6 Combinations of Platinum Compounds and Ionizing Radiation

Carsten Nieder and Florian Lordick

CONTENTS

6.1 Introduction

The contemporary clinical concepts of multimodal oncology include combined administration of ionizing radiation and three different platinum compounds (cisplatin, carboplatin and oxaliplatin) in a variety of common solid tumors. Examples are sites such as head and neck, esophagus, lung, cervix uteri, rectum, and bladder. All these platinum drugs have demonstrated efficacy against a variety of cell lines, tumor xenografts, and human tumors. Yet, their effects vary with several molecular features of the cells, e.g., p53 status and expression of drug resistance proteins (Blumenthal et al. 2003, Weaver et al. 2005). Resistance also results from increased expression of the *ERCC1* gene (excision repair cross-complementing 1), which is involved in nucleotide excision repair and the removal of DNA interstrand crosslinks, and other repair genes (Altaha et al. 2004). Both intrinsic and acquired drug resistance have been described. The simultaneous administration of platinum agents can be used to enhance the effects of radiation treatment, aiming either at additive cell kill or true radiosensitization ("radiopotentiation") within the target volume, or to treat distant, out-of-field tumor sites based on the principle of spatial cooperation. Thereby, it is hoped to achieve a therapeutic gain.

This chapter covers a broad range of mature and emerging data, published over several decades. Over time, our knowledge about cellular and molecular tumor biology and radiobiology has increased tremendously. Many of the methods used presently were not available at the time when early studies of platinum compounds took place. It should also be noted that this chapter does not contain any further discussion of platinum compounds that are clinically unavailable. Data on such agents is given by the following: Skov and MacPhail 1991; Monk et al. 1998; and Wang and Lippard 2005.

6.2 Cisplatin

Discovered 40 years ago and initially recognized for its bacteriostatic effects (Rosenberg et al. 1965), cis-dichlorodiammine-platinum(II) or cisplatin was found in 1969 to cause antitumor effects. In 1971, the drug was, for the first time, combined with irradiation in mice (Zak and Drobnik 1971) and subsequently was the first platinum-based drug entering the clinical practice of radiation oncology. Clinical reports date back to as early as 1981 (Creagan et al. 1981). The first randomized trial involved patients with bladder cancer, had an unusual design and a small number of patients, and compared intravesical cisplatin to combined cisplatin and radiotherapy (Hemstreet et al. 1984). Subsequently, positive ran-

C. Nieder, MD
Department of Radiation Oncology, Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 Munich, Germany
F. Lordick, MD
Third Department of Internal Medicine (Hematology/Medical Oncology), Klinikum rechts der Isar der Technischen Universität München, Ismaninger Strasse 22, 81675 Munich, Germany

domized trials were published for cervical cancer and non-small cell lung cancer (NSCLC; Choo et al. 1986, Schaake-Koning et al. 1990). The latter three-arm phase-II study suggested that daily administration of cisplatin is superior to once a week application. Presently, a large variety of administration schedules are in clinical use, including daily dosing with 6 mg/m^2, 20 mg/m^2 day^{-1} on days 1–5 and 29–33 of fractionated radiotherapy, 40 mg/m^2 day^{-1} on days 1, 8, 15, 22, 29, and 36, 100 mg/m^2 day^{-1} on days 1, 22, and 43, etc. Examples of such regimens are given in the organ-specific chapters of this book.

Figure 6.1 shows the structure and molecular weight of cisplatin. As for all drugs, tissue concentration varies with blood perfusion. Heterogeneity of

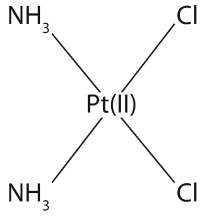

Fig. 6.1. Structure and molecular weight of cisplatin

tissue concentration has been examined in various tumor models, e.g., in mouse B16 melanoma, human NSCLC xenografts (Zamboni et al. 2002), and the human prostate cancer cell line PC-3 M grown in nude mice, where the tumor concentrations ranged from 478 to 937 ppb (Coughlin et al. 1994). In the same article heating is shown to increase the amount of platinum uptake in dog prostate, possibly as a result of better perfusion. Another group examined the levels of platinum in murine mammary adenocarcinoma after intraperitoneal injection of 20 mg/kg body weight cisplatin by atomic absorption spectrometry (Douple et al. 1988). The highest levels were found after 15 min, however, and at 30 min the concentration was still of the magnitude that produced potentiation of cell killing in those authors' experience. The next prerequisite for drug efficacy is cellular uptake and avoidance of either efflux or inactivation, e.g., by glutathione or other sulphur-containing molecules.

6.2.1 Mechanisms of Action

After transport into the cell, which appears to be linked to the copper metabolic pathway, but can also take place by passive diffusion, the chloride ligands are replaced by hydroxyl groups. This aquated, reactive form of the drug reacts with several proteins and DNA binding sites, as reviewed by Dewit (1987), and causes DNA-protein linkage and DNA interstrand and intrastrand crosslinks interfering with DNA replication and repair, including repair of double-strand breaks (Taylor et al. 1976; Richmond and Powers 1976; Begg 1990; Amorino et al. 1999). The cellular responses include replication arrest, transcription inhibition, cell-cycle arrest and DNA repair via several signal transduction pathways (AKT, p53, MAPK/JNK/ERK, etc.) reviewed, for example, by (Wang and Lippard 2005). Cisplatin adducts might be removed by nucleotide excision repair mechanisms, following first-order kinetics. In cell culture, knockout of the nonhomologous end-joining (NHEJ) repair pathway did not change the response to cisplatin, whereas mutation of the homologous recombination repair pathway through XRCC3 resulted in increased radiation and cisplatin sensitivity (Raaphorst et al. 2005). Other data also demonstrate that yeast mutants in double-strand-break repair by NHEJ and mutants in base excision repair showed no sensitivity to cis- or oxaliplatin (Wu et al. 2004). Recent work suggests that the cellular responses to cisplatin depend on DNA-activated protein kinase and DNA polymerase eta (Turchi et al. 1997; Albertella et al. 2005). It has been postulated that the loss of DNA mismatch repair is linked to the failure in detecting the DNA damage caused by cisplatin and to the lack of signal triggering the cell-death mechanisms (Fink et al. 1996). Putative defective repair of oxidative damage also resulted in sensitivity to cis- and oxaliplatin in yeast (Wu et al. 2004). Cell killing after higher drug doses appears apoptosis related, whereas after lower drug doses failure to overcome a G_2 block is more important (Ormerod et al. 1994). In p53-mutated 9L rat gliosarcoma, intraperitoneal cisplatin (1 mg/kg) led to an increase in micronuclei formation, most likely indicating induction of mitotic catastrophe, but produced little or no apotosis (Driessens et al. 2003). The drug is not cell-cycle specific.

6.2.2 Combinations with Ionizing Radiation

If cisplatin is not given concomitant to radiotherapy, in vivo data from R1H rhabdomyosarcoma of the rat treated with 30 fractions of 2 Gy over either 6 or 3 weeks indicate that intraperitoneal drug admin-