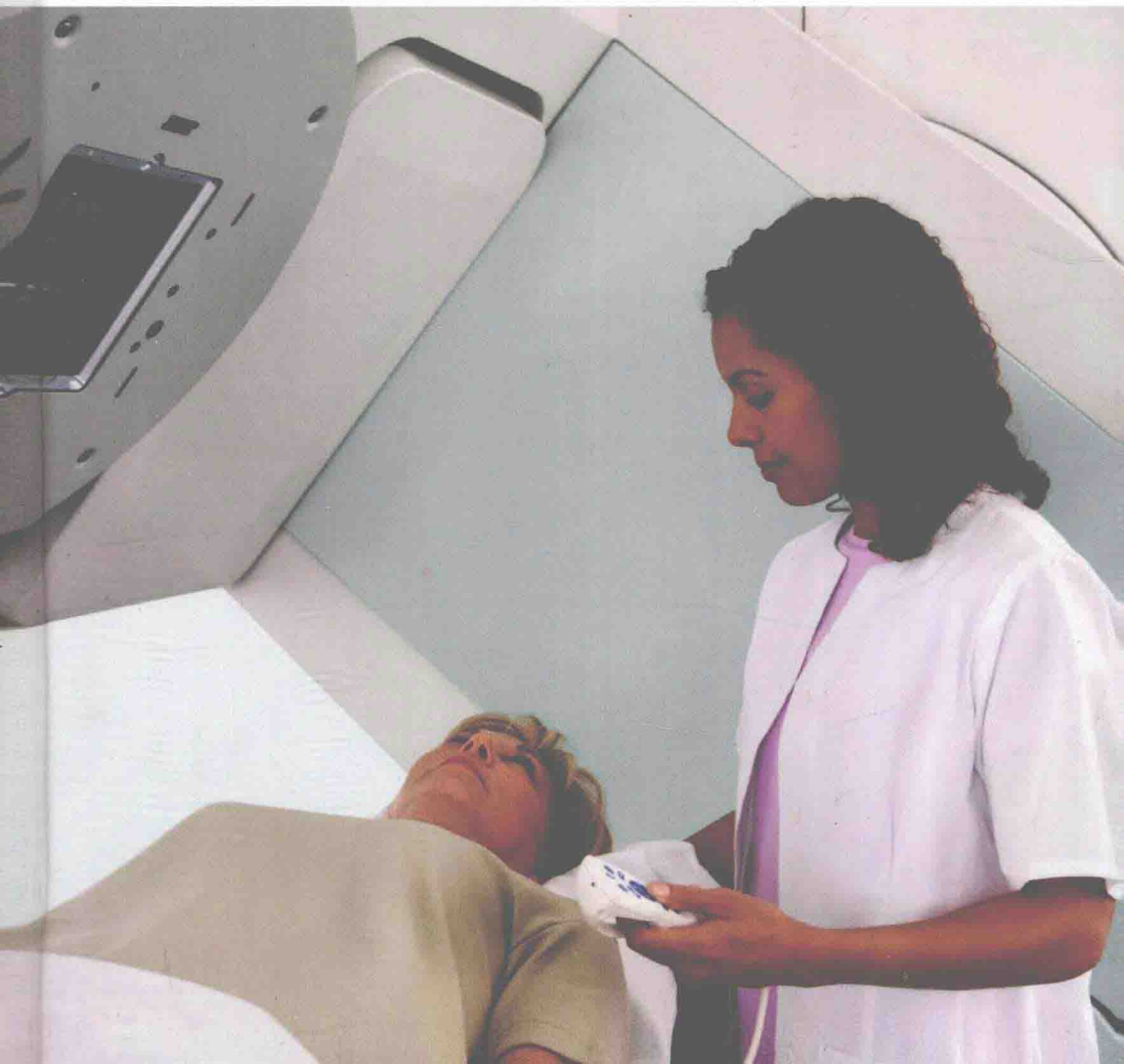
Advanced Cancer Treatment

Karen Miles
Richard Gray



Advanced Cancer Treatment

Edited by **Karen Miles and Richard Gray**

hayle medical
New York

Published by Hayle Medical,
30 West, 37th Street, Suite 612,
New York, NY 10018, USA
www.haylemedical.com

Advanced Cancer Treatment
Edited by Karen Miles and Richard Gray

International Standard Book Number: 978-1-63241-009-2 (Hardback)

Printed in China.

Advanced Cancer Treatment

Preface

This book has been a concerted effort by a group of academicians, researchers and scientists, who have contributed their research works for the realization of the book. This book has materialized in the wake of emerging advancements and innovations in this field. Therefore, the need of the hour was to compile all the required researches and disseminate the knowledge to a broad spectrum of people comprising of students, researchers and specialists of the field.

There are many modern techniques and mechanisms available for use in cancer treatment today. This reflects that an ultimate treatment has not yet been found, and it needs more time and research to develop more effective methods for cancer treatment. This book will serve not just physicians but also patients with an overview on new research and developments in this area. This book is a comprehensive and valuable account discussing various therapeutic methods in cancer treatment comprising of some rare classic treatment approaches like treatment of metastatic liver disease of colorectal origin, breast and ovarian cancer treatment, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer and laser photo chemotherapy as an alternative treatment.

At the end of the preface, I would like to thank the authors for their brilliant chapters and the publisher for guiding us all-through the making of the book till its final stage. Also, I would like to thank my family for providing the support and encouragement throughout my academic career and research projects.

Editor

Contents

Complementary / Alternative Cancer Therapy Modalities

1

Antioxidants in Cancer Treatment

Júlio César Nepomuceno
Universidade Federal de Uberlândia/Instituto de Genética e Bioquímica
Brazil

1. Introduction

There are many different chemotherapeutic agents used in cancer treatment. Most of the chemotherapeutic drugs can be divided into alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents. All of these drugs affect cell division or DNA synthesis and function in some way. Several classes of chemotherapy work by producing a reactive oxygen compound or free radical.

Alkylating agents work to add alkyl groups to negatively-charged groups. They are known to stop tumor growth through cross-linking guanine nucleobases in strands of DNA, which directly damages the DNA by making it unable to uncoil and separate. The cell, when attacked in this way, is unable to replicate. While it may not die, it also cannot grow. Cyclophosphamide, a cytotoxic alkylating agent, is extensively used as an antineoplastic agent for the treatment of haematological malignancies and a variety of solid tumours, including leukaemia, ovarian cancer and small-cell lung cancer. Cyclophosphamide is bioactivated by hepatic cytochrome P450 enzymes resulting in the formation of phosphoramide mustard and acrolein. The therapeutic effect of cyclophosphamide is attributed to phosphoramide mustard, while the other metabolite, acrolein is associated with toxic side effects. The cellular mechanism of cyclophosphamide toxicity is due to the production of highly reactive oxygen free radicals by these metabolites. It is obvious that high levels of ROS within the body could culminate in oxidative stress.

Anthracyclines (or anthracycline antibiotics) are a class of drugs used in cancer chemotherapy derived from Streptomyces bacteria. Anthracycline has three mechanisms of action: inhibits DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand, thus preventing the replication of rapidly-growing cancer cells: inhibits topoiosomerase II enzyme, preventing the relaxing of supercoiled DNA and thus blocking DNA transcription and replication: creates iron-mediated free oxygen radicals that damage the DNA and cell membranes.

Radiation therapy is another type of cancer treatment that uses ionizing radiation to produce cell death through free radical formation. The cell death occurs by damaging the DNA of cancerous cells. This DNA damage is caused by one of two types of energy: photon or charged particle, directly or indirectly ionizing the atoms which make up the DNA chain. Indirect ionization happens as a result of the ionization of water, forming free radicals, notably hydroxyl radicals, which then damage the DNA.

The oxidative stress produced during cancer treatment induces a range of side effects such as hair loss, nausea or vomiting and cardiotoxicity. Several authors believe that the use of antioxidants during cancer treatment can reduce these side effects. However, there is a

concern that antioxidants might reduce oxidizing free radicals created by radiotherapy and some forms of chemotherapy, and thereby decrease the effectiveness of the therapy. The authors that support the idea that administration of oral antioxidants is contraindicated during cancer therapeutics, suggest that a drug's ability to destroy micrometastases may be impaired by the addition of antioxidants and, this may result in an improved short-term tolerance to treatment followed by an increased long-term chance for recurrence. On the other hand, there are several articles showing no evidence of significant decreases in the efficacy of chemotherapy with antioxidant supplementation and that supplementation of antioxidant vitamins during cancer treatment is effective, increasing quality and life expectancy.

Considering that the use of antioxidants during treatment is a very contentious issue, the purpose of this chapter is to review studies in humans to evaluate the use of these antioxidants as a therapeutic intervention in cancer patients, and their interactions with radiation therapy and chemotherapy.

2. Classes of agents used in cancer treatment that produce a reactive oxygen compound or free radical

The ultimate clinical effectiveness of any anti-cancer drug requires that it kill malignant tumor cells *in vivo* at doses that allow enough cells in the patient's critical tissues (e.g., bone marrow, gastrointestinal tract) to survive so that recovery can occur. This is difficult to accomplish because, in general, anticancer drugs are most useful against malignant tumor with a high proportion of dividing cells, and some normal tissues such as the bone marrow and G1 tract also have a high cell-proliferation rate. Anticancer drugs used by themselves are primarily effective against high-growth-fraction tumors such as the leukemias and lymphomas. The most common malignant tumors, however, are "solid" tumors, including those of the colon, rectum, lung and breast. These tumors usually have a low proportion of dividing cells and therefore are less susceptible to treatment by drugs alone (Pratt, 1994).

There are some standard methods of cancer treaments: surgery, chemotherapy, radiation therapy, immunotherapy and biologic therapy. Undoubtedly, chemotherapy and radiotherapy are the treatments to fight cancer with more side effects.

Chemotherapy agents can be divided into several categories: alkylating agents (e.g., cyclophosphamide, ifosfamide), antibiotics which affect nucleic acids (e.g., doxorubicin, bleomycin), platinum compounds (e.g., cisplatin), mitotic inhibitors (e.g., vincristine), antimetabolites (e.g., 5-fluorouracil), camptothecin derivatives (e.g., topotecan), biological response modifiers (e.g., interferon), and hormone therapies (e.g., tamoxifen). The agents most noted for creating cellular damage by initiating free radical oxidants are the alkylating agents, the tumor antibiotics, and the platinum compounds (Lamson & Brignall, 1999).

2.1 Alkylating agents

Inhibiting DNA replication, therefore, affords a logical approach for retarding tumour growth. For this reason, DNA has become a critical target in cancer chemotherapy. Indeed, many of the antitumour agents currently in the cancer armamentarium are DNA-interactive. Among them, the DNA alkylators or cross-linkers, which include the platinum-based drugs, are the most active available for effective cancer management. By virtue of their high chemical reactivity, either intrinsic or acquired in a biological environment, all alkylating agents form covalent linkages with macromolecules having nucleophilic centres. They have

no specificity, but the chance reaction with DNA forms the basis for the antitumour effects. Bifunctional alkylating agents form covalent bonds at two nucleophilic sites on different DNA bases to induce interstrand (between two opposite strands) and/or intrastrand (on same strand) cross-links (Fig. 1). Monofunctional agents have only one alkylating group and, therefore, cannot form crosslinks (Siddik, 2002).

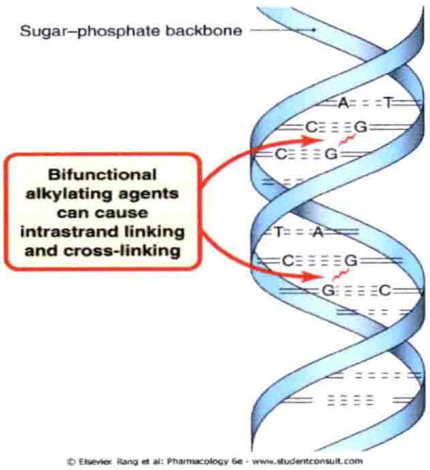


Fig. 1. The effects of bifunctional alkylating agents on DNA. Note the cross-linking of two guanines (www.studentconsult.com).

According to Siddik (2002), the end effect of these DNA-interactive agents is to inhibit DNA replication, which in turn may affect the production of RNA and protein. Such changes in the superhelical structure are then processed as distinct signals that determine whether a cell lives or dies.

The cyclophosphamide (CP) is a nitrogenous mustard pertaining to this group of substances named alkylating agents, which are effective against slow-growing tumors that damage cells at any phase of cellular growth. Cyclophosphamide is inactive per se and requires microsomal mixed function oxidase-mediated metabolism to activated metabolites capable of binding covalently to nucleic acids and proteins. The commonly accepted scheme of cyclophosphamide metabolism involves intermediate formation of 4-hydroxy-CP which undergoes ring-opening to form aldophosphamide, an isomer of 4-hydroxy-CP (Gurtoo et al., 1985). Aldophosphamide is metabolized to phosphoramide mustard and acrolein (Murgo & Weinberger, 1993).

Phosphoramide mustard forms DNA crosslinks between (interstrand crosslinkages) and within (intrastrand crosslinkages) DNA strands at guanine N-7 positions. This is irreversible and leads to cell death (Dong et al., 1995). According to Shanmugarajan et al. (2008), the therapeutic effect of cyclophosphamide is attributed to phosphoramide mustard and acrolein is associated with toxic side effects.

Adams and Klaidman (1993) showed that acrolein and its glutathione adduct, glutathionylpropionaldehyde, induce oxygen radical formation. Acrolein was oxidized by xanthine oxidase to produce acroleinyl radical and O2(.-). Aldehyde dehydrogenase metabolized acrolein to form O2.- but not acroleinyl radical. The fact that glutathionylpropionaldehyde is a more potent stimulator of oxygen radical formation than

acrolein indicates that glutathionylpropionaldehyde is a toxic metabolite of acrolein and may be responsible for some of the *in vivo* toxicity of acrolein (Adams & Klaidman, 1993). In this regard, evidences reveal that oxidative stress plays a key role in the pathogenesis of cyclophosphamide induced cardiotoxicity (Shanmugarajan et al., 2008).

2.2 Anthracyclines (antibiotics)

Anthracyclines attack cancer cells by multiple mechanisms, inhibiting replication and cells damaging in ways that promote cell death. They work primarily by DNA intercalation. In order for a cell to divide, the DNA in the cell's nucleus must be unravelled and then duplicated (a process known as transcription). Anthracyclines bind to portions of the unwound strand of nuclear DNA, halting the transcription process, which in turn prevents cell replication. Among other details, scientists have found that anthracyclines inhibit the action of topoisomerase II ("Topo II"), an enzyme that unzips the DNA molecule for replication. It is anthracycline's interference with topoisomerase II that is credited with both its cardiotoxicity and mutagenic effects, since its Topo II inhibition leaves DNA breaks at even low concentrations, resulting in an accumulation of DNA damage following prolonged, repeated, or higher exposures (Pratt, 1999).

The biological activity of several well-known and widely used anthracycline antibiotics such as daunomycin and doxorubicin is thought to be associated to the hydroxyquinone structure (Young et al., 1981). Quinones are classified by the aromatic moieties present in their structure and naphthoquinone constitutes the naphtalenic ring (Silva et al., 2003).

The naphthoquinones are a class of compounds having cytotoxic properties that can be advantageous in treating cancer. Two essential mechanisms are linked to the effects of naphthoquinone, oxidative stress and nucleophilic alkylation (Bolton et al., 2000). These substances are able to accept electrons and generate reactive oxygen species (O_2-., HO., H_2O_2), whose oxidative effects could explain the cytotoxicity produced by these compounds (Boveris et al., 1978; Silva et al., 2003; Witte et al., 2004).

Bolton et al. (2000) suggested that quinones are highly reactive molecules and can reduce the redox cycle using semi-quinine radicals, generating reactive oxygen species (ROS) that include superoxide radicals, peroxide radicals, hydrogen peroxide and hydroxyl radicals. ROS production can cause severe oxidative cell stress, forming oxidative macromolecule cells, affecting lipids, proteins and DNA.

Rajagopalan et al. (1988) demonstrated that Adriamycin, an anthracycline drug with a wide spectrum of clinical antineoplastic activity, stimulates the formation of OH in the isolated rat heart and suggests that this mechanism may be significant in Adriamycin-induced cardiotoxicity.

According to Minotti, Cairo and Monti (1999) the cardiotoxicity of anthracyclines is mediated by mechanisms that are distinct from those underlying the antitumor effects of these drugs. For these authors a major role in the development of cardiotoxicity has been assigned to iron, presumably because this metal can catalyze free radical reactions that overrule the antioxidant defenses of cardiomyocytes. For them some investigators have proposed mechanisms of cardiotoxicity that are independent altogether of both iron and free radicals. In an attempt to bridge the two extremes of this field, other studies have maintained a role for iron but not for free radicals, suggesting that anthracycline cardiotoxicity reflects disturbances in iron homeostasis within cardiomyocytes rather than the outcome of iron-catalyzed free radical injury.

2.3 Platinum compounds

The application of inorganic chemistry to medicine is a rapidly developing field, and novel therapeutic and diagnostic metal complexes are now having an impact on medical practice. Cisplatin, as one of the leading metal-based drugs, is widely used in the treatment of cancer. Significant side effects and drug resistance, however, have limited its clinical applications. Biological carriers conjugated to cisplatin analogs have improved specificity for tumor tissue, thereby reducing side effects and drug resistance (Kostova, 2006).

The history of platinum in cancer treatment began 150 years ago with the first synthesis of cisplatin, but it was not used in the clinic before 30 years ago. Then 3000 derivatives were synthesised and tested, with poor successes: three other derivatives only are available today. Clearly they are not more active, but they are less toxic than cisplatin, although two, carboplatin and nedaplatin, yield a cross-resistance, while one, oxaliplatin, does not. Their mechanisms of action are similar: these four pro-drugs form adducts with DNA, impairing DNA synthesis and repair then (Fig. 2). Their pharmacokinetics are complicated since we always measure two overlapping pharmacokinetics: those of the parent compound and of the bound platinum. Cisplatin is now recommended for few cancers, it is replaced by less-toxic carboplatin, and therefore more easily used in combination. Oxaliplatin give interesting results in a number of cancers (Desoize & Madoulet, 2002).

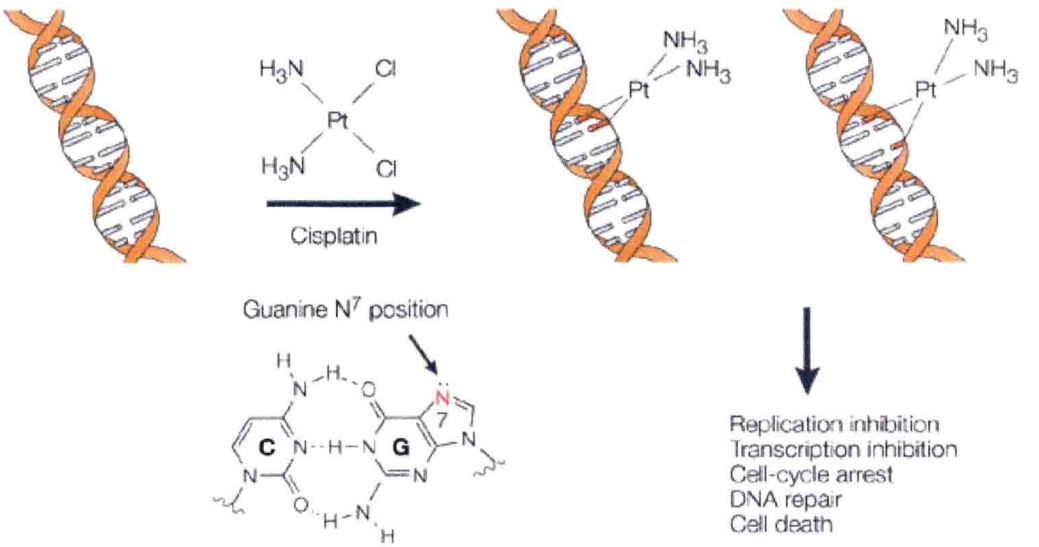


Fig. 2. The platinum atom of cisplatin binds covalently to the N7 position of purines to form 1,2- or 1,3-intrastrand crosslinks, and interstrand crosslinks. Cisplatin–DNA adducts cause various cellular responses, such as replication arrest, transcription inhibition, cell-cycle arrest, DNA repair and apoptosis (Wang & Lippard, 2005).

According to Boulikas and Vougiouka (2003) Cisplatin, carboplatin, oxaliplatin and most other platinum compounds induce damage to tumors via induction of apoptosis. Apoptosis is responsible for the characteristic nephrotoxicity, ototoxicity and most other toxicities of the drugs. The severity of cisplatin nephrotoxicity is related to platinum concentration in the kidneys. There is a growing amount of evidence that cisplatin-induced nephrotoxicity is

ascribed to oxidative damage resulting from free radical generation (Antunes & Bianchi, 2004). Reactive oxygen metabolites (superoxide, hydrogen peroxide, hydroxyl radical, and hypochlorous acid) are important mediators of renal damage in acute renal failure and glomerular and tubulointerstitial diseases (Klahr, 1997).

2.4 Radiation therapy

Radiation therapy has been used in cancer treatment for many decades. The primary focus in radiotherapy is to increase DNA damage in tumor cells, as double strand breaks are important in cell death. Another course of action is to alter cellular homeostasis, modifying signal transduction pathways, redox state, and disposition to apoptosis. The cellular changes ideally would enhance the killing of tumor cells while reducing the probability of normal cell death. Radiation damages cells by direct ionization of DNA and other cellular targets and by indirect effect through ROS. Indirect ionization happens as a result of the ionization of water, forming free radicals, notably hydroxyl radicals, which then damage the DNA (Fig. 3). Therefore, exposure to ionizing radiation produces oxygen-derived free radicals in the tissue environment; these include hydroxyl radicals (the most damaging), superoxide anion radicals and other oxidants such as hydrogen peroxide. Additional destructive radicals are formed through various chemical interactions (Borek, 2004a).

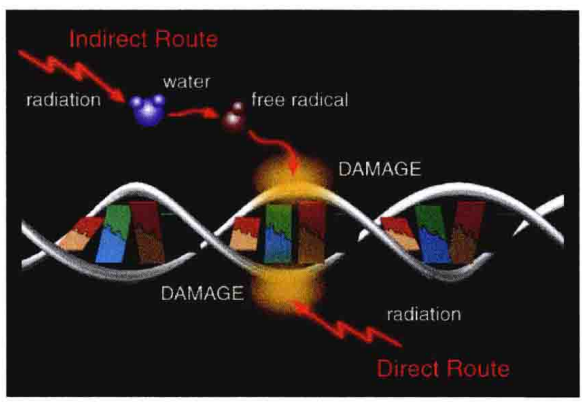


Fig. 3. There are two main ways radiation can damage DNA inside living cells. Radiation can strike the DNA molecule directly, ionizing and damaging it. Alternately, radiation can ionize water molecules, producing free radicals that react with and damage DNA molecules. Source unknown.

3. Antioxidants nutrients in cancer treatment

Cancer survivors receive a wide range of advice from many sources about foods they should eat, foods they should avoid, how they should exercise, and what types of supplements or herbal remedies they should take. Unfortunately, this advice is often conflicting (Doyle et al., 2006). Antioxidants vitamins show promise in cancer therapy by their palliative action, reducing painful side effects associated with treatment.

Examples of dietary antioxidants are vitamins A, C and E, selenium and flavonoids such as quercetin and genistein. In several *in vitro* and animal studies the hypothesis has been tested that antioxidants benefit patients receiving chemotherapy. In principle two opposing