Principles of chemotherapy and radiotherapy

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Abstract

Radiotherapy and chemotherapy are both widely used in the management of gynaecological malignancy. The reasons why tumours are destroyed and normal tissues recover after radiotherapy are complex and thought to be due to differences in intrinsic radiosensitivity and the ability to repair and repopulate between normal and malignant tissue. Some tumours are hypoxic, which makes them radioresistant. Most radiotherapy treatments are carried out using a linear accelerator, which produces photons or high energy x-rays that are 'skin sparing' and can treat deep-seated tumours. Brachytherapy (short distance treatment) with implanted or internal radiation sources can also be used, and indeed is an essential part of the radical radiotherapy for cervical carcinoma.

Chemotherapeutic agents currently in use are cytotoxic and affect both normal and malignant cells. Side-effects include bone marrow suppression, nausea and vomiting, epilation, renal, cardiac and neurotoxicity. Ideally, agents with different mechanisms of action should be given in combination to overcome potential drug resistance. Multiple drugs should have differing patterns of toxicity so the highest tolerable doses can be given. Chemotherapy can also be given concurrently with radiotherapy to enhance the therapeutic effect. Newer biological agents are increasingly being used in the treatment of cancers. As most gynaecological chemotherapy treatments are palliative, patients should be selected with great care; the possible benefits of the treatment must be balanced against the risk of side-effects.

Keywords cancer; cervix; chemotherapy; endometrium; ovary; radiotherapy

Radiotherapy

Radiotherapy is the art of using ionising radiation to destroy malignant tumours whilst minimising damage to normal tissues. It can be highly effective. Retrospective studies have shown cure rates of 80–85% following radiotherapy treatment of stage 1b carcinoma of the cervix. A large randomised controlled trial carried out in North Italy showed identical survival figures for patients with operable cervical cancer (stage 1b–2a) treated either by Wertheim's hysterectomy or radical radiotherapy. Interestingly, the serious complication rate was higher in patients treated by surgery or surgery plus radiotherapy, rather than radiotherapy alone.

Up until 1999, radical radiotherapy alone was the treatment of choice for stages 2b–4a carcinoma of the cervix. More recently, studies have shown that radiotherapy given concurrently with platinum-based chemotherapy can increase disease-free survival and overall survival in these patients and this has been adopted as the standard treatment in patients suitable for concurrent therapy.

Radiotherapy is also used as an alternative to surgery in patients with early endometrial carcinoma who are unsuitable for hysterectomy. The 5-year survival figure for this group of patients – as reported from Manchester – was 72%. Radiotherapy may be offered on a selective basis to patients after hysterectomy for endometrial cancer. The Postoperative Radiation Therapy for Endometrial Carcinoma (PORTEC) 2 study and the currently unpublished Medical Research Council (MRC) A Study in the Treatment of Endometrial Cancer (ASTEC) show no survival advantage for routine external beam radiotherapy for patients with low or intermediate risk stage 1b tumour. There is some evidence of survival advantage for patients with G3 stage 1c and stage 2 tumours for postoperative radiotherapy. Additional chemotherapy may reduce the incidence of distant metastases in this group of patients and this is being tested in the PORTEC 3 study.

Where cure is impossible, radiotherapy can be a very useful treatment for palliation. Pain from bony metastasis can be eased in 80% and abolished in 50% of patients receiving a single x-ray treatment, and vaginal bleeding from advanced pelvic malignancy can also be controlled with palliative radiotherapy.

The biological basis of radiotherapy treatment

The reasons why tumours are destroyed and normal tissues recover following radiotherapy are complex and poorly understood. Radiation kills cells by the production of secondary charged particles and free radicals, which interact with the nucleic acids. Cellular lethality seems to be related to the number of double-stranded DNA breaks produced in the nucleus. The sensitivity of tissues to radiotherapy seems to depend on their ability to repair radiation damage, repopulate and re-oxygenate. The capacity to repair double- and single-stranded DNA breaks varies between normal tissue and different tumours. The ability to repopulate is important, as cells can rapidly divide to replace cells killed by radiation. Normal tissues such as the buccal mucosa and bone marrow have a considerable number of cells in the G0 resting phase of the cell cycle, these can be rapidly stimulated to divide and replace dead cells. Unfortunately, well-differentiated and moderately well-differentiated squamous carcinomas of the head and neck region have a marked ability to repopulate and this may account for radiation failure in the treatment of some of these tumours. As tumours grow, new blood vessels develop to feed the neoplasm. By and large, the new blood vessels are primitive in nature and the blood supply is inadequate to supply the growing tumour. Necrotic areas develop within such tumours, which contain hypoxic cells and are a source of radioresistance. However, during a course of radiotherapy, cells that were hypoxic may re-oxygenate and become more radiosensitive.

Radiation dose

The interaction of radiation with tissues is measured as the absorbed dose, which is the quantity of energy absorbed per unit

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mass. In the SI system of units this is measured as joules per kilogram. One joule/kg is 1 Gray (Gy). 1 Gy is equal to 100 rad (the previous unit for radiation dose).

The limitation on radiation dose, when given in an attempt to cure a tumour, is the risk of normal tissue damage. This damage is seen initially as acute radiation effects in rapidly proliferating cells such a skin epithelium, mucosal lining of the upper digestive tract, or the surface lining of the small bowel. This may manifest itself as moist desquamation of the skin, mucositis inside the mouth or diarrhoea caused by damage to jejunal crypt cells. This damage normally heals. The greater concern is the risk of late damage to normal tissue. This appears 9 months to 5 years after treatment due to effects on slowly proliferating tissue, particularly vascular endothelium. This is expressed as progressive fibrosis and arteritis leading to necrosis, fistulae or stricture. The serious complication rate for patients treated for carcinoma of the cervix by radical radiotherapy is about 5%. Newer developments in radiotherapy, such as intensity-modulated radiotherapy (IMRT), should be able minimise these side-effects.

The therapeutic ratio

The therapeutic ratio has been defined as the relationship between the desired and unwanted effects of therapy. One method to reduce the risk of normal tissue injury and increase the therapeutic ratio is to fractionate treatment. The total dose of radiation to be delivered is divided into 20–30 separate treatments and given daily over 4–6 weeks. An alternative approach is to administer continuous low dose rate radiation directly into or adjacent to the tumour. Such treatments are referred to as brachytherapy (short distance treatment).

Radiotherapy machines

Modern radiotherapy departments use linear accelerator, which is used to produce x-rays of energies of 6–20 million electron volts (MeV). Such x-rays have major clinical advantages over low energy x-rays generated by older kilovoltage machines. Mega-voltage x-rays are relatively 'skin-sparing'. It is fairly easy to treat deep-seated tumours with a homogeneous radiation beam and the radiation dose to bone no higher than surrounding tissues. Older kilovoltage apparatus generates x-rays of 100,000–300,000 electron volts (KeV). These machines produce x-rays only 2–3 times more energetic than those used to take diagnostic radiographs. The maximum energy of the kilovoltage x-rays is deposited on the skin surface, this means that their usefulness is limited in treating deeper tumours At present, these machines are used for low-dose palliative treatments or for the treatment of skin/superficial tumours.

Brachytherapy

Brachytherapy involves implantation or insertion of radioactive seeds or sources directly into or adjacent to the tumour (or tumour bed). It allows a high radiation dose to the tumour with low doses to surrounding tissue to reduce toxicity. It is an essential part of the radiation therapy for carcinoma of the cervix and may also be used in the treatment of endometrial carcinoma. The patient has hollow tubes placed into the uterus or vagina. The current practice is to use an afterloading device, which is able to move the radioactive sources remotely from a machine (e.g. the Selectron) into the intra-uterine or vaginal applicators and back out again at a prescribed time to deliver the appropriate radiation dose. The patient is kept in isolation during the treatment but the sources can be moved back into the machines at the touch of a button in the case of an emergency. In the UK, the practice has been low- to medium-dose rate brachytherapy using radioactive caesium with treatment times of 18–36 hours. However, increasingly centres are switching to high-dose rate brachytherapy using iridium sources. The treatment is given over minutes but sometimes general anaesthetic is required. There are retrospective studies (but not randomised controlled trials) that suggest that high-dose rate brachytherapy is more effective than the old-style manually inserted low-dose rate sources or the intermediate dose-rate Selectron treatment.

New trial evidence (PORTEC-2) suggests that brachytherapy offers comparative reduction in local recurrence in intermediate risk endometrial cancer with better quality of life, shorter duration of treatment and reduced toxicity especially with relation to gastrointestinal side-effects from external beam radiotherapy.

Current developments in radiotherapy

The vast improvement in diagnostic imaging has been immensely helpful in radiation treatment planning. With the use of reconstructed matched computed tomograms and magnetic resonance images, the accuracy of treatment planning can be improved and this reduces the possibility of a 'geographical miss'. Moreover, the dose distribution to the target volume can be shaped to conform tightly to the shape of the tumour, reducing the volume of normal tissue irradiated by up to 50%. The risk of late damage (side-effects developing months or years following radiotherapy treatment) can, therefore, be reduced and the dose given to the tumour can be increased with a greater probability of tumour control. This 'conformal' radiotherapy is possible due to the introduction of the multi-leaf collimator. This is an apparatus in the head of the linear accelerator comprising of up to 40 pairs of tungsten bars (1 cm width). These can move independently to shape the treatment beam to irregular contours. Conformal radiotherapy is now the standard treatment for many solid cancers. Prospective dose escalation studies in prostate cancer showed that higher doses could be given using this technique with better tumour outcomes and no increase in late toxicity.

IMRT

IMRT is a more advanced form of conformal radiotherapy. Currently many centres in the UK are not using this routinely but it is increasingly the subject of interest and studies. The main interest in gynaecological malignancy is to improve the radiation treatment for cervical carcinoma by reducing bowel toxicity and looking at the possibility of increasing dose to the primary areas and the areas at risk. There is evidence to suggest that this modality of treatment could significantly reduce gastrointestinal and genitourinary toxicity.

It is possible that, using IMRT, different doses could be given to different targets. This means that whilst reducing normal tissue dose, it could potentially treat the primary tumour and high-risk areas with a higher dose. Some studies looked at IMRT boost as an alternative to brachytherapy; however, because of the increase in the size of treatment volume, brachytherapy still remains the method of choice for boosting tumour.