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ESSENTIALS Cancer therapy is underpinned by a detailed understanding of cancer biology and the complex interaction of tumour and host. Systemic therapies and radiation therapy are being used in many early stage cancers, with a ‘risk adaptive’ approach to maximize the likelihood of uncomplicated tumour cure, both as primary treatment and in the postoperative setting. Targeted therapies have changed the course of many common cancers. Patients with early stage disease benefit through enhanced cure rates, while rational treatment approaches to metastatic disease improve the outlook for many patients. Chemotherapy Chemotherapy drugs are cytotoxic agents which induce preferen- tial cell kill in tumour cells because of their increased rates of pro- liferation. Their mechanisms of action are diverse and complex, but typically involve: (1) impaired synthesis of DNA or nucleotides; (2) in- hibition of mitosis; or (3) damage to the DNA backbone or base pairs. Targeted therapies Targeted therapies have evolved alongside the discovery of key car- cinogenesis pathways and identification of druggable targets. They are designed to inhibit or interfere with a key pathway in tumour for- mation. The main classes of targeted therapy are: (1) small molecule tyrosine kinase inhibitors; (2) monoclonal humanized antibodies blocking growth factor receptors; and (3) immune-modulating antibodies. They are typically cytostatic, inhibiting tumour growth for the duration of the agent if prescribed, rather than inducing cell kill. Resistance to therapy is common and typically occurs after
9–12 months of treatment. Hormone therapies In some tumour types such as breast cancer and prostate cancer, differentiated tumour cells retain endocrine-dependent growth signalling mechanisms. Blockade of the hormonal signal, either by elimination of physiological production, or through a hormone re- ceptor antagonist, can inhibit tumour growth. Radiation therapy Ineffective DNA repair is a cancer hallmark, hence ionizing radi- ation induced DNA damage leads to preferential tumour cell death. Dose to normal tissues is minimized by shaping the radiation beams to match the shape of the tumour target (target conformation), imaging the patient treatment to ensure radiation is delivered to the target (image guidance), and—in some sites such as gynaecological malignancy—bringing the radiation source into close proximity with the tumour tissue (brachytherapy). Improvements in local disease control achieved by radiotherapy in breast, prostate, and head and neck cancer have translated into improved survival for these patients.

Introduction Over 110 years have passed since the first use of X-rays as anticancer therapy, and over 70 years since nitrogen mustards were first ob- served to induce remissions in a patient with refractory non-Hodgkin lymphoma. Since this time, developments in our understanding of the molecular biology of cancer have driven a change in the develop- ment pathway for systemic therapy. Many of the current chemotherapy agents were discovered using a large-scale screening approach, in which libraries of compounds were screened against tumour cell lines and in vivo rodent tumour models. Modern drug discovery, in contrast, is driven by a target- directed approach. The first step has shifted from discovery of lead compounds to the characterization of a specific druggable target that plays a key role in tumour proliferation. Once a suitable druggable target and its three-dimensional shape has been established, com- pounds directed against the target can be synthesized using rapid development approaches (Box 5.6.1). Conventional chemotherapy still plays a key role in tumour cell kill (cytoreduction) and is often used in combination with targeted agents. 5.6 Systemic treatment and radiotherapy Rajesh Jena and Peter Harper Box 5.6.1 Different approaches to drug discovery High-throughput screening—an established technique for drug dis- covery, using robotics and process automation to assay many putative compounds for activity against tumour cells. Fragment-based drug discovery—screening small molecules which bind weakly to the biological target, but which can be combined to form subunits of a novel drug. Diversity-oriented synthesis—large libraries of drug-like compounds are synthesized which are structurally similar to an intermediate agent, which has been proven to kill the target cells.

498 SECTION 5 Principles of clinical oncology Common principles of chemotherapy agents Most chemotherapy agents target processes relating to cell prolif- eration on the premise that cancer cells proliferate more rapidly than normal tissue cells. For both conventional agents and tar- geted therapies, the action is not entirely specific to cancer cells, resulting in normal tissue toxicity. Chemotherapy agents can be classified according to their rela- tionship with the cell cycle of tumours. Some agents are cell-cycle specific, acting only during certain phases of the cell cycle. Cell- cycle independent agents will have the same effect on cells, whether they are in resting phase or active proliferation. Optimum drug scheduling is dependent on the relationship of the action of the drug with the cell cycle. Phase specific agents will reach concentra- tion that gives a maximum effect, killing all cells in a specific phase of the cell cycle. Increasing cell kill requires a change in the duration of exposure of the drug. In counterpoint, cell-cycle independent drugs will typically have a linear relationship between dose and cell kill (Table 5.6.1). Chemotherapy can induce cell death by two mechanisms, namely apoptosis and necrosis. Apoptosis as a programmed mode of cell death, which is regulated by specific cell signalling pathways and energy (ATP) dependent. Both radiotherapy and chemotherapy typically induce DNA damage in tumour cells that is detected by the cell, leading to activation of the apoptosis pathway. In contrast, necrosis of cells is caused by gross mitotic catastrophe or injury to the cellular structure, and is associated with an inflammatory response. Principles of radiation therapy Radiation therapy utilizes ionizing radiation to induce tumour cell death through the formation of both single-stranded and double-stranded DNA breaks. DNA damage can be generated ei- ther through direct interaction of radiation with DNA (the direct effect), or by the interaction of radiation and water to produce free radicals, which in turn produce DNA damage breaks (the in- direct effect). Ionizing radiation can be in the form of electromagnetic radiation (X-rays when generated from electricity, γ rays when derived from naturally radioactive materials) or particle beams, such as electrons, protons, and heavier ions. For most radio- therapy in clinical practice, the indirect effect is the predominant mechanism of cell kill,

and oxygen is a prerequisite for DNA damage via the indirect effect (Fig. 5.6.1). As a result, hypoxic tumour cells are more resistant to the effects of radiation therapy. Heavier ions tend to cause more DNA damage by the direct Table 5.6.1 Cell-cycle phase specificity of chemotherapy agents Cell-cycle specific agents Cell-cycle independent agents Folic acid pathway Methotrexate, pemetrexed Alkylating agents Lomustine, carmustine, cyclophosphamide, procarbazine Pyrimidine analogues 5-fluorouracil, capecitabine Platinum agents Cisplatin, carboplatin, oxaliplatin Direct effect Indirect effect Fig. 5.6.1 Indirect and direct mechanisms of DNA damage by ionizing radiation. X-rays can interact directly with DNA, or hydrolyse water to produce intensely ionizing free radicals, which subsequently induce DNA damage. (Blue circles = oxygen; small orange circles = hydrogen.)

5.6 Systemic treatment and radiotherapy 499 effect, and are less dependent on the availability of oxygen to fix radiation damage. This may be advantageous in the treatment of hypoxic tumours. Radiation can trigger apoptosis or necrosis in tumour cells in the same way as chemotherapy. Furthermore, radiation sensitivity is not uniform through the cell cycle. Cells are most sensitive to radiation therapy during mitosis and late G2 phases, and most re- sistant to radiation during S phase. The SI unit of absorbed radiation dose is the Gray—defined as 1 joule of energy absorbed in 1 kg of tissue. Most tumours will exhibit a radiation dose response that is sigmoid in nature (Fig. 5.6.2). The curve can be described by two parameters the TCD50 (dose required to achieve 50% probability of tumour con- trol) and γ50, which is the gradient of the dose response curve at this point (or the change in the probability of tumour control for a 1% increase in radiation dose). Across a wide range of cancers, a dose of 60–75 Gy is required to control macroscopic (bulk) disease, 50–55 Gy is required to control microscopic tumour, and doses of 20–30 Gy are required for palliation of symptoms. Radiation dose can be delivered to the tumour target using one of three strategies (Table 5.6.2). Context of radiotherapy and chemotherapy Both radiotherapy and chemotherapy agents are used in a range of contexts as anticancer therapy. Understanding the context of therapy is vital in managing patient side effects and establishing appropriate ceilings of care (Table 5.6.3). 100 90 80 70 60 50 40 30 20 10 0 0 10 20 30 40 Radiation dose (Gy) Relationship between dose and tumour control Probability of tumour control (%) 50 60 70 TCD50 Fig. 5.6.2 Diagram of radiation therapy dose response for a hypothetical tumour. TCD50 is defined as the radiation dose required to yield a 50% probability of tumour control. The steepness of the dose response curve at the TCD50 point is defined as γ50. For many solid tumours, γ50 is between 1 and 2%, hence a 1% increase in dose to the tumour will yield a 1–2% increase in the probability of tumour cure. Table 5.6.2 Strategies for delivering radiation to tumour targets Teletherapy The tumour is targeted by X-ray beams at a distance from the patient (also known as external beam therapy). Teletherapy is used to treat a wide range of tumour types. Brachytherapy The tumour is irradiated by bringing a radiation source into close proximity to the tumour. Brachytherapy is used with great success in gynaecological tumours. Radionuclide therapy A radioisotope with a short half-life is selected, which either has specificity for a tumour target in its own right, or is bound to a biological ligand, which binds preferentially to tumour cells. Radioiodine with I-131 is used in the treatment of thyroid cancer. Table 5.6.3 Contexts of cancer treatments Primary Treatment used as a single modality to cure patient. Typically primary chemotherapy is used in haematological malignancies, germ cell tumours, and paediatric tumours. Primary radiotherapy can be used to cure head and neck cancers, cervix cancer, and anal cancer while preserving function of the organ. Neoadjuvant Chemotherapy or radiotherapy used prior to surgery, to downstage the tumour. Examples include breast cancer and sarcomas. Adjuvant Usage after macroscopic removal of tumour by surgery. Treatment is given to eradicate microscopic disease. Palliative Chemotherapy

is used in patients with locally advanced or metastatic disease with the aim of disease stabilization and symptom control, rather than cure. Radiotherapy can be used to alleviate symptoms of bone pain or visceral compression.

500 SECTION 5 Principles of clinical oncology Classes of chemotherapy agent Alkylating agents These agents were first isolated from the nitrogen mustards, fol- lowing observations of depleted white cell counts in Italian sol- diers exposed accidentally to mustard gas. They were used to treat advanced Hodgkin lymphoma in 1942 with short-lived but dra- matic disease remission. They are now used in a wide variety of solid tumours and haematological malignancies. Their mechanism of action is to form a covalent bond between an alkyl group and nucleic acids (Fig. 5.6.3). Many of the drugs in this class will have an alkyl moiety at each end of the molecule, allowing them to form cross-links in DNA. Antimetabolites These agents have a similar structure to key building blocks in DNA and protein synthesis, and compete with natural substrates for incorporation into DNA or RNA, or bind with key enzymes in biosynthetic pathways. Purine analogues of adenine (such as 6-mercaptopurine) and guanine (such as thioguanine) lead to defective DNA synthesis. Antifolates such as methotrexate in- hibit dihydrofolate reductase, a key enzyme in the production of purines (Fig. 5.6.4). Reduced availability of tetrahydrofolate re- duces the efficacy of thymidylate synthase, which in turns reduces production of dihydrofolate and thymidine monophosphate. Thymidine phosphate is a key enzyme in both DNA and RNA synthesis. The inhibitory effect of methotrexate can be partially reversed by administration of folinic acid to restore cellular pools of tetrahydrofolate. Pemetrexed is a novel antifolate therapy which targets multiple steps in the folate biosynthesis pathway. Cytotoxic antibiotics Several of the most successful chemotherapy agents have been isolated from cultures of fungi and bacteria (Table 5.6.4). The agents typically act by inhibiting DNA synthesis by a range of dif- ferent mechanisms. Anthracyclines (named after the red-coloured actinobacteria species from which they were originally extracted) have a range of cytotoxic effects, ranging from DNA intercal- ation and inhibition of replication, to inhibition of DNA uncoiling through the inhibition of the topoisomerase II enzyme, and free radical damage through the production of reactive oxygen spe- cies. Mitomycin C was also isolated from a Streptomyces species and leads to DNA cross-linking similar to the effect of alkylating agents. Bleomycin is a nonribosomal glycopeptide isolated from Streptomyces verticullus, which causes DNA strand breakage. Platinum compounds Organic heavy metal compounds containing platinum, such as cisplatin, carboplatin, and oxaliplatin, form DNA cross-links, interfering with mitosis. The platinum agents revolutionized the treatment of germ cell tumours and are utilized in a wide variety of solid tumours, as well as haematological malignancy. Mitotic spindle agents Both classes of agent in this group have an effect on the microtubules that form the mitotic spindle in preparation for cell division. Vinca alkaloids, such as vincristine, vinblastine, and vinorelbine, were iso- lated or derived from the periwinkle plant. They bind to tubulins and prevent further assembly of the mitotic spindle. The taxanes, such as paclitaxel and docetaxel, were originally derived from the bark of the pacific yew tree and have antimitotic effects through stabilization of the assembled microtubules, and preventing depolymerization at the end of mitosis. The taxanes have been used in a range of solid tu- mours, including ovarian, breast, lung, and pancreatic cancers. Topoisomerase inhibitors Topoisomerase enzymes control the winding of DNA, and facili- tate DNA transcription through DNA cleavage, unwinding, and rejoining. Cytotoxic agents have been developed to inhibit the action of two key topoisomerase enzymes. The Camptothecins (topotecan and irinotecan) were derived from the bark and stem of the Chinese tree Camptotheca acuminata. Irinotecan is used in the treatment of bowel cancer. Etoposide is a potent inhibitor of topoisomerase II, and is used in the treatment of

a range of solid tumours, including germ cell tumours and small-cell lung cancer. It is a semi-synthetic derivative of an epidophyllotoxin, derived from the mandrake plant. Hormone therapies Growth stimulus from endogenous hormone secretion can act as an important promoter of carcinogenesis in many tumours. In 1878, Thomas Beatson was the first to identify that modulation of en- dogenous hormone production could be used to treat advanced ma- lignancy by performing oophorectomies in women with advanced breast cancer. In 1941 Charles Huggins first utilized castration and Interstrand cross-linking Intrastrand cross-linking Intercalation Monoalkylation
Fig. 5.6.3 Mechanism of DNA damage induced by alkylating agents.

5.6 Systemic treatment and radiotherapy 501 exogenous oestrogen administration to induce disease regression in metastatic prostate cancer. Hormone therapies modulate the growth stimulus by reduction of endogenous hormone synthesis, or antagonism of a hormone receptor pathway. Hormone therapies are used extensively in the management of breast cancer, pros- tate cancer, ovarian and endometrial cancer, and a range of other malignancies. Oestrogen receptor modulators Tamoxifen is one of the most common hormone therapies used in the treatment of oestrogen receptor-positive breast cancer, both in early and advanced stages. It is one of the first approved agents of a class of selective oestrogen receptor modulators (SERMs), having an antagonistic effect against receptors in the breast, and a partial agonist effect against receptors in the endometrium and bone. The agonist action in bone is protective against postmenopausal osteo- porosis but increases the risk of endometrial cancer. Novel second- generation SERMs such as raloxifene and bazedoxifene have been developed as treatments for postmenopausal osteoporosis, and both have a preventive effect on breast cancer. Androgen receptor antagonists Androgen receptor antagonists are used in the treatment of pros- tate cancer. Cyproterone acetate was one of the first of this class of agent, having a combined androgen receptor antagonist and progesterone receptor agonist effect. The drug is associated with significant risk of hepatotoxicity, and has now been superseded by second-generation agents such as flutamide, bicalutamide, and enzalutamide. These agents are pure androgen receptor antagon- ists which bind the receptor with high selectivity. Aromatase inhibitors Aromatase inhibitors are a class of agents which act by inhibiting the aromatization of androgens into oestrogens. The agents are used for the treatment of breast and ovarian cancer in postmenopausal women by inhibiting extragonadal oestrogen synthesis. Nonster- oidal aromatase inhibitors such as anastrozole and letrozole in- hibit oestrogen synthesis through competitive interaction with the aromatase enzyme. Steroidal aromatase inhibitors, such as exemestane, bind and permanently deactivate the enzyme. 5-FdUMP (5FU) Methotrexate Pemetrexed dUMP N5, N10 methylene- tetrahydrofolate Glycine Serine Tetrahydrofolate 10-formyl-tetrahydrofolate PRPP GAR AICAR IMP NADP+ NADPH + H+ Dihydrofolate dTMP TS SHMT DHFR AICAR-FT GAR-FT
Fig. 5.6.4 Chemotherapy agents targeting the folate biosynthesis pathway. 5-Fluorouracil is metabolized to 5-FdUMP, which is a competitive inhibitor of thymidylate synthase. Methotrexate is an inhibitor of the dihydrofolate reductase enzyme. Pemetrexed inhibits both of these enzymes and inhibits multifunctional synthetic enzymes in the purine biosynthesis pathway.
Table 5.6.4 Cytotoxic agents: species of origin and their usage

Species	Cytotoxic agent	Usage
S. peucetius	Daunorubicin, Doxorubicin, epirubicin	Breast, ovarian cancer, sarcoma, leukaemia
S. caespositosus	Mitomycin C	Anal, bladder cancer
S. verticullus	Bleomycin	Hodgkin’s lymphoma, non-Hodgkin lymphoma, testicular cancer
S. parvullus	Actinomycin D	Gestation trophoblastic tumours, Wilm’s tumour, sarcoma

 Inhibition of gonadotrophin production Inhibition of gonadotrophin production is a potent form of androgen and oestrogen inhibition. Gonadotrophin release hormone (GnRH) agonists such as goserelin, leuprorelin, and degarelix are synthetic analogues of the decapeptide luteinizing hormone-releasing hor- mone (LHRH). The agents bind to LHRH receptors, leading to an initial increase in production of LHRH and downstream sex hor- mones. This increase can lead to a flare in tumour growth, particu- larly in men with advanced prostate cancer. The flare effect can be minimized by coadministration of an androgen receptor antagonist such as bicalutamide. After 14–21 days, downregulation of LHRH receptors leads to a profound suppression of sex hormone produc- tion. The peptide has been formulated for subcutaneous implant- ation, which can last for 12 months. Exogenous hormones Exogenous hormones may also be used an anticancer therapies. Steroidal progestogens such as medroxyprogesterone acetate are used in the treatment of breast, endometrial, and renal cancer. In breast and endometrial cancer, progestogens reduce production of oestrogen through reduced hypothalamic GnRH production. Megestrol acetate has similar progestogen and antigonadotrophic effects, and is used in the treatment of breast, endometrial, and prostate cancers. It also has a weak glucocorticoid effect, useful for constitutional effects and stimulation of appetite in patients with ad- vanced malignancy. Targeted therapies While conventional cytotoxic chemotherapy and hormone ther- apies are efficacious anticancer therapies, their action is not dis- ease specific, and drug–tumour combinations have been developed through large-scale screening of agents, both in the preclinical and clinical setting. Our enhanced understanding of the underlying gen- etic mechanisms in cancer provides a novel method for drug devel- opment. Targeted therapies are agents which have been designed to modulate specific targets that are known to be overexpressed or of vital importance in the proliferation and survival of a given tumour type. Development of predictive assays allows confirmation of the presence or absence of a target in tumour tissue from each patient. The targeted therapies typically inhibit key growth factor signalling pathways, either through competitive inhibition of a growth factor receptor or a key step in the signal transduction pathway, such as a tyrosine kinase enzyme. The targeted therapy agents follow a stand- ardized nomenclature (Table 5.6.5). Monoclonal antibody therapies are large proteins that can only act at the surface membrane of cells. They are given via subcutaneous infusion, typically have long biological half-life of 2–3 weeks, and are typically well tolerated. Many of the antibodies will also elicit a beneficial activation of the immune system, which enhances their antitumour effect. Small molecule targeted therapies are typically given as oral ther- apies and have a short half-life between 36 and 48 hours. They can pass into the cytoplasm and thus operate on intracellular targets. Side effects typically consist of cutaneous effects such as rash, acne and pruritus, and gastrointestinal toxicity such as diarrhoea, nausea, and vomiting. The targeted therapies can be grouped by class of action. Signal transduction inhibitors These agents work through inhibition of a transmembrane signal transduction pathway that provides growth stimulus to tumour cells. Examples include trastuzumab, which inhibits the HER2 receptor which is overexpressed in breast and gastric cancers. Antibodies may also prevent dimerization of surface growth factors and subsequent activation of signalling cascades. Pertuzumab inhibits dimerization of HER2 and HER3. Cetuximab is a monoclonal antibody targeting the epidermal growth factor receptor (EGFR), while gefitinib and erlotinib are tyrosine kinase inhibitors of the same receptor pathway demonstrating efficacy in head and neck cancers, lung cancer, and bowel cancer. The BCR-ABL fusion protein forms a constitutively active growth receptor tyrosine kinase, implicated in Philadelphia chromosome-positive chronic myeloid leukaemia. Imatinib inhibits this receptor tyrosine kinase pathway, also the c-kit pathway found commonly in gastrointestinal stromal tumours. ALK is a

receptor tyrosine kinase which exerts oncogenic effects in large cell lymphoma, non-small-cell lung cancer, and a range of other tumours. Agents such as crizotinib and ceritinib are used to treat ALK mutation-positive advanced lung cancers, typically found among nonsmokers with adenocarcinoma histology. ALK muta- tions and EGFR mutations are often mutually exclusive in lung cancer, thus patients with ALK mutation positive tumours typically do not respond to EGFR tyrosine kinase inhibitors. The BRAF protein kinase is an important regulator of cell growth, proliferation, and differentiation, and BRAF mutations are observed in approximately 50% of melanoma tumours. BRAK kinase inhibi- tors such as dabrafenib and vemurafenib have revolutionized the treatment of advanced melanoma. Angiogenesis inhibitors These inhibit tumour growth, typically through the vascular endo- thelial growth factor (VEGF) pathway. Bevacizumab is an inhibitor of circulating VEGF, thereby inhibiting tumour angiogenesis. It has been used successfully in a wide range of malignancies including colon cancer, breast cancer, ovarian cancer, and glioblastoma. Many tyrosine kinase inhibitors have been developed, targeting different isoforms of the VEGF receptor as well as other related receptors (Table 5.6.6). Proteasome inhibitors These block the action of proteasomes, leading to activation of proapoptotic pathways which have been suppressed in tumour cells. Table 5.6.5 Nomenclature of targeted systemic therapies Name element Meaning Example -mab Monoclonal antibody Trastuzumab -ib Small molecule inhibitor Erlotinib -ximab Chimeric human-mouse antibody Cetuximab -zumab Humanized mouse antibody Pertuzumab -ci- Circulating system target Bevacizumab -tu- Tumour target Cetuximab -tin- Tyrosine kinase inhibitor Afatinib -zom- Proteasome inhibitor Bortezomib

 Bortezomib is an example of such an agent, used in the treatment of multiple myeloma and mantle cell lymphoma. Targeted immunotherapy agents Immune modulation therapy through the use of naturally occurr ing cytokines such as interleukins and interferon has yielded poor response rates as anticancer therapy. Novel therapies target spe- cific checkpoints in immune surveillance which are used by tu- mour cells to bypass detection by the immune system. CTLA-4 is a receptor which mediates an inhibitory effect on cytotoxic T lymphocytes. Ipilimumab is a monoclonal antibody which binds to the receptor and blocks the inhibitory signal, permitting cyto- toxic T lymphocytes to destroy tumour cells. Ipilimumab has been used with great efficacy in advanced melanoma and renal cell carcinoma, though nonspecific T-cell activation can cause severe gastrointestinal toxicity. Programmed cell death protein-1 (PD-1) is a cell surface receptor expressed on T cells which plays a key role in immune regulation. It interacts with two ligands, PD-L1 (expressed on tumour cells) and PD-L2 (expressed on macrophages and dendritic cells). PD-1 inhibitors facilitate activation of the immune system to attack tu- mour cells. PD-1 inhibitors such as nivolumab have demonstrated durable disease remissions in melanoma, renal cancer, and lung cancer, but carry a high risk of immune-mediated hepatitis, colitis, and pneumonitis. Clinical applications of radiation therapy Radiation therapy can be utilized in both curative and palliative treatment for a wide range of tumour types. Approximately 50% of all patients will benefit from radiation therapy at some point in their cancer journey. In a curative setting, radiation therapy is often used alone or in conjunction with chemotherapy as an organ-preserving treatment where surgical excision would lead to sig- nificant loss of function. Examples include head and neck cancers, anal cancer, cervix cancer, and prostate cancer, as well as a range of brain tumours. Curative radiation therapy is typically given in daily treatment fractions in order to facilitate normal tissue repair and minimize late effects of therapy. Radiation therapy is often used in an adjuvant setting after sur- gery in the treatment of localized breast cancer, where local ex- cision and postoperative radiotherapy yield equivalent control rates to mastectomy. Adjuvant

radiation therapy also be used in a range of other conditions to reduce the risk of local disease re- currence. Neoadjuvant radiotherapy can be used with great effect to downstage rectal cancers prior to surgery. Radiation therapy can also be used effectively in the treatment of seminoma, early stage Hodgkin lymphoma and non-Hodgkin lymphoma, and in a range of paediatric tumours, although in modern practice con- cerns regarding the late effects of radiation therapy typically mean that radiation therapy in such conditions is reserved for patients with incomplete response to chemotherapy, using a risk adaptive approach. Rapid palliation of local symptoms can also be achieved by ra- diation therapy for symptoms such as bone pain, spinal cord com- pression, cerebral metastases, low-volume bleeding from tumour surfaces and ulcerating tumours. Palliative radiation therapy is often delivered in single large doses of radiation. Stereotactic radiosurgery uses high-precision delivery systems to achieve steep dose gradients of radiation dose between tumour targets and ad- jacent tissues. Uses include eradication of cerebral metastases as well as some brain tumours such as vestibular schwannoma and meningiomas of the skull base and pituitary gland region. Novel imaging techniques allow stereotactic body radiotherapy to be used to treat tumours in the lungs, liver, and spine. Particle therapy uses the characteristics of high-energy protons and carbon ions to improve conformation of radiation dose to tar- gets. The initial energy of a proton defines the depth to which it will penetrate in the body, allowing a sharp fall-off of radiation dose (Fig. 5.6.5). Particle therapy is of particular benefit in the treatment of tumours close to the spine or optic apparatus, where steep dose gradients are required between the tumour and nerve tissue. The lack of exit dose through healthy tissues is also benefi- cial in paediatric radiotherapy, reducing the risk of impaired organ growth and secondary malignancy. Brachytherapy utilizes naturally occurring radiation sources that can be placed inside or close to the surface of a tumour. As radiation dose falls with the square of distance, the dose to sur- rounding tissues can be minimized using brachytherapy treat- ment, allowing higher doses to be delivered to the tumour than would be feasible with external beam radiation therapy alone. Brachytherapy is used extensively in the treatment of gynaeco- logical malignancy, as well as early stage prostate cancer. Table 5.6.6 Multitargeted VEGF inhibitors Agent Target receptor Cediranib VEGFR-1, -2, -3, c-kit Sorafenib VEGFR-2, -3, Ras/Raf/Mek/ERK and PDGFR- β Sunitinib VEGFR-1, -2, -3, PDGFR -α and -β Pazopanib VEGFR-1, -2, -3, PDGFR -α and –β, c-kit 14 7 0.5 Relative energy 260 MeV proton ions 120 kV X-ray 18 mV X-ray Bragg peak Depth in water (cm) 1 Fig. 5.6.5 Dose deposition of low- and high-energy X-rays, and proton ions. Note that the Bragg peak defines a depth at which dose drops off rapidly in the path of a proton beam.

 Improving the specificity of treatments Chemotherapy Several strategies have been adopted to enhance the specifi- city of cytotoxic agents for tumour cells, reducing the incidence of dose-limiting toxicity and permitting safe escalation of drug dose. Tumours have an acidic and hypoxic environment due to poor vascular clearance and accumulation of extracellular lactate. Temozolomide is a prodrug with increased activation at low pH when compared to physiological pH. Similarly, hypoxia-activated prodrugs are activated at the low oxygen tensions found in the core of tumour tissues. Liposomal formulation of drugs can reduce bio- availability in healthy tissues by increasing the effective circulation time of the drug. Liposomal doxorubicin formulations reduce the risk of cardiac toxicity without loss of antitumour effect. Nanoparticles of metallic gold or platinum, measuring up to 100 nm in size, can be enveloped in peptides to facilitate entry into tu- mour cells and evade immune surveillance. Metal ions can be directly toxic to tumour cells through free radical production, and act as ra- diation sensitizers with X-rays through the production of secondary electrons. The coated particles can be conjugated to peptides, mono- clonal antibodies, or cytotoxic agents. Paramagnetic nanoparticles can also induce

thermal injury when activated by nonionizing elec- tromagnetic radiation (laser light) or alternating magnetic fields. Radiation therapy Radiation therapy effects are not intrinsically specific to cancer cells, and normal tissue effects in structures adjacent to the tumour target limit the maximum radiation dose that can be delivered. Various strategies are employed to maximize the effect of radiation on tumour cells while minimizing the effect on normal tissues (Table 5.6.7). Late effects of cancer therapy Where cancer therapies are given with curative intent, care must be taken to consider long-term toxicities from treatment. Systemic therapies may be associated with organ-specific late effects such as dose-dependent cardiac toxicity from anthracycline chemotherapy, lung fibrosis from bleomycin, and sensorineural hearing loss from vincristine. Radiation therapy also carries a risk of normal tissue damage, dependent on the dose and volume of tissue that is irradiated. Common side effects in curative treatment include fibrosis fol- lowing breast irradiation, xerostomia due to irradiation in the salivary glands in head and neck cancer, and radiation proctitis fol- lowing pelvic radiotherapy. The mechanism of radiation injury is typically due to small vessel ischaemia and tissue fibrosis. Second malignancy is a rare yet important complication of both systemic therapies and radiation therapy. Alkylating agents, cis- platin, and etoposide have been associated with secondary leu- kaemia, typically between 2 and 10 years after treatment. Leukaemia may be preceded by a myelodysplastic syndrome. Ionizing radiation therapy also increases the risk of acute leukaemia, typically with ex- posures that irradiate large volumes of bone marrow. For targeted radiation therapy, second malignancy often manifests with earlier onset (especially breast cancer, lung cancer, and osteosarcoma). Unlike secondary leukaemia, epithelial malignancies typically occur decades after treatment. Patients undergoing cranial irradiation are also at increased risk of meningioma. FURTHER READING Begg AC, Stewart FA, Vens C (2011). Strategies to improve radio- therapy with targeted drugs. Nat Rev Cancer, 11, 239–53. Davita VT Jr, Chu E (2008). A history of cancer chemotherapy. Cancer Res, 68, 8643–53. Hanahan D, Weinberg RA (2011). Hallmarks of cancer: the next gen- eration. Cell, 144, 646–74. He J, Hu Y, Hu M, Li B (2015). Development of PD-1/PD-L1 pathway in tumor immune microenvironment and treatment for non-small cell lung cancer. Sci Rep, 5, 13110. Krause DS, Van Etten RA (2005). Tyrosine kinases as targets for cancer therapy. N Engl J Med, 353, 172–87. Table 5.6.7 Strategies to improve radiotherapy treatment Conformal radiotherapy This involves shaping of the radiation dose to match that of the target. At its simplest level, this can be achieved by shaping the radiation beam to match the shape of the target, known and 3D-conformal radiotherapy. The radiation field can be broken down into thousands of small beamlets directed at the tumour from different directions. The intensity of radiation of each beamlet can be controlled such that the summation of dose from all beams delivers a dose distribution that closely matches the shape of the tumour target. This technique is known as intensity modulated radiotherapy. Fractionated radiotherapy Radiation therapy is often delivered in a series of daily treatments, or fractions. This is because most tumour cells will have defective DNA repair pathways, and accumulate DNA damage from one treatment to the next. In contrast, the repair half- time for DNA damage in healthy mammalian cells is approximately 8 hours, hence in the 24 hours between treatments nearly 90% of the DNA damage caused by radiation will be repaired. Chemo-radiotherapy Low-dose chemotherapy can be used in conjunction with radiotherapy with specific synergistic effects. For example, cisplatin induces interstrand and intrastrand cross-links that interfere with double-strand break repair, leading to perpetuation of radiation-induced double-strand breaks.

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