S.A.

In view of the social importance of this application of platinum, a further paper will be presented just as soon as fuller details of the present trials become available.