



# ASCO 2008: new challenges for cancer care

Presented by



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## **Introduction**

The 44<sup>th</sup> Annual Meeting of the American Society of Clinical Oncology (ASCO) took place from 30 May to 2 June 2008 in Chicago. This year nearly 4300 abstracts were presented in the scientific program while more than 33 000 delegates could also participate in an elaborate educational program.

R. L. Schilsky, president-elect of ASCO, emphasized that treating cancer is about both treating the disease and caring for the individual patient. The conference highlights, therefore, addressed the full range of cancer care – from new therapies to managing the long-term effects of treatment. However, he also stressed the important challenges to advancing cancer care because of the stalled federal funding for cancer research and the limited access to high-quality cancer care resulting in the fact that fewer patients will benefit from scientific advances.

## **Prevention**

Smoking is one of the leading causes of lung cancer but also contributes to other cancers and cardiovascular disease. Although cigarette use has steadily declined in the United States over the past 3 decades, approximately 47 million people in the US and 1 billion people worldwide continue to smoke. In 2002, 3 million people died from tobacco-related causes. No single therapy has proven universally effective at reducing nicotine dependency and thus allowing individuals to quit smoking successfully. The associations between genetic variations, nicotine use, and the potential effects on smoking cessation techniques were discussed during an educational session chaired by M. R. Spitz.

Nicotine dependency has a clear genetic component as evidenced by studies involving twins. Twins raised apart have a high concordance of becoming either smokers or non-smokers, and these rates of concordance are higher for monozygotic than di-zogytic twins.

The initiation and maintenance of smoking also have notable heritability.

There seems to be a genetic risk for nicotine dependency and suggestive linkage have been described on chromosomes 6, 8, and 15, all of which are near candidate genes of interest in nicotine and opioid pathways. Individuals with the risk AA genotype have a higher level of nicotine dependency. By taking a genetic approach to nicotine addiction, in future tailored interventions based on genetic profiles should be possible.

The “dopaminergic hypothesis” states that by the binding of acute nicotine to nicotinic receptors, the release of neurotransmitters such as dopamine is stimulated, causing an increase in feelings of pleasure and some cognitive functions. With long-term use, the function of nicotinic and dopaminergic receptors is reduced, and thus more nicotine is required to maintain the same effects on mood and cognition. During nicotine withdrawal, the up-regulation of nicotinic receptors and down-regulation of dopaminergic receptors occurs; to the smoker, avoidance of the effects of withdrawal (negative reinforcement) and the pursuit of nicotine’s positive effects (positive reinforcement) becomes the foremost consideration.

The wide variability in the success of pharmacogenetic approaches to smoking cessation among individual smokers may be related to genetic variations at the receptor level, the drug metabolism level, or both:

- Women smokers with one or two copies of the A1 risk allele of the D2 dopamine receptor gene DRD2 are more likely to return to smoking after bupropion treatment than women who were homozygous for the A2 non-risk allele. However, no true pharmacogenetic models have been investigated in these first-generation studies of nicotine addiction studies.

Genomic approaches should make it possible to use platforms to genotype many variants within and across pathways, and bio-informatic approaches will be utilized to examine variation within a pathway and relate it to variation within a phenotypic pathway.

Genetic variations in the hepatic enzyme cytochrome P450 2A6 (CYP2A6) and nicotine metabolism, and their implications for smoking behaviors may also prove significant in the future. CYP2A6 is the main enzyme that metabolically inactivates nicotine in humans, mediating the inactivation of nicotine into cotinine, a molecule with essentially no pharmacologic activity.

- Variations in CYP2A6 activity are associated with the wide spectrum of individual abilities to quit smoking and differences in responses to smoking cessation drugs. CYP2A6 slow metabolizers maintain higher and more prolonged plasma levels of nicotine, and smoke less frequently and consume fewer cigarettes than those who metabolize CYP2A6 at a normal

rate. These slow metabolizing individuals are also less likely to become smokers. Slow metabolism is associated with a lower risk of becoming nicotine-dependent and developing lung cancer, along with an increased likelihood of quitting successfully.

- Variations in CYP2A6 affect response to nicotine replacement therapy (NRT), and an individual’s CYP2A6 genotype or phenotype might be a consideration when recommending a dose and type of NRT. The nicotine patch has proven to be a highly effective cessation method for slow metabolizers, who achieve higher plasma levels of nicotine than normal metabolizers with the same patch dosage. Fast metabolizers respond well to bupropion, an oral antidepressant also found to be efficacious in smoking cessation, as it reduces the severity of nicotine cravings.
- Therapies that manipulate CYP2A6 activity to mimic slow metabolizers may also be useful in aiding smoking cessation. CYP2A6 inhibitors could enhance the efficacy of NRTs by increasing nicotine levels and prolonging their duration. Methoxsalen is one such agent that has proven effective in recent pilot studies. These inhibitors also allow for the prescription of oral nicotine, which is otherwise metabolized quickly and rendered ineffective, rather than a nasal spray or transdermal patch.

Celecoxib appears to decrease expression of a protein associated with cell proliferation (Ki-67) in current and former smokers, suggesting it could potentially serve as a chemopreventive agent for lung cancer. In a study reported by Kim et al., 212 current or former smokers were randomized to one of four treatment arms over a 6 month interval: celecoxib for 3 months then placebo for 3 months; celecoxib for 6 months; placebo for 3 months then celecoxib for 3 months; or placebo for 6 months. Celecoxib was administered at 200 mg bid (low dose, 81 pts), then changed to high-dose (400 mg bid, 123 patients). Ki-67 expression was determined at baseline and after 3 months. Multi-variable analyses revealed that basal layer Ki-67 expression decreased in current and former smokers treated with high-dose ( $P=0.003$ ) but not low-dose ( $P=0.88$ ) celecoxib (vs. placebo). No cardiac problems were observed in patients in this study. Celecoxib was safe and tolerable and may have an effect of down-regulating proliferation in the bronchial epithelium of current smokers [1].

## Breast cancer

### Epidemiology

Vitamin D acts through a nuclear transcription factor to regulate many aspects of cellular growth and differentiation. Low levels of vitamin D have been associated with increased breast cancer risk. Vitamin D

levels and its prognostic effects were studied in a cohort of 512 consecutive women with newly diagnosed breast cancer. Vitamin D levels were deficient (<50 nmol/L) in 192 (37.5%), insufficient (50-72 nmol/L) in 197 (38.5%) and adequate (>72 nmol/L) in 123 (24.0%). Low vitamin D levels were associated with premenopausal status, high body mass index (BMI), high insulin and high tumor grade (all  $P < 0.03$ ). Low vitamin D levels were associated with low dietary intake of retinol, vitamin E, grains and alcohol (all  $P < 0.02$ ). Distant disease-free survival was worse in women with deficient (vs. adequate) vitamin D levels (Hazard ratio [HR] 1.94, 95% Confidence Interval [CI] 1.16-3.24,  $P = 0.02$ ) as was overall survival (HR 1.73, 95%CI 1.05-2.86,  $P = 0.02$ ). The authors concluded that vitamin D deficiency is common at breast cancer diagnosis and is associated with poor prognosis [2].

### Early stage disease

For women with early-stage breast cancer, adding paclitaxel to standard chemotherapy with 5-fluorouracil (5-FU), epirubicin, and cyclophosphamide (FEC) can improve disease-free survival, as shown in the GEICAM 9906 trial presented by M. Martin et al. The results also suggest that HER2 and hormone receptor status should not guide the use of paclitaxel. The study assessed the outcomes of 1246 patients with node-positive disease who underwent breast cancer surgery and then were randomized to receive FEC alone or FEC followed by paclitaxel. FEC was given for six cycles, while FEC-paclitaxel was given for four. At 5 years, the disease-free survival rate in the FEC-paclitaxel group was significantly higher than the rate in the FEC group: 78.5% vs. 72.1% ( $P = 0.006$ ). Relative to FEC alone, FEC-paclitaxel reduced the risk of relapse by 23% and the risk of death by 22%. An analysis of 928 patients with centrally analyzed tumor samples, chemotherapy type, number of involved axillary lymph nodes, tumor size, hormone receptor status, and HER2 status were all significant predictors of disease-free survival. However, both HER2 and hormone receptor status had no influence on the efficacy of paclitaxel treatment. Overall survival at 5 years was also higher in the FEC-paclitaxel group but not significantly different from that seen in the FEC group: 89.9% vs. 87.1% [3].

The Austrian Breast and Colorectal Cancer Study Group Trial 12 (ABCSCG-12) examined the efficacy of ovarian suppression by the gonadotropin-releasing hormone analogue goserelin in combination with anastrozole or tamoxifen  $\pm$  zoledronic acid in 1801 premenopausal women with endocrine-responsive breast cancer. They were randomized to goserelin (3.6 mg q 28 days SC) with tamoxifen (20 mg/d PO) or anastrozole (1 mg/d PO)  $\pm$  zoledronic acid (4 mg IV q 6 months) for 3 years. With a median follow-up of 60 months, there was no significant difference in disease-free survival between patients who received tamoxifen alone versus anastrozole alone (HR

1.10, 95%CI 0.79-1.54,  $P = 0.59$ ). However, endocrine therapy plus zoledronic acid significantly reduced the risk of disease-free survival events by 36% (HR 0.64, 95%CI 0.46-0.91,  $P = 0.01$ ) and the risk of relapse-free survival events by 35% (HR 0.65, 95%CI 0.46-0.92,  $P = 0.015$ ) compared with endocrine therapy alone. For overall survival, there was a non-significant trend favoring zoledronic acid treatment (HR 0.60, 95%CI 0.32-1.11,  $P = 0.10$ ). The authors concluded that the addition of zoledronic acid (4 mg q 6 months) to adjuvant endocrine therapy significantly prolonged disease-free and relapse-free survival compared with adjuvant endocrine therapy alone in premenopausal women with endocrine-responsive breast cancer [4].

### Advanced disease

The addition of bevacizumab to docetaxel seems to slow disease progression in patients with newly diagnosed locally advanced or metastatic breast cancer better than docetaxel alone. In the AVADO study reported by Miles et al., 736 patients with locally recurrent or metastatic breast cancer were randomized in a double-blind fashion to docetaxel 100 mg/m<sup>2</sup> plus placebo or either bevacizumab 7.5 mg/kg or 15 mg/kg. After a median follow-up of 11 months, progression-free survival and overall response rate were significantly higher for both bevacizumab-containing arms compared with docetaxel alone. Bevacizumab added limited toxicity relative to control [5].

During the Karnofsky lecture, the paradoxical actions of estrogen in breast cancer were discussed by V. C. Jordan. After an inauspicious start in the 1960s as failed investigational oral contraceptives, selective estrogen receptor modulators (SERMs) have proven their value in breast cancer treatment and chemoprevention. An additional benefit may be realized for SERMs and other anti-estrogens by sensitizing breast cancer to estrogen and allowing the hormone to be used as third-line breast cancer therapy.

Long-term therapy with SERMs or aromatase inhibitors may diminish their antitumor properties and may lead to a window for the potential use of estrogen to kill cancer cells. Studies in animal models indicate that long periods of estrogen deprivation, roughly equivalent to 5 years of anti-estrogen treatment for estrogen receptor-positive breast cancer, can supersensitize cancer cells to estrogen. The hormone can then trigger apoptosis when it combines with its receptor on tumor cells. A clinical trial of estrogen involving patients whose disease has developed resistance to anti-hormone therapies is planned.

In the late 1960s, using hormones to treat cancer was not an option. The anti-estrogen, ICI 46474 prevented embryonal implantation in rats and had potential as a morning-after contraceptive pill. When the agent actually

increased the rate of pregnancies in human clinical trials, further development as a contraceptive was dropped. After description of its estrogen receptor binding the anti-estrogen eventually became tamoxifen.

In the 1970s, tamoxifen became the first targeted therapy for breast cancer. The estrogen receptor, previously viewed only as a prognostic marker, became the first drug target. Knowledge of the complexity of SERM activity in different tissues and in the presence of co-activator and co-repressor substances continues to evolve. Despite the development of aromatase inhibitors for breast cancer treatment, SERMs maintain their important public health role; when used to prevent osteoporosis, they reduce rates of breast cancer, and they have lipid-lowering effects.

Drug resistance remains a problem in anti-estrogen therapy of breast cancer. After a long period of initial responsiveness to SERMs, estrogen receptor-positive tumors enter phase I resistance, in which growth is stimulated not only by SERMs but by estrogen as well. During this phase, the tumor continues to be responsive to aromatase inhibitor therapy. After approximately 5 years of treatment with tamoxifen, the entire configuration of the cancer cell changes drastically (phase II); growth is now stimulated by anti-estrogens, but exposure to physiologic levels of estrogen causes cell death. In experimental animals, dramatic regression of small tumors has been demonstrated with physiologic levels of estrogen given during phase II resistance to SERMs. Large tumors treated in this way recover their sensitivity to anti-hormone agents, which then appear to work when reintroduced. This schedule of sequential resistance and responsiveness underlies the clinical trial that is now going forward. The trial will enroll postmenopausal women with metastatic breast cancer who have first succeeded with and then lost their responsiveness to two consecutive anti-hormone therapies. Those who respond to 12 weeks of low-dose estrogen therapy — an expected 30% based on observations of women given high-dose estrogen — will receive an aromatase inhibitor to maintain tumor control. If three women out of 10 have a good response, the remaining seven can serve as a test population to identify other mechanisms that may be keeping those tumors from responding to estrogen.

## Lung cancer

### Early stage non-small cell lung cancer

Adjuvant treatment has become standard treatment in patients with stage II-IIIa non-small cell lung cancer (NSCLC). However, it still remains difficult to identify patients that really benefit from this treatment. Based on the data of the JBR.10 trial in patients with stage IB-II NSCLC, an expression profile to identify patient groups with significantly different prognosis and to select patients benefiting from adjuvant chemotherapy was determined. Gene expression profiling by Affymetrix U133A was

performed on RNA isolated from snap-frozen banked tumor tissues of 133 (62 observation ; 71 chemotherapy) JBR.10 patients. A 15-gene expression signature was identified that separated the 62 observation patients into groups with high- ( $n=33$ ) and low-risk ( $n=29$ ) for death (HR 60.1,  $P < 0.0001$ ). This prognostic signature was validated in five independent public gene expression datasets (stage I-II patients, total  $n=372$ ). Chemotherapy significantly reduced the risk of death in high-risk patients (HR 0.27, 95%CI 0.14-0.51,  $P < 0.0001$ ). The benefit of chemotherapy was seen both in high-risk stage IB (HR 0.28,  $P=0.007$ ) and stage II (HR 0.26,  $P=0.0059$ ) patients, but not in low-risk patients (HR 15.49,  $P=0.008$ ). Interaction of chemotherapy and expression signature was highly significant ( $P=0.0001$ ). The authors stated that they identified a 15-gene signature that is an independent prognostic marker in early stage NSCLC for identifying more selectively than stage patients who may benefit from adjuvant chemotherapy [6].

### Advanced non-small cell lung cancer

In the FLEX study, Pirker et al. randomized 1125 patients with epidermal growth factor receptor (EGFR)-detectable advanced NSCLC to cisplatin (80 mg/m<sup>2</sup> d1 a 3 weeks) and vinorelbine (25 mg/m<sup>2</sup> d1,8 q 3 weeks) with or without cetuximab (400 mg/m<sup>2</sup> initial dose, then 250 mg/m<sup>2</sup>/week). The overall survival was significantly improved in the combination arm (11.3 vs. 10.1 months, HR 0.871, 95%CI 0.762-0.996,  $P=0.0441$ ). There was a remarkable difference between the outcome of Asian (17.6 vs. 20.4 months, HR 1.179, 95%CI 0.730-1.905,  $P=0.4992$ ) and Caucasian (10.5 vs. 9.1 months, HR 0.800, 95%CI 0.692-0.924,  $P=0.0025$ ) patients [7].

In a multicenter phase III trial, the efficacy and safety of maintenance pemetrexed was compared with placebo in 663 patients with stage IIIB/IV NSCLC who had not progressed on four cycles of platinum-based induction chemotherapy. They were randomized (2:1 ratio; balanced for stage, ECOG performance status, sex, response to induction therapy, non-platinum component of induction therapy, and brain metastases) to receive pemetrexed (500 mg/m<sup>2</sup>, day 1 q 21 days) plus best supportive care or placebo plus best supportive care until disease progression. Pemetrexed had better efficacy with respect to progression-free survival (4.3 vs. 2.6 months, HR 0.502, 95%CI: 0.42-0.61,  $P < 0.00001$ ) and tumor response ( $P < 0.001$ ), especially in patients with non-squamous NSCLC. There was no significant difference in overall survival at the time of reporting. There were no significant toxicity differences between arms except for grade 3-4 anemia (pemetrexed 4.5%, placebo 1.4%) and total serious adverse events (4.3% vs. 0%). This study showed that maintenance therapy with pemetrexed is well tolerated and offers a superior progression-free survival compared with placebo in patients with advanced NSCLC [8].

A Japanese study looked at the value of adding maintenance gefitinib after chemotherapy in patients with advanced NSCLC. In a randomized phase III trial 603 patients were treated with a platinum-doublet chemotherapy (carboplatin AUC 6 + paclitaxel 200mg/m<sup>2</sup> d1 q 3 weeks, cisplatin 80mg/m<sup>2</sup> d1 + irinotecan 60mg/m<sup>2</sup> d1,8,15 q 4 weeks; cisplatin 80mg/m<sup>2</sup> d1 + vinorelbine 25mg/m<sup>2</sup> d1,8 q 3 weeks, cisplatin 80mg/m<sup>2</sup> + docetaxel 60mg/m<sup>2</sup> d1 q 3 weeks, or cisplatin 80mg/m<sup>2</sup> d1 + gemcitabine 1,000mg/m<sup>2</sup> d1,8 q 3 weeks) up to 6 cycles or a platinum-doublet chemotherapy for 3 cycles followed by gefitinib 250 mg orally once daily. There was a statistically significant improvement in progression-free survival (HR 0.68, 95%CI 0.57-0.80, *P*<0.001) in the gefitinib arm. However, overall survival was not different. In a pre-specified analysis of overall survival by histological groups, the gefitinib arm had a significantly better overall survival compared to the chemotherapy-only arm in patients with an adenocarcinoma histology (*n*=467; HR 0.79, 95%CI 0.65-0.98, *P*=0.03)[9].

## Colorectal cancer

### Early stage disease

Several studies have demonstrated the beneficial effect of adding oxaliplatin (OX) to 5-FU/leucovorin (LV) as adjuvant treatment in stage III colorectal cancer. Wolmark et al. reported on the overall survival at 5 years in 2409 eligible patients with (1209 FULV and 1200 FLOX) with stage II (28.9%) or III carcinoma of the colon. They were treated either with FULV (5-FU 500 mg/m<sup>2</sup> iv bolus weekly x 6; LV 500 mg/m<sup>2</sup> iv weekly x 6, each 8 week cycle x 3) or FLOX (same FULV regimen with oxaliplatin 85 mg/m<sup>2</sup> iv administered on weeks 1, 3, and 5 of each 8 week cycle x 3). The HR (FLOX vs. FULV) was 0.853 with a 95%CI between 0.723-1.008 and a 14.7% reduction in the risk of death in favor of FLOX. The authors concluded that there is a trend towards improved survival with the addition of oxaliplatin to weekly FULV (*P*=0.061) in patients with stage II and III colon cancer [10].

### Advanced disease

Predictive factors aim at determining patients that benefit from anticancer treatment. For the first time in colorectal cancer, a biomarker was determined to predict treatment efficacy. Several groups evaluated the mutation status of KRAS and correlated the presence of the wild type of KRAS with efficacy of the EGFR-blocker cetuximab.

E. Van Cutsem et al. analyzed efficacy data of the randomized phase III CRYSTAL trial. This trial showed a significant improvement in progression-free survival, overall response, and curative surgery rate when cetuximab was added to FOLFIRI in the first-line treatment of metastatic colorectal cancer and it was already shown that KRAS mutation status related to the outcome in patients treated with cetuximab as a single agent or in

combination with irinotecan. Efficacy analyses have been repeated to evaluate the influence of KRAS mutation status in patients treated in the CRYSTAL study. Blocks from archived tumor material were available from 587 of 1198 of the total patient population. Isolation of genomic DNA was performed directly from slides and a determination was done by quantitative polymerase chain reaction (qPCR)-based KRAS mutation analysis of codons 12/13. The KRAS-evaluable patients (*n*=540) were analyzed statistically to evaluate treatment effect stratified by KRAS mutation status [wild-type (wt) or mutation (mt)] and the given randomization strata using Cox regression for progression-free survival time and the Cochran-Mantel-Haenszel test for best overall response. KRAS mt were detected in 35.6% (192/540) of patients with evaluable samples. A statistically significant difference in favor of cetuximab was seen in KRAS wt patients for progression-free survival (HR 0.68, 95%CI 0.051-0.934, *P*=0.0167) and best overall response [59.3% (cetuximab + FOLFIRI) vs. 43.2% (FOLFIRI), *P*=0.0025]. Subgroup analyses by KRAS mt status for cetuximab + FOLFIRI vs. FOLFIRI showed no significant differences between treatment groups for progression-free survival (HR 1.07, 95% CI: 0.71-1.61, *P*=0.75) or best overall response (*P*=0.46). This analysis showed the predictive value of KRAS mutation status for treatment with cetuximab plus FOLFIRI in first-line treatment of metastatic colorectal cancer [11].

In the randomized phase II OPUS study, the influence of KRAS mutation status in first-line patients treated with standard therapy with or without cetuximab was evaluated in genomic DNA samples isolated from archived tumor material. The KRAS mutation status of codons 12/13 was determined using a sensitive, qPCR-based assay. Best overall response and progression-free survival time were evaluated in 233 patients. Of these, 42% showed KRAS mutations and in these patients no benefit could be shown of the addition of cetuximab to FOLFOX [12].

In a study reported by Tejpar et al. in patients with metastatic colorectal cancer after failure of irinotecan-based therapy, the efficacy could be improved by escalating the dose of cetuximab in combination with standard-regimen irinotecan (180 mg/m<sup>2</sup> q 2 weeks) compared with standard-dose cetuximab. Archived tissue from 77 of 89 randomized patients was analyzed for KRAS mutation status. Efficacy parameters were determined and compared with the outcome of KRAS mutation analysis. In 45 patients in which the dose of cetuximab was not increased, 19 patients (42%) were KRAS wt, 19 (42%) were KRAS mt, and 7 patients (16%) were non-evaluable. In the escalation arm in 44 patients these figures were 28 (64%), 11 (25%), and 5 (11%), respectively. In patients with KRAS mt there were no responses seen while they were 21.1% in the non-escalation and 46.4% in the escalation arm. These data suggest that patients with

KRAS wt achieve considerable benefit from irinotecan plus cetuximab treatment. Patients with KRAS mt did not profit from irinotecan plus cetuximab treatment and cetuximab dose escalation did not increase responses in these patients [13].

These data indicate that in studies including antibodies against the EGFR, such as cetuximab or panitumumab, the KRAS status is of great importance. Based on these data, the European Medicines Agency (EMA) has restricted the use of anti-EGFR antibodies, such as panitumumab and cetuximab, to patients with metastatic colorectal cancer who express normal KRAS.

Therefore, all patients with metastatic colorectal cancer should be tested for the mutational status of KRAS prior to utilization of EGFR-based antibody therapy. In addition, it is important to convey to patients with tumors containing KRAS mutations that current chemotherapy regimens still remain active in their disease.

## Pancreatic cancer

### Early phase disease

Prognosis of patients with pancreatic cancer is dismal, even after curatively intended resection and therefore the role of gemcitabine as adjuvant chemotherapy was examined in CONKO-001, a prospective, open, multicenter, controlled randomized study. It was designed to evaluate the efficacy and toxicity of gemcitabine after complete (R0 or R1) resection and patients were stratified for R0/R1, nodal tumor involvement and tumor stage. In an intent-to-treat-analysis, 722 patients were randomized to receive either gemcitabine (368 patients) (1g/m<sup>2</sup> d1,8,15 q 4 weeks) for 6 months or observation. There was a significant improvement in median disease-free survival (13.4 vs. 6.9 months,  $P<0.001$ ) for gemcitabine and the estimated disease-free survival at 3 and 5 years was 23.5 and 16.0% in the gemcitabine group vs. 8.5 and 6.5% in the observation arm, respectively. Gemcitabine also significantly improved median overall survival (22.8 vs. 20.2 months,  $P=0.005$ ) and the estimated survival at 3 and 5 years was 36.5 and 21.0% for chemotherapy-treated patients vs. 19.5 and 9.0% for observation, respectively. This study shows that treatment with gemcitabine for 6 months after complete resection significantly increases disease-free and overall survival compared with observation alone [14].

## Gynecological cancer

### Endometrial cancer – Early stage disease

Vaginal brachytherapy was compared with external beam pelvic radiotherapy in patients with intermediate-to-high-risk endometrial cancer in the randomized PORTEC-2 trial.

Study conception was based on the fact that pelvic

external beam radiotherapy reduces the risk of vaginal and pelvic recurrence for stage I endometrial carcinoma, but without resulting in a survival benefit. In the PORTEC-1 trial, the 5-year risk of vaginal and pelvic recurrence for intermediate-to-high-risk patients was 19% without further treatment, compared with 5% after external beam pelvic radiotherapy and most recurrences were located in the upper vagina. The PORTEC-2 trial randomly allocated 427 patients with an intermediate-to-high risk (age > 60 years and stage 1C grade 1-2 or stage 1B grade 3; any age and stage 2A grade 1-2 or grade 3 with < 50% invasion) after surgery (1:1) to external beam pelvic radiotherapy (46 Gy in 23 fractions) or vaginal brachytherapy (21 Gy high-dose rate in 3 fractions, or 30 Gy low-dose rate). After a median follow-up of 34 months, 3-year actuarial rates of vaginal relapse were 0.9% in the brachytherapy arm and 2.0% after external beam radiotherapy ( $P=0.97$ ) but with pelvic relapse rates of 3.6% and 0.7% ( $P=0.03$ ), respectively. Three-year rates of vaginal, pelvic and distant relapse as first failure were 0%, 1.3% and 6.4% in the brachytherapy group, and 1.6%, 0.7% and 6.0% in the external beam group. There were no significant differences in 3-year overall (90.4 vs. 90.8%,  $P=0.55$ ) and relapse-free survival (89.5 vs. 89.1%,  $P=0.38$ ). The authors concluded that vaginal brachytherapy is effective in preventing vaginal recurrence. Despite the slightly but significantly increased pelvic failure rate in the brachytherapy arm, rates of distant metastases, overall and relapse-free survival were similar. Patient-reported quality of life was better after brachytherapy than after external beam radiotherapy and, therefore, brachytherapy should be the treatment of choice for patients with intermediate-to-high-risk endometrial carcinoma [15].

## Urogenital cancer

### Testicular cancer – Early stage disease

Treatment strategies for stage I seminoma testicular cancer have recently been changed, and strict surveillance, retroperitoneal radiotherapy or 1 cycle of carboplatin have been proposed as treatment options in the adjuvant setting.

Three Medical Research Council randomized non-inferiority trials of adjuvant therapy for stage I seminoma looked at the risk of late relapses and the method of detection of relapse in patients treated according to different treatment protocols: 30 Gy dog-leg (DL) vs. para-aortic (PA) irradiation; 30 Gy vs. 20 Gy; or radiotherapy vs. single-dose carboplatin at AUC7. There were no important differences among the treatment protocols in relation to relapse-free survival. A total of 106 patients relapsed after treatment, of whom 4 died of seminoma. Relapse sites differed by treatment with abdominal relapses most common with carboplatin and pelvic relapses most common with PA radiotherapy. Four relapses occurred after 3 years [at 50 (carboplatin), 61, 64 and 91 months (radiotherapy)]; all were cured

by chemotherapy. Based on their findings, Mead et al. concluded that abdominal computer tomography is required for 2 years after carboplatin; late relapses are rare and prolonged follow up after adjuvant treatment seems unnecessary [16].

T. Olivier et al. reported on a large randomized study in 1447 patients with stage I seminoma testicular cancer comparing a single dose of carboplatin (AUC7) on an outpatient basis (573 patients) or radiation therapy given for two or three weeks (904 patients). After five years, the rate of cancer recurrence was comparable in both arms (5% for carboplatin vs. 4% for radiotherapy). After a median follow-up of 6.5 years, patients who received carboplatin were 78% less likely to develop a tumor in the remaining testicle (15 patients after radiotherapy vs. two in the carboplatin arm). One patient in the radiation therapy arm died of seminoma, versus none in the chemotherapy arm. The side effects for both treatments were low, although those in the radiotherapy group reported higher levels of moderate or severe lethargy (24 vs. 7%) four weeks after starting treatment [17].

## Renal cell carcinoma

Everolimus is an oral inhibitor of mTOR, an intracellular kinase that regulates cell proliferation and angiogenesis. Antitumor activity has been shown in a single-arm phase-2 trial in pretreated patients with metastatic renal cell carcinoma with continuous daily therapy and therefore a randomized study was performed in 410 patients with renal cell carcinoma with a clear-cell component progressing on or <6 months after vascular endothelial growth factor receptor-tyrosine kinase inhibitor (VEGFR-TKI) therapy (sorafenib, sunitinib, or both). They were randomized 2:1 to everolimus (10 mg/d PO) or placebo, both with best supportive care after stratification by Memorial Sloan-Kettering Cancer Center (MSKCC) risk criteria and prior VEGFR-TKI therapy (1 vs. 2). Preliminary data showed that progression-free survival was longer in the treatment group (4.0 vs. 1.9 months, HR 0.30, 95%CI 0.22-0.40,  $P < 0.0001$ ). Most common side effects (all grades/grade 3-4) were stomatitis (everolimus 36/4% vs. placebo 7/0%), anemia (28/7% vs. 15/5%) and asthenia (28/2% vs. 20/4%). Ten percent of patients had adverse events leading to discontinuation with everolimus vs. 4% with placebo whereas dose reductions were required by 4% vs. <1%, respectively [18].

## Melanoma

### Early stage disease

The role of adjuvant treatment with interferon in patients with melanoma has been a matter of debate. While in the USA, patients at risk are treated with adjuvant interferon, in Europe this is not common practice. The introduction of the sentinel node procedure made it possible to

differentiate patients more clearly. In a retrospective study, J. Cormier et al. assessed the impact of interferon therapy on the survival of 486 patients who underwent surgery for metastatic lymph node cutaneous stage III melanoma. Outcomes were compared between the 141 (29%) patients who also received adjuvant treatment with interferon and those who had surgery alone. The primary outcome was recurrence-free survival; the secondary outcome was overall survival. For the whole cohort, the median recurrence-free survival was 2.27 years and the estimated 5-year recurrence-free survival was 41%. The median overall survival was 5.6 years and the estimated 5-year overall survival was 53%. Multivariate analysis demonstrated that interferon was the only independent predictor for recurrence-free survival in patients with stage IIIA disease (HR 0.4,  $P = 0.02$ ). However, interferon had no effect on overall survival or on patients with more advanced disease.

## Supportive care

### Side effects of targeted therapies

Molecularly targeted therapies hold great promise in cancer treatment but many of these therapies are presenting new complications and side effects that differ from those typically observed with traditional cytotoxic chemotherapy. They were addressed in an educational session chaired by J. M. Brell that focused on six agents recently approved by the US Food and Drug Administration (FDA) for the treatment of various malignancies: bevacizumab, sorafenib, temsirolimus, lapatinib, sunitinib, and dasatinib.

Some of the side effects observed with these drugs such as diarrhea or skin and nail changes mirror the responses patients typically exhibit during traditional chemotherapy regimens. However, some are totally new such as interstitial-like lung disease, pleural effusions, increases in pancreatic enzymes and an elevation of triglycerides and are among the unique symptoms that are linked with certain molecularly targeted therapies. In addition, common side effects associated with chemotherapy such as nausea, vomiting, and decreased white blood cell and platelet counts are notably absent with these new agents, unless they are combined with chemotherapy.

The pathophysiology of these toxicities can either be related directly to the inhibition of the target by the drug or may simply be an off-target incidental effect. The mechanisms of some side effects, such as hypertension, are better understood but many of the theories about the mechanisms these drugs employ in attacking their targets are still in the formative stages.

A unique set of cardiovascular side effects and clinically significant toxicities may occur with targeted therapies such as hypertension, proteinuria, coronary syndromes, left ventricle dysfunction, and QTc interval prolongation. These side effects are of increasing

importance in an aging cancer population exhibiting heightened levels of cardiovascular co-morbidities. Therefore oncologists should thoroughly assess patients' pre-existing conditions, such as hypertension and chronic obstructive pulmonary disease, before incorporating these drugs into anticancer treatment.

### Caution in prescribing erythropoiesis-stimulating agents

It is important that clinicians also understand the full mechanism of action of erythropoiesis-stimulating agents (ESAs) and prescribe them only for symptomatic patients. ESAs have been shown to decrease the need for blood transfusion in patients with anemia who are undergoing chemotherapy for non-myeloid malignancies. These agents were also approved to relieve fatigue for patients receiving chemotherapy, but an improvement in quality of life is not associated with their use. ESAs are not indicated for active malignant disease without concurrent chemotherapy or radiotherapy. Practice guidelines promulgated by ASCO and the American Society of Hematology call for treatment when hemoglobin is 10 g/dL or less.

Analysis of recent clinical trials has identified adverse outcomes associated with their use: treatment with ESAs is associated with higher mortality, reduction in progression-free survival, and/or other adverse outcomes. In addition, several trials were halted after interim analysis because of increased adverse events in the treatment group.

Worse outcomes in clinical trials have been associated with rapid increases in hemoglobin levels and with attainment of high-target hemoglobins. Possible increases in fatal thromboembolic events also have been seen. A Cochrane meta-analysis of 57 randomized controlled trials using either epoetin alfa or darbepoetin alfa that included 9353 patients found a lower risk of transfusion, increased relative risk of thromboembolic events, and a possibility that survival may be decreased. ESAs shortened overall survival and/or time to progression when dosed to a target hemoglobin level of 12 g/dL or more for patients with breast, head and neck, lymphoid, and cervical cancers. Studies to elucidate the biologic mechanisms underlying these results are ongoing. Evidence is emerging that tumor cells may use the erythropoietin system for growth and increased survival in certain tumor types.

The FDA has issued a safety advisory regarding the use of ESAs and has changed the labeling to include a "black box" warning which states:

- ESAs shortened overall survival and/or time to progression when dosed to target hemoglobin of 12 g/dL or greater for patients with breast, head and neck, lymphoid, and cervical cancers.
- The risks of shortened overall survival and time to progression have not been excluded when ESAs are dosed to target a hemoglobin of less than 12 g/dL.
- To minimize these risks, as well as the risk of serious

cardio- and thrombovascular events, use the lowest dose needed to avoid red blood cell transfusions.

- Use only for the treatment of anemia as a result of concomitant myelosuppressive chemotherapy.
- Discontinue following the completion of a chemotherapy course.

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