RELATIONSHIPS BETWEEN NEUROTOXICITY, ACCUMULATION, AND PHYSICOCHEMICAL PROPERTIES OF A SERIES OF PLATINUM DRUGS

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Abstract

Peripheral neurotoxicity induced by some platinum chemotherapy agents is the dose limiting factor, seriously affecting the quality of life of chemotherapy patients who receive this treatment. The cause of the peripheral neurotoxicity remains unknown. Using an animal model, the neurotoxic profiles of a series of platinum compounds and their related stereoisomers were determined. The series consisted of cisplatin, carboplatin, oxaliplatin, *S,S*-oxaliplatin, ormaplatin, *R,R*- and *S,S*- ormaplatin and JM216. The neurotoxicity of these compounds in the animal model was correlated with their hydrophobicity, accumulation and reactivity. Also, using peripheral nerve tissues dissected at the end of treatment (or at specific timepoints) from the animals, morphological changes induced by the platinum compounds were also measured.

Animals were administered the platinum compounds at the maximally tolerated dose, for a period of eight weeks, to determine the onset of neurotoxicity as indicated by changes in the sensory nerve conduction velocity (SNCV). The cumulative doses at which the platinum compounds in the series induced neurotoxicity (neurotoxic dose potency) in the animal model varied. Oxaliplatin induced neurotoxicity at the smallest dose and therefore at the earliest timepoint (15μmol/kg, 3 weeks of treatment) and carboplatin induced neurotoxicity at the highest dose and the latest timepoint (322 μ mol/kg, 8 weeks of treatment). The neurotoxic dose potency was compared to data obtained from the literature of incidence of neurotoxicity in patients. There was a strong correlation (r^2= 0.9871).

It has previously been hypothesised (Gregg. et al. 1992) that platinum accumulation in peripheral nervous tissues plays a role in platinum induced neurotoxicity. Using tissues obtained from animal studies, the platinum concentration in peripheral nerve tissues was determined via Inductively Coupled Plasma-Mass Spectrometry. There was no correlation between the amount of platinum accumulated in these tissues (dorsal root ganglia, sural nerve and sciatic nerve) and neurotoxicity. Furthermore it was expected that the accumulation of these compounds in the peripheral nervous system would be related to the hydrophobicity of the compound. The inverse was found to be true. The more hydrophilic the platinum compound, the greater the accumulation in the peripheral nerve tissues, and the more hydrophobic the platinum compound the lesser the accumulation in the peripheral nerve tissue (eg. drg $r^2 = 0.99$, $P=0.004$).

Using *in vitro* protein binding half life, the reactivity of compounds in the platinum series was assessed. It was determined that the neurotoxic compounds had a shorter half life and were more reactive than the non neurotoxic compounds. A positive correlation was also observed between reactivity and the incidence of neurotoxicity in patients ($r^2 = 0.89$, $P=0.0005$).

Tissues obtained from the animals were used to measure changes in dorsal root ganglia nucleolar diameter, and comparison made between the nucleolar diameter of each of the treatment groups, and their changes in SNCV. Strong correlations were observed between nucleolar diameter changes and altered SNCV in animals ($r^2 = 0.9971$).

From the above-mentioned studies, insight was gained into the physical parameters of the platinum compounds in the series that were associated with different neurotoxicity profiles. As yet a definite mechanism has not clearly defined but it is hypothesised to involve molecular nucleolar changes.

Publications resulting in part or full from this thesis

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Screnci, D., Er, H.M., Hambley, T.W., Galettis, P., Brouwer, W., and McKeage, M.J. Stereoselective Peripheral Sensory Neurotoxicity of Diaminocyclohexane Platinum Enantiomers Related to Ormaplatin and Oxaliplatin. *BRITISH JOURNAL of CANCER* 76:502-510, 1997.

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Abbreviations

AAS	Atomic Absorption Spectroscopy
ADP	Adenosine Di-Phosphate
AMU	Atomic Mass Units
ATP	Adenosine Tri-Phosphate
cbdca	carboplatin
cddp	cisplatin
cm	centimetre
CNS	Central nervous system
CxT	Concentration-Time products
DACH	Diaminocyclohexane
DLT	Dose Limiting Toxicity
DNA	Deoxyribose Nucleic Acid
drg	dorsal root ganglion
er	endoplasmic reticulum
HMG	High Mobility Group
HPLC	High Performance Liquid Chromatography
hr	hour
ICP-MS	Inductively Coupled Plasma – Mass Spectrometry
i.p	intraperitoneal
kDa	kilo Daltons
L	Litre
m	metre

M	Molar
mL	milli Litre
MNCV	Motor Nerve Conduction Velocity
m/s	metres/second
min	minutes
MTD	Maximum Tolerated Dose
MW	Molecular Weight
NOR	Nucleolar Organising Region
PNS	Peripheral Nervous System
Pt	Platinum
Rb	Retinoblastoma Protein
RNA	Ribose Nucleic Acid
rRNA	ribosomal Ribose Nucleic Acid
SL1	promoter selectivity factor
$t_{1/2}$	half life
SNCV	Sensory Nerve Conduction Velocity
UBF	Upstream Binding Factor
µL	microlitre