

Clinical Development of Carboplatin – A personal perspective

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Carboplatin was developed in a collaboration between the Institute of Cancer Research and the Johnson Matthey company in the UK. The objective was to find an analogue of cisplatin with reduced toxicities, in particular reduced oto-, nephro-, and neuro-toxicity. It was established that the stability of the leaving groups affected the toxicities with more stable compounds being less toxic than more reactive ones. It was also found that anticancer activity could be preserved in more stable analogues. Carboplatin was chosen for Phase I evaluation that started in 1982. The Phase I results showed dose-limiting thrombocytopenia. Nausea and vomiting were moderate, but the other non-haematological toxicities were minimal or absent. Numerous responses were seen in patients with ovarian cancer. A small randomised trial was conducted in first line ovarian cancer comparing carboplatin at 400 mg/m² with cisplatin at 100 mg/m². This confirmed showed similar response rates for the two drugs and confirmed that non-haematological side were significantly reduced with carboplatin. Thrombocytopenia was more frequent with carboplatin (9% versus 0%) while leukopenia was similar (36% versus 31%). Following these results, carboplatin was adopted for clinical development by Bristol-Myers Pharmaceuticals. It soon became clear that there were some cases of severe thrombocytopenia and that these were unpredictable. Pharmacokinetic studies had shown that carboplatin was mostly eliminated by the kidneys by glomerular filtration. This allowed the development of formulae to calculate the dose of carboplatin required to produce a targeted systemic exposure, also known as Area Under the Curve or AUC. The adoption of AUC-based dosing essentially eliminated the problem of unpredictable thrombocytopenia and permitted the successful clinical development of carboplatin. When paclitaxel was introduced into the treatment regimens for ovarian cancer it was found that its combination with carboplatin induced less thrombocytopenia than giving carboplatin alone, making the paclitaxel-carboplatin combination well tolerated. This combination is now the standard of care for ovarian cancer and is very popular for treating non-small cell lung cancer. Carboplatin is used for treating testicular seminoma. However, it has not been adopted for non-seminoma germ cell tumours. This is because two early trials show higher relapse rates compared to cisplatin. It is possible that this may have been because of under-dosing of carboplatin. Recently carboplatin has found a role alongside trastuzumab in treating Her2 positive breast cancer. Essentially it replaces doxorubicin in treatment regimens in order to avoid cardiotoxicity and drug-related leukaemia. Carboplatin is also used in head and neck, endometrial, oesophageal, bladder, breast, and cervical cancers, central nervous system or germ cell tumours, osteogenic sarcoma and as preparation for a stem cell or bone marrow transplant. Thirty-six years on, carboplatin remains one of the most commonly used anticancer medications in the world.