

A selection of significant papers from the past year as recommended by the US Oncological Disease 2006 Advisory Panel

New Science-based endpoints to accelerate oncology drug development

Kelloff G A, Sigman C C

Eur J Cancer (2005);41: pp. 491–501

Although several new oncology drugs have reached the market, more than 80% of drugs for all indications entering clinical development do not get marketing approval, with many failing late in development often in phase III trials because of unexpected safety issues or difficulty determining efficacy, including confounded outcomes. These factors contribute to the high costs of oncology drug development and clearly show the need for faster, more cost-effective strategies for evaluating oncology drugs and better definition of patients who will benefit from treatment. Advances in the understanding of neoplastic progression at the cellular and molecular levels have spurred the discovery of molecularly targeted drugs. This progress, along with advances in imaging and bioassay technologies, are the basis for describing and evaluating new biomarker endpoints, as well as for defining other biomarkers for identifying patient populations, potential toxicity and providing evidence of drug effect and efficacy. New, promising tools for measuring biomarkers have also been developed and are based on genomics and proteomics, direct visualisation by microscopy, nanotechnologies and direct and remote imaging. The identification and evaluation of potential surrogate endpoints and other biomarkers require access to and analysis of large amounts of data, new technologies and extensive research resources.

Health-related quality of life in patients with glioblastoma: a randomised controlled trial

Taphorn M J, et al.,

Lancet Oncol, (2005);6: pp. 937–944

A randomised controlled trial of radiotherapy alone versus radiotherapy with concomitant and adjuvant

temozolomide for patients with glioblastoma showed that survival was higher for patients assigned combination treatment compared with those assigned standard radiotherapy alone. This paper reports the health-related quality of life (HRQOL) of the patients in this trial. Five hundred and seventy-three patients with newly diagnosed glioblastoma were randomly allocated either radiotherapy alone or radiotherapy and temozolomide. The primary endpoint was survival, and HRQOL was a secondary endpoint. HRQOL was assessed at baseline and at every three months during treatment until progression using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaire core-30 (QLQ-C30) and the EORTC brain cancer module (EORTC BN-20). Changes from baseline score for seven predefined HRQOL measures and differences between groups for these measures at every time point were calculated. The significance of and proportions of patients with improved HRQOL scores – defined as a change of 10 points or more – were recorded. Baseline questionnaires were available for 86% of patients. Baseline HRQOL scores did not differ between groups. At first follow-up, groups differed only in social functioning, favouring the radiotherapy-only group. Over subsequent assessments, HRQOL was much the same between treatment groups. In summary, addition of temozolomide during and after radiotherapy for patients with newly diagnosed glioblastoma significantly improved survival without a negative effect on HRQOL.

The role of aromatase inhibitors as adjuvant therapy for early breast cancer in postmenopausal women

Mouridsen H T, Robert N J

Eur J Cancer (2005);41: pp. 1,678–1689

For endocrine therapy of hormone-sensitive advanced breast cancer in

postmenopausal women, the third-generation aromatase inhibitors, letrozole, anastrozole, and exemestane, are effective both as alternatives to tamoxifen in first-line treatment and following first-line tamoxifen failure. These three agents are currently being evaluated as adjuvant therapy of early breast cancer, again relative to the standard, tamoxifen. Three treatment strategies are under investigation: replacement of tamoxifen as adjuvant therapy for five years (early adjuvant therapy); sequencing of tamoxifen before or after an aromatase inhibitor during the first five years (early sequential adjuvant therapy); or following five years of tamoxifen (extended adjuvant therapy). Results of the first early adjuvant trial (Arimidex, Tamoxifen Alone or in Combination (ATAC)) demonstrated that anastrozole was significantly more effective than tamoxifen in reducing the risk of disease recurrence. Two trials sequencing 2–3 years of an aromatase inhibitor after 2–3 years of tamoxifen have also reported results. A large trial (International Collaborative Cancer Group (ICCG) trial 96) found switching to exemestane to be significantly superior to continuing on tamoxifen in disease-free survival, and in a small study (Italian Tamoxifen Arimidex (ITA) trial), similarly sequencing anastrozole after tamoxifen significantly reduced the hazard of recurrence compared with remaining on tamoxifen. Extended adjuvant therapy with five years of letrozole versus placebo following five years of tamoxifen was evaluated in the MA.17 trial. Compared with placebo, letrozole resulted in a significant improvement in disease-free survival that was irrespective of whether patients had lymph node-positive or -negative tumours. Results of these four trials emphasise the important role of aromatase inhibitors in the adjuvant setting, yet the optimal approach still needs to be defined. A number of trials further evaluating the three adjuvant treatment strategies are on-going.

Human papillomavirus vaccines in development: if they're successful in clinical trials, how will they be implemented?

Shaw, A R

Gynecol Oncol (2005);99: pp.5,246–5,248

There are some 30–40 genotypes of human papillomavirus (HPV) that cause anogenital lesions in humans, primarily cervical, vaginal, and vulvar dysplasias and cancer in women, anal dysplasias in some men, and genital warts in both sexes. Vaccines being developed by GlaxoSmithKline and Merck stimulate an antibody response against HPV types 16 and 18.

Cancer-related fatigue: a critical appraisal

Pruea G, Rankinb J, Allena J, et al.

Eur J Cancer 42 (2006);42: pp. 846–863

Studies investigated cancer-related fatigue (CRF) in adult cancer patients using a multidimensional fatigue measure with the aim to determine the prevalence and pattern of CRF and identify factors associated with its development. CRF is apparent both during and after anti-cancer therapy; however, the prevalence of CRF varied between studies. The variables associated with the development and persistence of CRF remain to be identified and inconsistencies were evident in the pattern of CRF and its associated factors. This is likely to have arisen from the inherent difficulties in the measurement of a subjective sensation, further complicated by the myriad outcome measures used.

Clinical applications of newer Radionuclide Therapies

Bransa B, Lindenb O, Giammarilec F, et al.

Eur J Cancer (2006);42: pp. 994–1,003

Radio-iodine was first used in the treatment of metastasized thyroid carcinoma in 1943. Its success in terms of tumour response, quality of life improvement and survival was considered a 'miracle', as metastatic cancer then was generally fatal. Inspired by this, many efforts have been made to apply radioisotope therapy to other tumours. Radionuclide therapy uses radioactive

isotopes labelled with specific targeting agents that aim to deliver the irradiation of the isotope to the tumour, while sparing normal tissues. Its unique modality allows to systemically target radiosensitive tumours throughout the body. Another important principle is its so-called 'cross-fire' action, whereby, owing to the larger reach of the radiation in relation to the cell diameter, a tumour cell receives lethal hits also from isotopes in the neighbourhood that are not directly associated with this cell. The treatment is therefore less hampered by inhomogeneous distribution and metabolism than for example chemo- or immunotherapy. Newer therapies include radio-peptide therapy, radio-immunotherapy of lymphoma and microsphere therapy for liver cancer.

Selection of adjuvant chemotherapy for treatment of node-positive breast cancer

Trudeau M, Charbonnea F, Gelmon K, et al.

Lancet Oncol (2005);6: pp. 886–898

A meta-analysis by the 2005 Early Breast Cancer Trialists' Collaborative Group confirmed that about six months of anthracycline-based polychemotherapy in the adjuvant setting reduced the yearly death rate from breast cancer by about 38% for women younger than 50 years and by 20% for women aged 50–69 years. Although this meta-analysis found that survival was better with regimens that contain anthracycline than with regimens based on cyclophosphamide, methotrexate, and fluorouracil, the best use of anthracycline-based regimens remains unclear. Adjuvant regimens in use can be categorised into three groups: standard-dose anthracycline; escalated-dose epirubicin; and anthracyclines and taxanes. The duration of treatment and combination of dose and drugs varies between these three categories. Three types of regimen were reviewed to establish which provide a better outcome in terms of safety, efficacy, cost, and convenience to patients. It was found that both escalated-dose epirubicin and anthracycline-taxane regimens were most effective in terms of disease-free survival and overall survival.

New therapeutic approaches for early stage non-small cell lung cancer

El-Sherif A, Luketich J D,

Landreneau R J, Fernando HC

Surgical Oncol (2005);14: pp. 27–32

Surgical resection remains the mainstay of therapy for early stage non-small cell lung cancer (NSCLC). Unfortunately, many patients present with advanced stage disease, and many with resectable early stage disease are unable to tolerate pulmonary resection because of compromised cardiopulmonary function. Standard and some alternative therapies that are being introduced into clinical practice for early stage NSCLC are reviewed here. New therapies such as sublobar resection with brachytherapy, radiofrequency ablation and stereotactic radiosurgery offer some hope for those patients who are considered poor candidates for curative resection.

Use of trastuzumab in the treatment of metastatic endometrial cancer

Jewell E, Secord A A, Brotherton T, Berchuck A

Int J Gynecol Cancer (2006);16(3): pp. 1,370–1,373

Systemic therapy of metastatic endometrial cancer is relatively ineffective. Response rates to chemotherapy and hormonal therapy in published studies range from 11% to 57%, but most responses are partial and of limited duration. In this case study, a 76-year-old woman presented with stage IIIA endometrial adenocarcinoma. The patient had been initially treated with surgery and pelvic radiation. The patient developed multiple pulmonary metastases. Following treatment with weekly paclitaxel chemotherapy, immunostaining revealed that the primary endometrial cancer overexpressed HER-2/neu. Trastuzumab was added to the regimen, and a dramatic partial response was achieved. After a second pulmonary relapse following discontinuation of prior therapy, that patient was again successfully treated with trastuzumab in combination with paclitaxel and then docetaxel. Therefore, trastuzumab may be a useful adjuvant to taxane-based chemotherapy in some patients with metastatic endometrial cancers that overexpress HER-2/neu. ■