ONCOLOGY PRO
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2011 European Multidisciplinary Cancer Congress

23-27 September, 2011
Stockholm, Sweden

SUMMARY

2011 marked the advent of the European Multidisciplinary Cancer Congress (EMCC), created from a merger of the 16th European CanCer Organisation (ECCO), 36th European Society for Medical Oncology (ESMO), and 30th European Society for Therapeutic Radiology and Oncology (ESTRO) Congresses. The 2011 EMCC capitalized upon the success of the first joint ECCO-ESMO Congress two years ago and the strong collaboration among European cancer organizations, including contributions from European Society of Surgical Oncology (ESSO), European Association for Cancer Research (EACR), European Oncology Nursing Society (EONS) and European Society for Pediatric Oncology (SIOPE). The EMCC emerged as a truly pan-European cancer community effort.

Held in Stockholm, Sweden, 23 - 27 September 2011, EMCC drew 12,768 delegates, 1683 exhibitors and 423 guests. Congress coverage was provided by 380 media representatives who reported on the presentations of 694 invited speakers, in all totaling 15,931 participants. Delegates came from 116 countries around the world, making this a truly global event. The USA was represented by 1144 delegates with 1065 representatives from the UK, followed closely by approximately 1000 attendees from both Germany and France. Over 1000 delegates travelled from as far as China and Japan with Australia also represented, all joining this unique platform to exchange ideas intended to shape oncology care and practice. Twitter provided a new dimension, with 3,192 "tweets" posted during the congress using the hashtag #emcc2011.

INTRODUCTION

The multidisciplinary focus of the Congress expressed in the tagline -"Integrating basic and translational science, surgery, radiotherapy, medical oncology and care"- was reflected in the scientific program developed by Co-Scientific Chairs Jean Charles Soria (ESMO) and Anne-Lise Børresen-Dale (ECCO), Vice Chairs Jean Bourhis and Peter Naredi, and Education Chairs Dirk

Schrijvers (ECCO) and Rolf Stahel (ESMO), together with the help and expertise of the Scientific Committee. The program consisted of 33 individual disciplines and offered 285 sessions, including four Presidential Sessions and 25 Proffered Paper Sessions, reporting state of the art developments in research, treatment and patient care. The Congress is grateful to the 694 cancer specialists who shared their ideas and latest data in over 2000 abstracts and 34 Late Breaking Abstracts, many containing practice-changing information, and all with thought provoking and inspiring analyses.

Fig.1. Chairpersons at the Opening session of 2011 EMCC

Participants in the landmark EMCC were welcomed by Michael Baumann (ECCO President, Congress Chair) and David Kerr (ESMO President, ECCO Board Member) with the promise of a productive conference which would set the stage for successive congress collaborations.

Fig.2. Attendees visiting the ESMO dedicated booth

Besides active participation in creation of the complex educational and scientific Congress program tracks, ESMO enhanced its visibility at the Congress with a dedicated booth, Members Launch, Award ceremony, and educational session with new guidelines presentation.

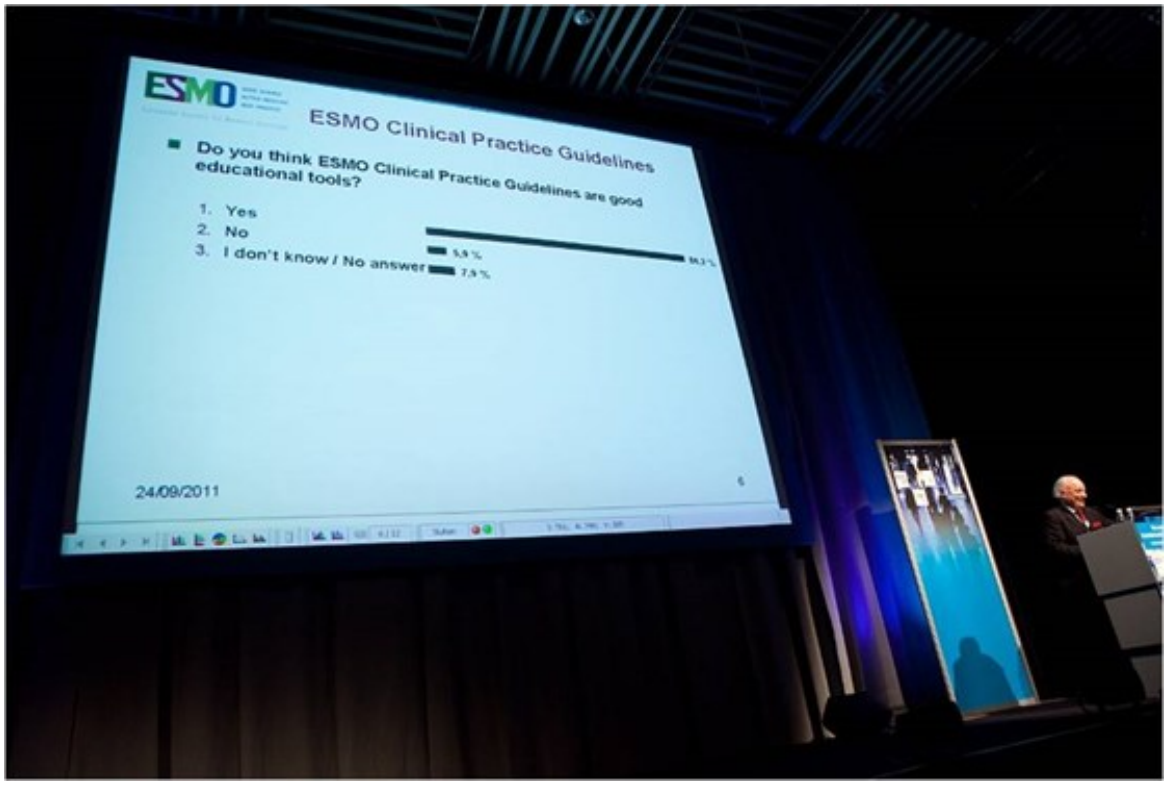

Fig.3. A detail from the ESMO Guidelines Interactive Session

This report will attempt a small overview of the expert scientific presentations made during the congress by medical oncologists, radiotherapists, surgical oncologists, basic scientists, oncology nurses, palliative care professionals and other clinicians involved in cancer diagnosis and treatment.

BASIC SCIENCE

Small-molecule inhibition of Ras oncoprotein

Fang *et al*. reported on a novel approach to target Ras, the major driver of oncogenesis in many tumor types. The group identified and characterized several small-molecules that bind a site next to the SOS interface of the Ras protein, preventing the nucleotide exchange that activates Ras oncoprotein. They screened fragments by Nuclear Magnetic Resonance (NMR) and characterized the candidates by NMR and X-ray crystallography. The subsequent effect upon Ras activation and signaling was described by biochemical and cellular assays. They tested a subset of the Ras-binding molecules and demonstrated that it blocks assembly of the Ras SOS complex by steric hindrance, thus inhibiting nucleotide exchange and preventing Ras activation and signaling. The biological activity of these compounds is being tested further in Ras mutant tumors that are dependent upon nucleotide exchange. (Fang, Abstract LBA 15)

Practice point and future research opportunities

A functionally significant binding pocket plus a compound that competitively inhibits nucleotide exchange and Ras activation have been described, providing new intervention targets for Ras driven oncogenesis

Novel mutations in SF3B1 implicate abnormalities of mRNA splicing, a pathway not previously known as a target in the pathogenesis of myelodysplastic syndromesChemotherapy during pregnancy: Large study on cognitive and cardiac outcome in children with prenatal exposure to chemotherapy

Mutations in SF3B1, a gene coding for a key protein in mRNA processing, have been identified and shown to associate with the presence of ring sideroblasts, a morphological feature indicative of myelodysplastic syndromes (MDS). Papaemmanuil et al. searched for somatically acquired point mutations across all protein-coding exons in the genomes of nine MDS patients by massively parallel sequencing and then identified these recurrent mutations in the SF3B1 gene in 619 patients. They further characterized the prevalence of these mutations by re-sequencing samples of 2087 patients

with MDS, primary cancers and cancer cell lines; SF381 was found to be mutated in 28.1% of MDS patients, 19.3 % of patients with acute myeloid leukaemia and 5.3% of patients with myeloproliferative neoplasms. Similar genetic mutations were also seen in 1% to 5% of other tumor types examined, including breast cancer, multiple myeloma and renal cancer. Mutated SF381 associated with the presence of ring sideroblasts in the bone marrow (P<0.001), which are abnormal red blood cell precursor cells that have a ring of iron-laden mitochondria around the nucleus. Of 123 MDS patients, 34 had the SF3B1 mutation; by multivariate analysis, mutated SF3B1 independently associated with improved overall survival (P=0.028) and a lower risk of leukemic progression (P=0.048). Mutations in SF381 are detectable in blood samples and offer a simple and quick method for MDS diagnosis, which usually is made by invasive bone marrow biopsy that detects ring siderobsts. Mutations in this gene may be predictive for patient outcome and useful in identifying patients with a good prognosis who may benefit from less aggressive treatment. This presentation coincided with the simultaneous publication of a paper about the research in the New England Journal of Medicine. (Papaemmanuil, Abstract LBA 11)

Practice point and future research opportunities

The close association between novel somatic acquired mutations in SF3B1 and ring sideroblasts makes this the first gene to be strongly associated with a specific morphological feature in myelodysplastic syndromes. This molecular lesion has relevant clinical significance, as it is independently associated with a favorable clinical outcome. Besides confirming relevance of this pathway in myelodysplastic syndromes and probably some other epithelial tumors, this discovery may simplify diagnosis and aid in identifying patients who will benefit from optimized treatment.

DNA vaccination against ALK in NSCLC

Voena *et al*. built upon their previous results demonstrating Anaplastic Lymphoma Kinase (ALK) to be an effective oncoantigen for ALK positive lymphoma vaccination to test whether it could also represent a feasible target for vaccination in ALK positive non-small cell lung cancer (NSCLC). They generated transgenic mice ectopically expressing human TFG- or EML4-ALK gene products, that developed multifocal adenocarcinomas similar to human tumors approximately one month after birth. The mice were then vaccinated with 50 ug of either plasmid DNA or mock plasmid DNA. The immune response was determined after 30 days showing a strong ALK specific CTL response was elicited in vaccinated mice that overcame immune tolerance to the ALK protein. Vaccinated mice showed a reduced number of neoplastic foci and a smaller tumor mass compared to controls by NMR measurement. Vaccinated mice showed a significantly increased number of T lymphocytes infiltrating both the tumors and the spared lung. It was also observed that specific CTL activity against ALK and the ability to limit the tumor expansion decreased proportionally to the age of the mice. (Voena, Abstract 1007)

Practice point and future research opportunities

This ALK+ transgenic mouse model allowed demonstration of the role of ALK in lung tumor pathogenesis and offered an opportunity to test the immune response to innovative treatment strategies. ALK-DNA vaccination elicited a specific cytotoxic response and delayed tumour progression, suggesting that DNA vaccination combined with standard chemotherapy or specific ALK inhibitor treatment may be an alternative in ALK positive NSCLC for preventing tumor relapse or metastasis.

Prognostic factors in patients with metastatic renal cell carcinoma treated with sunitinib

Motzer *et al*. conducted a retrospective analysis of pooled data from six clinical trials testing single agent sunitinib treatment in 1059 patients with metastatic renal cell carcinoma (mRCC) to determine prognostic factors for progression free-survival (PFS), overall survival (OS) and long term survival, defined as survival of thirty or more months. Baseline variables were analyzed for prognostic significance using a Cox proportional hazards model, in univariate and then multivariate analyses using a stepwise algorithm. The same independent predictors were identified for PFS and OS, with the presence/absence of bone metastases, baseline hemoglobin and corrected calcium being the most significant (all $P<0.0001$), which also associated with Memorial Sloan-Kettering Cancer Center (MSKCC) ($P<0.0001$) prognostic criteria (Motzer, 2002). Favorable risk factors by MSKCC criteria were seen in the baseline data of 70% of patients with long term survival compared with 31% of non-long-term survivors. In the non-long-term survivor group, 42% had intermediate and 5% had poor risk features compared with 28% and 0%, respectively, of long-term survivors. Additional predictors of ethnic origin and the presence of bone metastasis were identified; sunitinib benefit favored Caucasian patients who demonstrated increased OS of 10.5 versus 6.6 months in Asian patients ($P=0.0002$). Patients with bone metastasis had OS of 16.1 compared to 27.8 months in patients without bone metastasis ($P=0.0001$). Long term survival with continued sunitinib use was observed in 215 (20%) patients. A separate analysis of their baseline characteristics identified the same predictive indicators of ethnicity, normalized calcium, no prior cytokine use and the absence of bone metastasis. Even within long term survivors, patients with bone metastasis fared less favorably than those without, demonstrating long term survival of 42.7 compared to 54.5, respectively ($P=0.0061$). (Motzer, Abstract 1006)

Practice point and future research opportunities

Previously reported MSKCC clinical risk factors were validated and shown to be predictive of shorter progression-free survival; favorable MSKCC risk status is associated with higher likelihood of achieving long term survival after treatment with sunitinib. The same predictors were independently

identified for overall and progression free-survival, supporting the utility of progression free-survival as a surrogate endpoint. Further exploration of tumor-specific biology is needed.

BREAST CANCER

Everolimus overcomes resistance to hormonal therapy in postmenopausal women with advanced breast cancer

Baselga reported findings from the BOLERO-2 phase III trial that evaluated whether the addition of the mTOR (mammalian Target Of Rapamycin) inhibitor everolimus to exemestane could improve response to aromatase inhibitors. The trial was conducted in 24 countries and enrolled 724 postmenopausal women with estrogen receptor (ER)-positive, HER2-negative disease who were refractory to letrozole or anastrozole. Following randomization, 485 patients received everolimus plus exemestane and 239 received sole exemestane. BOLERO-2 was halted prematurely after a preplanned analysis demonstrated median 6.9 months PFS for combination treatment, compared to 2.8 months with exemestane alone ($P<0.0001$) by local investigator assessment. Progression-free survival by central assessment also significantly favored combination treatment, with these patients experiencing a median PFS of 10.6 versus 4.1 months for the exemestane group ($P<0.0001$); both analyses met the pre-specified criteria for significance. Response rates were 9.5% and 0.4% with combination and exemestane, respectively ($P<0.0001$). The improvement was consistent across all subgroups including the number of prior therapies, presence of visceral disease, bone metastases, and prior use of chemotherapy. Overall survival data were not yet mature. Numerically, more grade 3 to 4 side effects occurred with combination treatment than in the exemestane group; commonly reported adverse events were consistent with those reported for everolimus (stomatitis, anemia, dyspnea, hyperglycemia, fatigue and pneumonitis). (Baselga, Abstract LBA 9)

Practice point and future research opportunities

Although hormonal therapy is a mainstay of treatment for estrogen receptor-positive breast cancer, nearly all patients who develop metastatic disease become resistant to hormonal therapy. The rationale for combination therapy with everolimus plus exemestane in this trial rests on the crosstalk between estrogen receptor and mTOR signalling. Everolimus is the first agent to enhance the clinical benefit of hormonal therapy in patients refractory to aromatase inhibitors. Combination therapy significantly improved response rate and more than doubled the time to disease progression over exemestane alone in patients highly resistant to hormonal therapy. The improvement was consistent across all subgroups, including number of prior therapies, presence of visceral metastases, bone metastases, and prior use of chemotherapy. Overall survival data will be presented upon maturity and an analysis of the effect of everolimus on bone metabolism is underway. This treatment represents a

paradigm shift in the treatment of breast cancer, and a world-wide application is being filed for licensing of everolimus for the treatment of estrogen receptor-positive advanced breast cancer.

Reversal of tamoxifen resistance by addition of mTOR inhibitor sirolimus

Findings from Bhattacharyya et al. suggested that tamoxifen resistance may be overcome by co-treatment with sirolimus, an mTOR (mammalian Target Of Rapamycin) inhibitor with activity against AKT kinase. AKT kinase is a key molecule in oncogenesis that antagonizes tamoxifen binding to the estrogen receptor and is expressed at high levels in tamoxifen resistance. This two-part study enrolled 400 patients with metastatic breast cancer who were estrogen receptor/progesterone receptor (ER/PgR) positive. Part 1 of the study enrolled 200 patients who could not afford aromatase inhibitors and were randomized to receive tamoxifen or tamoxifen plus sirolimus. Part 2 included 200 patients who had failed treatment with an aromatase inhibitor and/or tamoxifen and were randomized to receive sirolimus/tamoxifen combination. Patients in part 1 demonstrated a response rate of 36% with tamoxifen only and 68% with tamoxifen plus sirolimus. Time to progression was 9 and 16 months with sole tamoxifen and combination, respectively. In part 2, the response rates were 4% and 40%, with time to progression of 3 and 11 months in patients receiving tamoxifen alone and tamoxifen plus sirolimus, respectively. (Bhattacharyya, Abstract LBA 16)

Practice point and future research opportunities

Combination treatment with tamoxifen and sirolimus could offer an alternative to treatment with aromatase inhibitors in patients with ER/PgR positive metastatic breast cancer and also restore response in patients with hormone receptor positive tumors and acquired tamoxifen resistance.

Synchronous chemoradiation can reduce local recurrence in early stage breast cancer

Fernando reported long term follow-up results at median 8.8 years of the SECRAB trial, which found a 35% risk reduction of local recurrence following treatment of early breast cancer in women who received synchronous, wherein radiation was delivered during or in-between chemotherapy cycles, rather than sequential chemoradiation. The study enrolled 2296 women who had completely excised early breast cancer that required adjuvant chemotherapy and radiotherapy and were fit for treatment. No difference between arms was seen in PFS or OS; PFS was 79% with synchronous therapy and 78% with sequential therapy and OS was 83% versus 82%, synchronous and sequential, respectively. However, the five-year incidence of local recurrence was 2.8% with synchronous therapy and 5.1% among women who received sequential administration of adjuvant chemotherapy followed by radiotherapy (P=0.19). Subgroup analysis of patients with local recurrence revealed a statistically significant advantage in favor of synchronous therapy (P=0.03) which was seen across all treatment and biological subgroups, including tumor grade and size, lymph node status, vascular

invasion and excision margin. Primary analysis showed no difference in the recurrence rate between the two groups, 5.4% with synchronous therapy versus 7.4% with sequential therapy (P=0.19); however, upon further analysis it was found that 80% of regional recurrences were outside the radiation field. Synchronous chemoradiation had minimal adverse side-effects but did show an increased risk for moderate or severe radiation-associated skin toxicity; 24% of synchronous patients compared to 15% of patients in the sequential arm experienced skin reactions, and severe reactions were seen in 4% of patients. However, 96% of cases resolved within four to six weeks post therapy. Quality of life data showed no difference between the two arms, however synchronous treatment was shorter, allowing women to resume normal family and work routines sooner, making it a popular therapy among participants. (Fernando, Best Abstract 2)

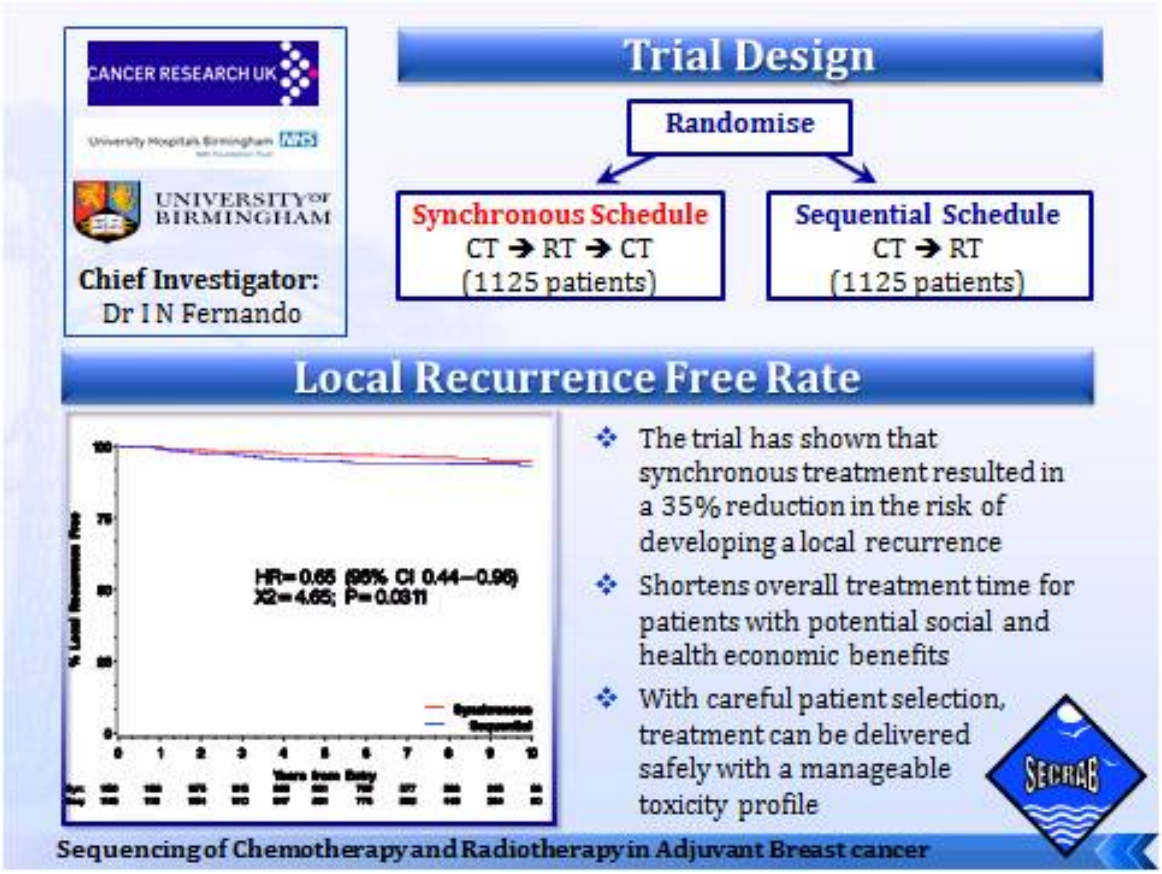

Fig.4. Synchronous chemotherapy and radiotherapy resulted in reduced risk for developing a local recurrence (courtesy of Dr Indrajit Fernando)

Practice point and future research possibilities

This trial raises the important issue of how radiotherapy and chemotherapy after surgery should be sequenced or integrated to obtain the best outcome in the treatment of early breast cancer. The largest study to investigate synchronous chemo-radiation produced firm evidence that the risk of loco-regional recurrences could be reduced by applying radiotherapy simultaneously with chemotherapy.

Longer follow-up is necessary to assess potential late side-effects and the benefits versus the risk of this approach.

Patients' baseline characteristics after a successful MINDACT trial accrual

The MINDACT (Microarray in Node Negative and 1 to 3 Positive Lymph Node Disease May Avoid ChemoTherapy) trial seeks to bring personalized medicine forward by comparing the clinical utility of genomic profiling with standard clinicopathological criteria for risk assessment and adjuvant chemotherapy use in breast cancer therapy. Piccart *et al.* successfully completed patient accrual in 104 sites in nine European countries for the largest randomized prospective trial ever designed to determine risk factors based on genomic profile, which will allow optimal selection of breast cancer candidates for adjuvant chemotherapy. As of the presentation date, 11300 patients had registered, genomic testing was done in 7491 and 6527 (58%) patients suitable for enrollment. The patients baseline characteristics were presented: 33% of the trial population is less than 50 years of age, 80% are node negative, 71% have lymph node status verified by sentinel node biopsy, 63% had breast conservation surgery, 72% have tumors approximately 2 cm, 88% are hormone receptor positive (estrogen or progesterone receptor or both), 11% are HER2 positive, and 9% of patients have triple negative breast cancer. The study accrual was completed one month after the presentation of baseline characteristics. (Piccart, Abstract LBA10)

Practice point and future research possibilities

MINDACT is the largest European randomized prospective trial evaluating the clinical value of a gene expression profile for risk assessment and adjuvant chemotherapy prescription in breast cancer patients. Accrual has been successfully completed and the trial's complex logistics, including real-time collection of frozen tumor tissue, were proven feasible in a multinational, multicentric setting. Data from this large, well planned trial should provide additional information in determining optimal therapies for several subsets of breast cancer patients and identify patients who will benefit from personalized treatment strategies.

CANCER IN OLDER PATIENTS

Standard thoracic radiotherapy with or without concurrent daily low-dose carboplatin in elderly patients with locally advanced NSCLC

Atagi *et al.* presented results on behalf of the Japan Clinical Oncology Group (JCOG) from the first trial to demonstrate significant clinical benefit in patients over 70 years with unresectable stage III NSCLC from treatment consisting of thoracic radiotherapy plus daily low-dose carboplatin compared

to radiotherapy alone. Following the second-planned interim analysis, the trial was halted upon recommendation from the JCOG Data and Safety Monitoring Committee due to the difference in OS which strongly favored the combination treatment arm. Overall survival was 22.4 months in the combination arm and 16.9 in the radiotherapy arm (P=0.0179). Median PFS was 8.9 and 6.8 months with combination therapy and radiotherapy, respectively (P=0.0044). The objective response rates were 51.5% and 44.9% in 99 patients treated with radiotherapy plus low-dose of daily carboplatin and in 98 patients treated with radiotherapy, respectively. Stable disease was achieved in 34 (34.3%) patients who received combination treatment compared to 37 (37.8%) patients treated with radiotherapy only. Disease progression also favored combination treatment, with 8 (8.1%) and 13 (13.3%) patients receiving combination therapy and radiotherapy progressing to disease, respectively. Major grade 3/4 toxicities associated with combination treatment and radiotherapy were febrile neutropenia (2.1% versus 0%), and infection (14.9% versus 4.1 %), respectively. Adverse events resulting in death were reported in 3 patients in the combination group and in 4 patients treated with radiotherapy. (Atagi, Abstract 4001)

Practice point and future research possibilities

This is a first trial which demonstrated that concurrent daily low-dose carboplatin and thoracic radiotherapy provides clinically significant benefit in elderly patients with locally advanced NSCLC, and this combined modality could be considered as a standard treatment in this population.

Clinical outcomes after stereotactic radiotherapy in stage I NSCLC patients 80 years and older

With the aim of shifting the primary focus of treatment to curative from simply avoiding toxicity in patients 80 years and older, Testolin *et al*. conducted this study to determine the tolerance and outcomes following stereotactic body radiation therapy (SBRT) in this age group. They used a real-time tumor tracking technique to determine the local tumor control rate, and treatment related toxicity after SBRT in 25 octogenarian patients with stage I NSCLC that was considered inoperable. All patients were treated using a CyberKinife System with Synchrony® Respiratory Tracking System device and followed-up for a median of 15 months. At that time, five patients demonstrated local recurrence; one local recurrence was in a patient who received a biologically effective dose (BED) and 4 recurrences were seen in patients receiving a lower dose. The overall actuarial local progression free probability (LPFP) at 2 years was 63.6%; LPFP for patients receiving BED 100Gy10 was 42.8% and 90.9% in patients who were treated with BED >100Gy10. Overall and cancer specific survival at 2 years were 66.5% and 75%, respectively. Octogenarian patients tolerated the treatment well, with only 7 (28%) patients reporting fatigue, 2 (8%) patients had local chest wall pain, 1 (4%) patient suffered rib fracture, and symptoms of increased dyspnoea were reported by 2 (8%) patients. Asymptomatic radiation induced lung fibrosis was detected in 9 (36%) patients but no clinically symptomatic pneumonitis was observed. Six patients died during the 40 month follow-up, 4 from

disease progression, which occurred at 21, 23, 24 and 37 months after SBRT and 2 patients from intercurrent disease between 6 and 13 months. (Testolin, Abstract 4002)

Practice point and future research opportunities

Stereotactic body radiation therapy appears to be safe and minimally invasive modality for treatment of patients 80 years and older with medically inoperable stage I NSCLC. Even those with comorbidities, tolerated treatmentwell and biological effective dose >100Gy achieved high local control with minimal toxicity. Longer follow-up is needed to establish the probability of local failure and overall toxicity profile.

Age specific competing mortality in breast cancer patients

Women diagnosed with breast cancer later, as opposed to earlier in life, may experience poorer outcome due to different treatment based upon perceptions that the elderly are not fit enough for aggressive therapies. Markopoulos *et al.* analyzed data from the TEAM trial wherein 9766 women with hormone receptor positive tumors were randomized to receive either daily exemestane for 5 years or daily tamoxifen for 2.5 to 3 years, followed by daily exemestane for an additional 2 to 2.5 years. Upon analysis at 5 years, no difference in outcome between either arm was seen, as reported in *Lancet*. Given the equivalent results, patients could then be stratified by age at diagnosis into groups of younger than 65 years, ages 65 to 74 and 75 years and older. At a follow-up of median 5.1 years, 50% had node negative disease, 68% had received radiotherapy and 36% had received chemotherapy. Data analysis using a Cox Proportional Hazard Model showed the risk of dying from both breast cancer and non breast cancer-related causes increased with age ($P<0.001$). However, when data were further analyzed by statistical methods accounting for the risk of competing causes of death, findings emerged that showed the risk of dying from breast cancer was greater for patients diagnosed at older age. When hazard ratios (HR) were adjusted for country, histological grade, tumor size, nodal status, estrogen receptor, progesterone receptor, type of surgery, radiotherapy and chemotherapy, the risks of dying overall were HR 1.0 (reference), 1.22 and 1.50 while the risks of breast cancer mortality were HR 1.0 (reference), 2.46 and 6.57 in the three increasing age groups, respectively ($P<0.001$). It was also observed that radiotherapy and chemotherapy were administered less frequently with increasing patient age and that deaths from breast cancer were higher in older compared to younger patients who had similar tumor characteristics. Taken together, the data suggested that older breast cancer patients were being under-treated. (Markopoulus, Abstract 5015)

Practice point and future research opportunities

Although the risk of mortality from breast cancer and other causes both rose with increasing age, deaths from breast cancer increased more sharply in older patients, even in groups of women with

similar tumor characteristics but different ages, suggesting the possibility of suboptimal treatment. Elderly patients are often considered unfit for state-of-the-art cancer care, but health status rather than age per se should be the basis when deciding to provide standard cancer treatments. It is needed to improve the breast cancer prognostic classification in the elderly, developing specific tools or implementing those developed for younger patients, in order not to deprive those who might derive a real benefit from additional treatment including chemotherapy.

CENTRAL NERVOUS SYSTEM

Everolimus in subependymal giant cell astrocytomas associated with tuberous sclerosis complex

Everolimus was tested by Bebin *et al*. for treating the genetic disorder Tuberous Sclerosis Complex (TSC), which is characterized by constitutive activation of the mammalian Target Of Rapamycin (mTOR), and results in the growth of benign tumors in several organs including the brain, where the presence of subependymal giant cell astrocytomas (SEGA) can cause hydrocephalus and require surgery. This double-blind, placebo controlled phase III trial enrolled 117 patients definitively diagnosed with TSC who had SEGA of 1 cm or larger, and documented serial SEGA growth. Patients were randomized 2 to 1 to receive oral everolimus or placebo until SEGA progression or unacceptable toxicity; randomization was stratified by concomitant use of antiepileptic drugs. Response was monitored by brain magnetic resonance imaging (MRI), kidney MRI or CT-scan, and 24-hour video electroencephalogram (EEG) at baseline and other timepoints. Patients in the placebo group were offered everolimus upon SEGA progression. Everolimus was given to 78 patients for a median of 41.93 weeks (range, 24.0-78.9) and 39 patients received placebo for median 36.14 weeks (range 13.9-79.7 weeks). The primary trial endpoint of SEGA response rate of 50% or greater reduction was achieved by 35% of patients receiving everolimus compared to 0% of placebo patients ($P<0.0001$). Seizure reduction, as recorded by video EEG, was similar in both groups. No everolimus treated patients progressed, while 15% of placebo treated patients experienced progression. Response rates were higher with everolimus: 41.7 % of everolimus compared to 10.5% of placebo treated patients had a skin lesion response and 53.3% compared to 0% response rates were seen for angiomyolipomas in the everolimus and placebo treated patients, respectively. No new safety signals were raised for everolimus treatment, and no patients discontinued due to adverse events. (Bebin, Abstract LBA 4)

Practice point and future research opportunities

Tuberous sclerosis complex is a devastating disease affecting multiple organ systems with limited treatment options available. This phase III trial is the first placebo-controlled study to demonstrate

that everolimus is an effective and safe pharmacotherapeutic option to reduce subependymal giant cell astrocytomas volume and improve other clinical manifestations of tuberous sclerosis complex, including renal angiomyolipomas and skin lesions.

Clinical and molecular profile exploratory subset analysis of study comparing standard adjuvant temozolomide with a dose-dense schedule for glioblastoma

Although the RTOG 0525 phase III trial reported earlier this year did not show an advantage for dose dense temozolomide over standard temozolomide treatment of patients with glioblastoma, upon extensive *post hoc* subset analyses, Mehta *et al.* reported two subsets that demonstrated benefit; subset analyses were performed on data from patients who had received either dose dense or standard temozolomide and had an appropriate sized tissue sample for prospective analysis of the MGMT (O6-methylguanine-DNA methyltransferase) gene. Data from all randomized patients and over eleven subgroups were reviewed. No significant difference was seen for median OS or PFS in all randomized patients or in the intent to treat (ITT) population for dose dense temozolomide. However, MGMT methylation was linked to improved overall survival of 21.2 compared to 14 months (P<0.0001) and PFS of 8.7 compared to 5.7 months, (P<0.0001) in patients receiving dose dense and standard temozolomide, respectively. Dose dense temozolomide showed PFS benefit in two functional subsets; patients with recursive partitioning analysis (RPA) class III experienced PFS of 12.6 and 6.2 months (P=0.03) and the neurological dysfunction = minor subset of patients had PFS of 7.1 compared to 5.4 months (P=0.01) with dose dense and standard temozolomide, respectively. In the RPA III subset, progression was delayed with dose dense treatment but after progression patients died more quickly than those who received standard temozolomide. A similar pattern was observed in the subgroup with minor neurological dysfunction. (Mehta, Abstract LBA 18)

Practice point and future research opportunities

This study did not demonstrate improved overall survival for dose dense temozolomide in any subgroup, but on post-hoc exploratory analysis, progression-free survival was signicantly increased in two patient subgroups, including those with the neurological dysfunction. These data generate the testable hypothesis that intensive treatment may selectively improve disease control in some subsets, but the lack of a survival advantage still limits the value of this observation. Interpretation of this should be considered carefully due to small sample size, the process of multiple observations, and other confounders.

DIAGNOSTIC/BIOMARKERS

Evaluation of plasma VEGFA and VEGFR2 as potential predictive pan-tumor biomarkers for bevacizumab

Van Cutsem *et al.* reported on a retrospective analysis that evaluated the utility of baseline levels of several angiogenic markers as predictors for clinical outcome using AVITA phase III data, wherein 607 patients with metastatic pancreatic cancer were randomized to receive either bevacizumab or placebo until disease progression. The AVITA primary endpoint of OS was not met, but significant improvement in PFS was demonstrated (HR 0.74). Plasma samples from 225 AVITA participants were collected at baseline, cycle 2, and at time of disease progression for analysis of 4 biomarkers, including VEGFA and VEGFR2, using a novel multiplex ELISA assay; SearchLight® was used for analysis of ten other angiogenic markers. Higher baseline levels of plasma (p)VEGFA was associated with improved outcome in patients treated with bevacizumab compared to placebo, respectively in term of PFS (P=0.06) and OS (P=0.03). Association between baseline pVEGFR2 levels was seen only with OS in bevacizumab and placebo treated patients, respectively (P=0.06). No association was seen between pVEGFA and pVEGFR2, suggesting that they are independent biomarkers for outcome of bevacizumab treatment of metastatic pancreatic cancer. No correlation with outcome was found for other biomarkers analysed. (Van Cutsem, Abstract 803)

Practice point and future research opportunities

Circulating factors involved in tumour angiogenesis might influence cancer therapy with antiangiogenics. In this retrospective analysis, high plasma levels of VEGFA and VEGFR2 were identified as promising biomarker candidates for predicting progression-free survival and overall survival with bevacizumab in patients with metastatic pancreatic cancer. These data confirm the potential predictive value of pVEGFA and pVEGFR2 already observed in metastatic breast cancer. Similar findings for pVEGFA were also seen in advanced gastric cancer. Further evaluation of these biomarker candidates in bevacizumab studies across different cancer types should be considered.

To identify pVEGFA as a potential pan-tumor biomarker for bevacizumab response, Jayson *et al*. used a novel assay that detected shorter, more soluble forms of VEGFA (VEGFA 110, 121, 154 and 189) to retest a total of 1661 residual baseline samples from patients with different metastatic diseases who participated in six trials: metastatic breast cancer (AVADO), colorectal cancer (AVF2107g), non small cell lung cancer (AVAiL), metastatic renal cell carcinoma (AVOREN), metastatic pancreatic cancer (AVITA), and advanced gastric cancer (AVAGAST). This analysis showed pVEGFA to be potentially predictive for improved OS and PFS in the AVITA and AVAGAST trials and for PFS in AVADO, but demonstrated no predictive value for improved outcome following bevacizumab treatment of metastatic colorectal cancer, renal cell carcinoma or non-small cell lung cancer; patients in all three trials with high pVEGFA isoform levels experienced shorter OS than patients with low pVEGFA levels. No interaction was demonstrated between high PEGFA levels and

OS or PFS in the AVF2107g, AVAil and AVOREN trials, respectively. Variations in sample handling may have confounded the results but investigations as to whether VEGFA121 and/or VEGFA110 could be driving predictive value and might be diverse in different tumor types are ongoing. (Jayson, Abstract 804)

Practice point and future research opportunities

The novel assay used in this study showed potential predictive value for high baseline levels of pVEGFA in breast, pancreatic and gastric cancer that correlated with improved progression-free survival and/or overall survival following bevacizumab treatment; however no predictive value was seen for pVEGFA in metastatic colorectal cancer, non small-cell lung cancer or renal cell carcinoma. These differences might have been confounded by variations in sample handling. Further investigation on the role of VEGFA isoforms in different tumor types is underway.

Evaluation of antiangiogenic treatments with DCE-US

The need for functional evaluation of tumors was addressed by Lassau *et al*. who pointed out that new angiogenesis targeting treatments reduce tumor related angiogenesis often without changing tumor volume. Semi-quantitative measures proposed for identification of perfusion parameters that would predict tumor response included the measurement of blood volume by peak intensity, or the area under the curve (AUC), and of blood flow by the time to peak intensity, reflected by the slope of the curve. Prior to antiangiogenic treatment, 539 patients underwent an examination to generate a tumor perfusion curve that was repeated on days 1, 7 14, 30, 60 and bimonthly thereafter. Raw data were analyzed with a mathematical model to evaluate seven parameters characterizing the tumor perfusion curve. The quantification of dynamic contrast-enhanced ultrasonography (DCE-US) raw data was done blinded to the clinical data in determining the association of blood flow parameters to disease free survival and other clinical aspects. Of the 539 trial participants, 432 had metastases from melanoma, gastrointestinal stromal tumors, renal cell carcinomas, breast and colon cancers and 107 patients had primary hepatocellular carcinoma, and had received prior treatment with sorafenib, bevacizumab, sunitinib and imatinib. After a median follow-up of 712 days, variation in blood volume between day 0 and day 30 was significantly related to disease free survival for five parameters ($P<0.05$); of these, a decrease of 40% or more in AUC was determined to be predictive of survival as early as day 30 ($P=0.001$). (Lassau, Abstract 805)

Practice point and future research opportunities

DCE-US could be effective in monitoring antiangiogenic treatments, with a greater than 40% AUC being predictive of survival in patients treated with angiogenesis inhibitors for several tumor types.

DRUG DEVELOPMENT

Smaller, faster phase III trials: New approach for assessing targeted agents

As knowledge of tumor biology increases, cancer trial populations are recognized to contain subsets of patients whose tumors have specific aspects that are not necessarily addressed by traditional large-scale clinical trials. According to Le Deley *et al*. gains in survival can be improved in cancer patients by running smaller and faster clinical trials with less stringent evidence criteria, which also presents the opportunity to test more promising targeted therapies, as opposed to running a single large trial on one or two agents over several years. To test this hypothesis, an evaluation was done of different trial design strategies by simulating a series of two-treatment superiority trials over a 15-year period, varying parameters such as the number of positive trials needed to establish superiority (1 versus 2), the number of trials run over the 15 years and relaxing the level from 0.025 to 0.50. Other factors analyzed included different disease scenarios, median survivals, accrual rates, and distributions of treatment effect. The metrics used included gain in survival rate and the risk for an overall effect of harm. The overall gains were found to be greater using the criterion of one positive trial opposed to two. The key parameter was the level, which afforded greater gains as it was increased from 0.025 to 0.20 but reached a plateau thereafter. The relaxed level allowed use of sample sizes smaller than those usually required for clinical trials, but still gave results that were consistent under different assumed distributions for treatment effect. Although the certainty of the findings would be reduced this could be addressed by the additive effect of conducting more trials. This schema was not meant to replace traditional clinical trials but to offer an alternative for testing new agents for rare cancers and in trials with difficulty in patient accrual, and would be dependent upon acceptance by regulatory agencies. (Le Deley, Abstract 1206)

Practice point and future research opportunities

Advances in the treatment should get out of the laboratory to the patients as soon as possible. The current risk-averse trial design strategy is not always appropriate as patient populations become more and more specific, and hence smaller. The traditional, large-scale randomized clinical trial remains the mainstay but a series of smaller, targeted trials could yield meaningful results where accrual is problematic and for rare diseases. A salient point was made, that the advent of genetic profiling has demonstrated that subsets of patients with tumors having specific mutations within a trial population constitute rare diseases and often skew results. Targeted trials could lead to quicker results, and in the long term, greater treatment outcome gains.

GASTROINTESTINAL - COLORECTAL CANCER

Results from VELOUR study of aflibercept versus placebo in continuation with FOLFIRI in patients with previously treated metastatic colorectal cancer

Findings from prespecified subgroup analyses of data from the Velour trial conducted by Tabernero *et al.* confirmed efficacy results previously presented at the ESMO World Congress on Gastrointestinal Cancer (Barcelona, 2011). This phase III, multinational randomized trial enrolled 1200 patients with metastatic colorectal cancer who had progressed following first-line treatment and showed that patients treated with aflibercept, a fusion protein that blocks all isoforms of VEGF-A and VEGF-B as well as placental growth factor, plus standard FOLFIRI chemotherapy had median OS at a median follow-up of 22.28 months of 13.5 months compared to 12.06 months for patients receiving only FOLFIRI (P=0.0032). Median PFS of 6.9 and 4.67 months was demonstrated with aflibercept and FOLFIRI, respectively, and a 24% reduction in the hazard ratio (P=0.00007). Among 1061 patients evaluable for response, the aflibercept arm had an objective response rate of 19.8% compared with 11.1% in the FOLFIRI arm (P=0.0001). New results from a subgroup analysis showed these results to be consistent across all subgroups, including ECOG performance status, prior bevacizumab exposure, patient demographics and disease characteristics. A significant interaction was observed between aflibercept and patients with metastasis confined to the liver, indicating a greater treatment effect in this group compared with patients with disseminated disease (P=0.0899). Among patients with liver metastases only, mortality was reduced by 35%, compared with an 11% risk reduction among other groups. Progression-free survival followed a similar pattern. Improvement in overall survival seen with aflibercept was consistent, regardless of prior treatment with bevacizumab; patients (30%) with prior bevacizumab exposure had a median OS of 12.5 months with aflibercept and 11.7 months with FOLFIRI. Overall survival in patients without prior exposure was 13.9 months with aflibercept and 12.4 months with FOLFIRI. Progression-free survival in patients previously treated with bevacizumab was 6.7 months with aflibercept and 3.9 with FOLFIRI. Adverse events were similar between groups, and included proteinuria, dysphonia and headache. Anti-VEGF related adverse events including venous and arterial thromboembolic events occurred at similar rates in patients with and without prior bevacizumab, respectively. (Tabernero, Abstract LBA 16)

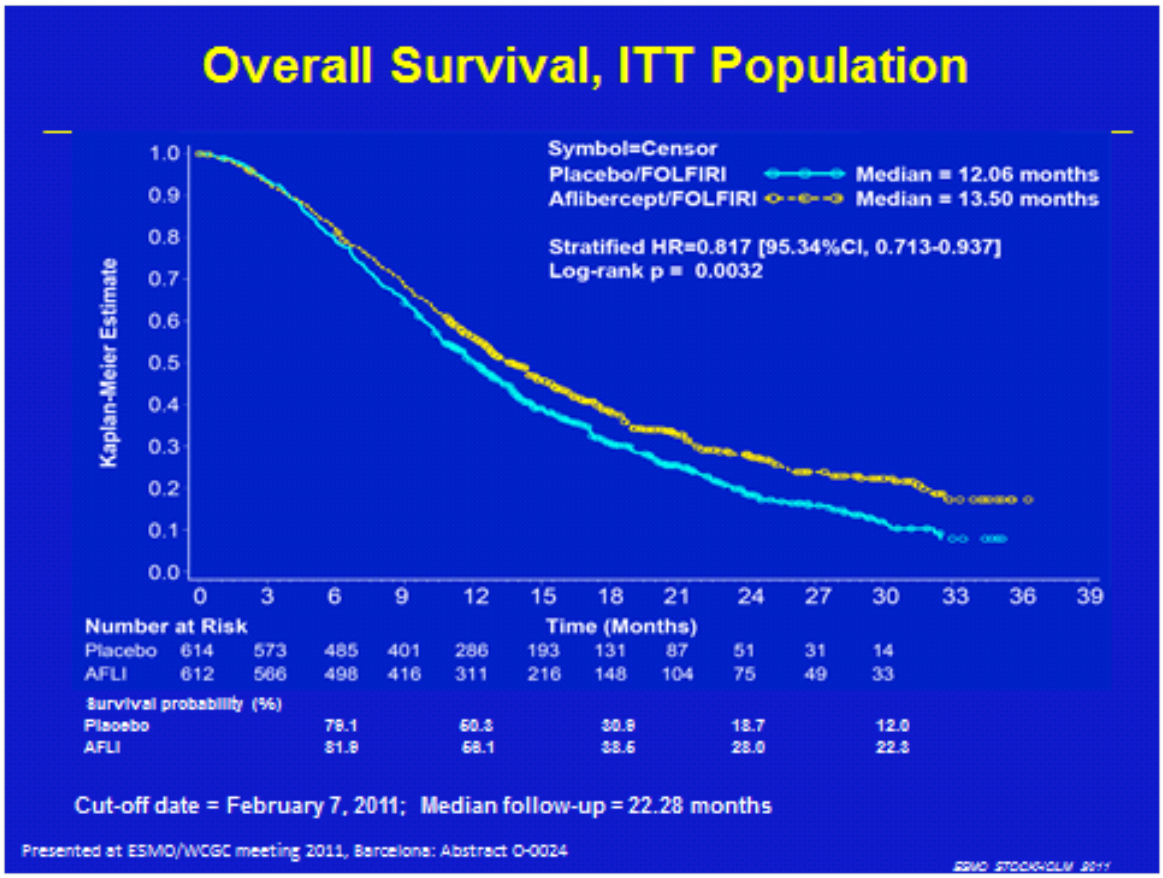

Fig.5. Overall survival curve shows advantage in favor of aflibercept/FOLFIRI arm (courtesy of Dr Josep Tabernero)

Practice point and future research opportunities

The primary efficacy results of the VELOUR study were presented at the ESMO World Congress on Gastrointestinal Cancer earlier this year and showed significant improvement in overall survival and progression free survival in favor of the aflibercept arm. The improved outcome favoring FOLFIRI plus aflibercept over FOLFIRI alone was statistically and clinically significant and unaffected by prior bevacizumab exposure, according to preplanned subgroup analyses, which also showed a treatment advantage for aflibercept in patients with metastases confined to the liver only compared to patients with disseminated disease.

Laparoscopic surgery versus open surgery for rectal cancer

Bonjer *et al.* compared laparoscopic and open surgery for treatment of patients with cancer of the rectum in the multicenter, non-inferiority phase III COLOR II trial. Patients with a solitary rectal carcinoma (T1, T2 or T3) within 15 cm from the anal verge and with a margin greater than 2 mm to the endopelvic fascia were randomly assigned 2:1 to undergo laparoscopic or open surgery. Data from 1044 (94.7%) of the randomized patients were evaluated; patients experienced less blood loss

of median 320 mL with laparoscopic surgery than those assigned to open resection who had blood loss of median 552 mL (P<0.001), even though laparoscopic surgery took a median 247 min compared to 200 minutes with open surgery (P<0.001). Conversion from laparoscopic to open surgery was necessary for 114 (16.4%) patients. The number of lymph nodes removed and the circumferential and distal resection margins were similar in both groups but the proximal resection margin was 17.0 cm and 19.0 cm following laparoscopic surgery and open resection (P<0.001), respectively. Anastomotic leakage was similar in both groups and occurred in 10 % of patients after laparoscopic surgery and in 8.8 % of patients after open resection. However, significant advantages favoring laparoscopic surgery were seen; it was associated with earlier recovery of bowel function (P<0.001), better tolerance of oral fluid intake (P=0.006), decreased need for epidural analgesics (P<0.001) and overall shorter hospital stay (P=0.037) compared to open resection of rectal cancer. Mortality rates within 28 days post surgery were similar between both groups. (Bonjer, Abstract LBA 2)

Practice point and future research opportunities

This trial is the first large clinical randomised study assessing short and long term outcomes after laparoscopic or open resection in rectal cancer patients. The results show that laparoscopic surgery requires longer operating time, and skilled surgical team, but it can be safely used for radical resection in most cases of non-invasive rectal cancer. Laparascopic procedure allows faster surgical recovery, cause less pain, less blood loss, fewer infections, fewer incisional hernias, and requires shorter hospitalization. Longer follow-up is needed to demonstrate that radicality of resection is not inferior to open surgery in term of local recurrence and other treatment specific outcomes.

BIBF 1120 plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 in patients with metastatic colorectal cancer

The efficacy and safety with addition of BIBF, a novel inhibitor of VEGFR 1-3, FGFR 1-3 and PDGFR- -, to modified FOLFOX6 (mFOLFOX6) was compared by Van Cutsem *et al.* to bevacizumab plus mFOLFOX6 for treatment of chemo-naive metastatic colorectal cancer (mCRC) patients in a phase I/II study. Patients with unresectable, measurable, histologically confirmed mCRC, and ECOG performance status (PS) 2 and adequate organ function were stratified by ECOG PS, LDH levels, and receipt of adjuvant treatment and randomized 2:1 to receive first-line treatment with continuous mFOLFOX6 plus either BIBF1120 (BIBF1120 arm, n=85) or bevacizumab (BEV arm, n=41) until disease progression or non-tolerable toxicity. The primary endpoint of PFS rate at nine months was 63% and 69% in the BIBF1120 and BEV arms, respectively; median PFS was 10.6 months in both arms. The overall response rates were 61.2% and 53.7%, with response duration of 8 and 10.5 months, respectively, in the BIBF1120 and BEV arms. Complete response, partial response and stable disease were achieved by 7.1%, 54.1% and 28.2% of patients treated with BIBF1120 and by

7.3%, 46.3% and 16 39.0% of patients receiving bevacizumab. Treatment with BIBF1120 did not impact exposure or intensity of mFOLFOX6 treatment, with a similar proportion of patients in both arms receiving full dose. Safety profiles were similar in both arms, but fewer serious adverse events were reported in the BIBF1120 arm, possibly due to a lower incidence of gastrointestinal perforations. Detailed serious adverse event and quality of life assessments are ongoing. (Van Cutsem. Abstract LBA 14)

Practice point and future research opportunities

This randomized, open-label phase I/II trial compared novel anti-angiogenic agent BIBF 1120 (triple angiokinase inhibition of VEGFR 1-3, PDGFR- -, and FGFR 1-3) with bevacizumab, both in combination with mFOLFOX6 in the first-line treatment of metastatic colorectal cancer. Results indicate that BIBF 1120 has similar antitumor activity and a similar safety profile to bevaclzumab, but possibly fewer serious adverse events. These are exploratory data from a small sample that require confirmation in larger, randomized studies.

GASTROINTESTINAL CANCER - NON-COLORECTAL

Global investigation of therapeutic decisions in hepatocellular carcinoma and its treatment with sorafenib: Barcelona Clinic Liver Cancer stage subgroup analysis

Findings were presented from the second interim analysis of data from the GIDEON study, which enrolled over 3000 patients from 39 countries. Lencioni *et al.* evaluated the use and efficacy of sorafenib in treating hepatocellular carcinoma in actual clinical practice. Preliminary results from a preplanned analysis of data from the 1612 patients in the intent to treat population demonstrated median OS of 9.1 months. In patients stratified by Barcelona Clinic Liver Cancer (BCLC) criteria, OS was 13.6, 12.6, 7.9, and 3.4 months, respectively, in patients with stage A (n=117), B (n=311), C (n=877), and D (n=93) at baseline. Sorafinib dose levels were similar across all stages; however, early stage patients had received more previous locoregional treatment, as well as more prior and concomitant transarterial chemoembolization. Treatment related adverse event reports and serious adverse events were also similar between early and late stage patients in the safety population, which was comprised of 1571 patients. (Lencioni, Abstract 6001)

Practice point and future research opportunities

Sorafenib is used in actual practice to treat patients with hepatocellular carcinoma at all stages according to Barcelona Clinic Liver Cancer criteria at equivalent doses with similar safety profiles. Treatment duration and preliminary overall survival of treatment by sorafenib supports the robust

nature of the study data.

Preoperative chemotherapy does not influence the number of evaluable lymph nodes in resected gastric cancer

Evaluation of 15 or more lymph nodes is recommended for accurate staging of gastric cancer, but the lymph node yield in western countries is generally low, with the impact of preoperative chemotherapy on yield currently unknown. Verheij *et al.* analyzed data from two large databases to evaluate the impact of preoperative chemotherapy upon the number of lymph nodes obtained from patients who underwent a total or distal gastrectomy for gastric adenocarcinoma, with and without preoperative radiotherapy. Data from 1205 patients in a US center and 1220 patients from the Netherlands Cancer Registry were analyzed by multivariate poisson regression to identify significant predictors of lymph node retrieval. The number of surgeries performed in the US center was found to be double that in the Natherlands and median lymph node yields were 23 in the US institution and 10 in the Netherlands Cancer Registry; of the 2425 patients in both databases, 340 (14%) patients received preoperative chemotherapy, which did not associate with yield. Variables that did associate with increased lymph node yield were institution, female sex, lower age, total versus distal, gastrectomy and increasing T stage. (Verheij, Abstract 6502)

Practice point and future research opportunities

In both the high-volume cancer center, and the population-based cancer registry, female sex, younger age, total gastrectomy and advanced tumor stage were associated with an increase in lymph node retrieval in surgical specimens. Preoperative chemotherapy did not associate with decreased lymph node yield in patients who underwent a total or distal gastrectomy for gastric adenocarcinoma. The threshold for what should constitute an adequate assessment of regional lymph nodes after curative surgery for gastric cancer should remain unchanged after administration of preoperative chemotherapy.

GENITOURINARY - INCLUDING PROSTATE

First phase III trial of an alpha-pharmaceutical shows improved survival in patients with bone metastases and advanced prostate cancer

Findings were presented by Parker *et al.* from the The ALSYMPCA phase III trial of radium-223 chloride, a first-in-class alpha-pharmaceutical targeting bone metastases, which develops in about 90% of advanced prostate cancer cases. Radium-223 has high-energy alpha-particles of extremely short range (<100 m) with an affinity for bone similar to that of calcium, thus preferentially targeting areas of new bone formation.This double-blind, randomized, multinational study demonstrated that

men with metastatic castration-resistant prostate cancer lived significantly longer after receiving treatment with radium-223, which also was associated with a 30% reduction in the odds of dying during follow-up. A planned interim analysis done after 314 deaths revealed a HR of 0.695 in favor of the radium-223 arm (*P=0.*00185) and median OS of 14.0 months in the 615 patients in the study arm compared to 11.2 months in 301 placebo treated patients. Radium-223 treatment had highly favorable safety and tolerability profiles with a low incidence of hematologic toxicity, which consisted of neutropenia in 4% of patients and thrombocytopenia in 8%; half of each of these were of grade 3/4 severity. Patients receiving the investigational agent also had fewer skeletal-related events. (Parker, Abstract LBA)

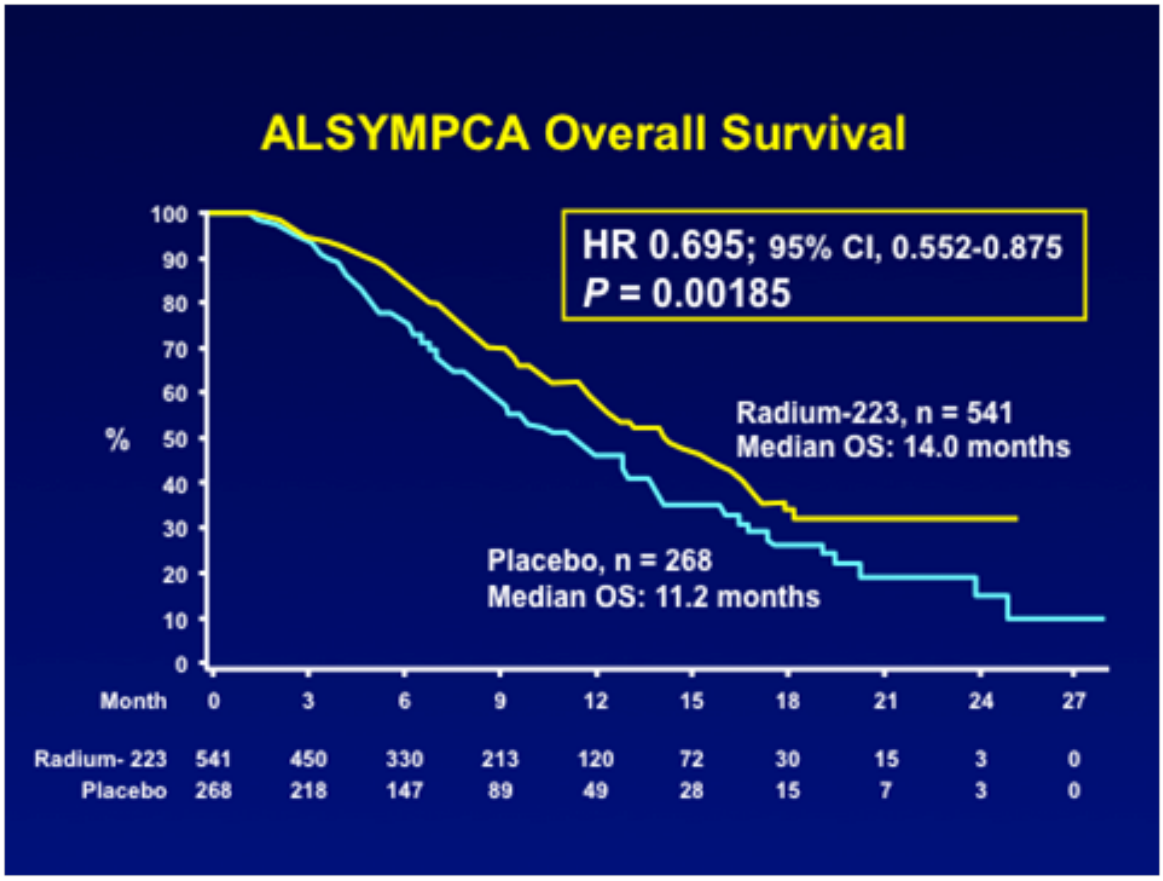

Fig.6. A difference in median overall survival in favour of radium-223, an agent highly targeted to bone metastases (courtesy of Dr Chris Parker)

Practice point and future research possibilities

An overall survival benefit with the first-in-class alpha-pharmaceutical radium-223 was observed in patients with symptomatic bone metastases and castration-resistant prostate cancer in the phase III, randomized, international trial. Results from the pre-planned interim analysis caused that Independent Data Monitoring Committee recommend stopping the trial early and offering radium-223 to patients in the placebo group. Compared to chemotherapy, radium-223 is highly targeted to the

bone metastases and has minor hematological side effects. Comparing to standard radiotherapy (beta radiation), radium-223 as alpha-emiter has advantage of being less toxic to bone marrow. Theoretically, the smaller the tumor, the more advantage of alpha over beta radiation, and microscopic disease would be better indication than macroscopic disease. Thinking about more routine use, it is important to mention that radium-223 is outpatient treatment, requiring 5-min i.v. injection. There are no specific storage requirements, but the drug should be utilized within 2 weeks from manufacturing. An application for regulatory approval is being filed for radium-223.

Ibandronate versus single dose radiotherapy for localized metastatic bone pain in prostate cancer

The current standard of care for metastatic bone pain, which occurs in approximately 75% of patients with prostate cancer, is a single dose of radiotherapy. Hoskin *et al*. conducted the largest randomized trial to date comparing ibandronate, an osteoclast inhibitor, to single dose radiation for the reduction of bone pain in 470 patients with prostate cancer. At four weeks, 53% and 49% of patients receiving radiotherapy and ibandronate, respectively, reported a similar reduction in bone pain and non-responders were allowed to cross-over to the opposite treatment. Equivalent results for pain reduction were seen at nine and twelve months with either treatment, suggesting that ibandronate may be an alternate therapy for patients who do not respond to standard single dose radiation. No difference between patients treated with either single agent was seen in OS; median survival was 11.8 and 11.4 months in the radiotherapy and ibandronate only patients. However, in the crossover patients who received both treatments an increased survival advantage was seen of 12.7 months in patients who received radiotherapy followed by ibandronate, and 16.8 months in patients treated with ibandronate and then radiotherapy. Side effects with ibandronate were flu like symptoms and transient nausea was seen in patients receiving abdominal radiotherapy. Future research plans include correlating biomarkers for bone resorption and response to radiotherapy and ibandronate to predict which patients would respond best to either treatment. (Hoskin,Abstract LBA 7)

Practice point and future research possibilities

Many prostate cancer patients develop bone metastases, and controlling the pain can be difficult. Furthermore, bone matastases can cause fractures and spinal cord compression. Now the first large randomised phase III trial comparing a bisphosphonate drug with radiotherapy in these patients has shown that a single dose of ibandronate is equivalent for pain relief as single dose radiotherapy, the standard treatment for bone metastases. Results after crossover suggest that radiotherapy or ibandronate represent a treatment option for non-responders. Radiotherapy remains standard of care for metastatic bone pain, and it is a treatment of choice in patients with solitary metastases, pathological fracture, and neurological complications of bone metastases. However ibandronate represents an effective treatment option for special clinical situations, such as contraindications for

radiotherapy). Findings could also be applicable to other primary cancers that can lead to bone metastases, for example breast cancer, where they are very common. The researchers intend to follow up their work with a study looking at biomarkers for bone resorption.

Celecoxib plus hormone therapy versus hormone therapy alone for hormone-sensitive prostate cancer

The STAMPEDE trial is investigating whether early use of adjuvant docetaxel, zoledronic acid or celecoxib can improve upon overall survival achieved by hormone therapy, which remains the standard of care for men with metastatic or high-risk non-metastatic prostate cancer. The STAMPEDE is an international randomized controlled trial that is using novel multi-arm, multi-stage methods to assess the addition of these agents to 2114 men with prostate cancer who are starting long-term hormone therapy for the first time in five research arms. Of the 814 men in this comparison of hormone therapy alone and hormone therapy plus celecoxib, the failure free survival in the hormone therapy arm was 51% at 2 years, with no advantage seen with adjuvant celecoxib. Accrual to this study arm and Celecoxib administration was ended. Toxicity rates were similar, with 25% and 23% of patients treated with and without celecobix reporting grade 3 toxicities or adverse events. (James, Abstract LBA 20)

Practice point and future research opportunities

Celecoxib shows no evidence of activity in this setting. Accrual continues seamlessly to the other treatment arms.

Escalated-dose conformal radiotherapy for localized prostate cancer

Dearnaley presented long term survival results from the RT01 trial of dose escalation, the largest trial to date, that randomized 843 men who had received no prior treatment for histologically confirmed T1b-T3a, N0, M0 prostate cancer, WHO performance status 0-1, normal blood counts and PSA<50ng/mL into equal arms to receive standard-dose conformal radiotherapy or escalated-dose conformal radiotherapy. Patients were offered neo-adjuvant hormone therapy for 3 to 6 months prior to and throughout radiotherapy. Median patient age at entry was 67 years and two thirds were at moderate risk for seminal vesicle involvement, with the remainder of patients at low risk. With median follow-up of 10 years, OS was 70% in both arms. There was also no difference in mortality, with 120 and 119 deaths in the standard and escalated dose arms, respectively. Previously reported biochemical free survival (bPFS) that favored the escalated treatment arm was maintained, with these patients experiencing bPFS of 54% compared to 42% in the standard treatment arm. Fewer men began hormone therapy and began at a later date in the escalated compared to standard groups (P=0.05). (Dearnaley, Abstract LBA 21)

Practice point and future research opportunities

Escalated dose radiotherapy with neo-adjuvant hormone therapy showed an advantage in early efcacy outcome measures but this did not translate into an improvement in overall survival. Patients receiving escalated dose did show improved biochemical progression-free survival and five extra fractions of radiotherapy may have led to less exposure to long-term hormonal therapy.

Association of single nucleotide polymorphisms in VEGF pathway genes with progression-free survival and blood pressure in mRCC

In the pivotal AXIS phase III trial, axitinib demonstrated significantly better PFS compared with sorafenib in patients with advanced renal cell carcinoma (RCC); patients in the axitinib arm experienced median PFS of 6.7 months compared with 4.7 months for those receiving sorafenib with a HR of 0.665 in favor of axitinib. Additionally, objective response rates were more than doubled with axitinib at 19.4% versus 9.4% for sorafenib. However, incidence of hypertension was higher in the axitinib group. Escudier *et al.* conducted an analysis of AXIS data using DNA samples of 249 Caucasian patients to determine the genetic profile, including single nucleotide polymorphisms (SNPs) in VEGF pathway genes that associated with improved response with axitinib and also looked at blood pressure association. Differences in PFS were seen with three *VEGF-A* SNPs: rs1570360, rs699947, and rs833061 (Cox regression interaction test; P=0.127, P=0.058 and P=0.058, respectively). By Log-rank analysis, potential associations between PFS and genotype for these three SNPs suggested that genotype variability had more effect on PFS following treatment with axitinib than with sorafinib. No statistically significant correlations were observed between SNPs and hypertension or high diastolic blood pressure; none of the VEGF pathway SNPs examined was associated with hypertension reported to be related to axitinib treatment. (Escudier, Abstract LBA 21)

Practice point and future research opportunities

Specific single nucleotide polymorphisms may explain some of the observed interpatient variability in progression-free survival following axitinib therapy and might be important tools in the future to guide selection of VEGF inhibitors in the treatment of patients with renal cell carcinoma.

GYNECOLOGICAL CANCER

Efficacy of chemotherapy and bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or Fallopian tube cancer

Aghajanian *et al*. presented new findings from subgroup analyses of data from the OCEANS trial, a

randomized, double-blinded, placebo-controlled, phase III trial in patients with platinum-sensitive recurrent epithelial ovarian cancer, primary peritoneal or Fallopian tube cancer. All patients had front-line treatment with paclitaxel and gemcitabine prior to randomization into equal arms of 242 patients to receive bevacizumab or placebo until disease progression or unacceptable toxicity occurred. Improved PFS favoring bevacizumab of 12.4 months over 8.4 months with placebo was seen (P<0.0001); at median follow-up of 24 months, overall response was 78.5% with bevacizumab compared to 57% with chemotherapy (P<0.0001). Bevacizumab had benefit across all subgroups of 484 patients stratified by platinum sensitivity. In platinum partially-sensitive patients who had been off-treatment with platinum-based chemotherapy for six to 12 months and those off treatment for over a year, risk of progression was reduced by 64% and 48% with bevacizumab over placebo, respectively. With bevacizumab, 171 platinum partially-sensitive women had reduced risk of disease progression by 64% (HR 0.36) and 209 platinum sensitive women had reduced risk of progression of 48% (HR 0.52). At the time of analysis, 41% of patients on the bevacizumab arm and 65% of the patients on the placebo arm had ended the trial due to disease progression. However, 23% of patients discontinued bevacizumab because of adverse events versus 5% of those on chemotherapy. Febrile neutropenia was experienced by 2% of patients in each arm. One patient in the bevacizumab arm with newly diagnosed brain metastasis died of brain hemorrhage and one patient in the placebo group died of a heart attack. Overall survival data are not yet mature. (Aghajanian, Abstract LBA 5)

Practice point and future research opportunities

Addition of bevacizumab to chemotherapy in women with recurrent ovarian cancer yielded significant clinical benefit that was consistent across the majority of clinically relevant subgroups, including prespecified partially platinum sensitive ovarian cancer. Bevacizumab plus chemotherapy shows promise as the standard of care in women with platinum sensitive recurrent ovarian cancer. However, overall survival data are not mature yet.

Hysterectomy or no in patients with a clinical and radiological complete response after chemoradiation therapy in patients with stage IB2/II cervical cancer

Whether or not a woman underwent hysterectomy after achieving complete response following chemoradiation including brachytherapy for early-stage ovarian cancer did not impact survival according to Morice, who reported results of the GYNECO 02 study. This phase III trial evaluated the clinical benefit of hysterectomy in women who achieved a complete clinical and radiological response, based on magnetic resonance imaging, within 8 weeks of chemoradiation therapy for stage IB2/II cervical cancer. The trial was halted in 2006 due to poor accrual after 31 patients had been randomized to receive hysterectomy following chemoradiotherapy and 30 to chemoradiotherapy alone; the results of these patients after a median follow-up of 3.8 years were presented. The primary endpoint of the event-free survival rate at 3 years was 72% in women who underwent extrafascial

hysterectomy and 89% among those who did not (P=0.17). Overall 3 year survival rates were 86% in patients with hysterectomy and 97% in patients without (P=0.15). Disease relapse was experienced by eight patients in the hysterectomy arm and by three with chemoradiation alone. In women with hysterectomy, the site of recurrence for two patients was centropelvic alone, centropelvic plus nodal, pelvic node and distant, paraaortic nodes alone, and distant without pelvic or nodal (each occurring in one patient) with three patients having paraaortic nodal involvement and distant recurrence. In the chemoradiation arm, the first recurrence site was centropelvic alone in two patients and distant without pelvic or nodal involvement in one patient. (Morice, Abstract 8000)

Practice point and future research opportunities

The trial results are limited by the lack of power but suggest that hysterectomy has no therapeutic benefit for patients with stage IB2/II cervical cancer, who demonstrate a clinical and radiological complete response following chemoradiation.

Mutation and protein expression biomarkers correlate with response to AKT inhibition in patients with platinum resistant ovarian cancer

Activation of the AKT pathway is a key element in clinical platinum resistance, leading Gungor *et al*. to test the downstream effects of AKT inhibition by GSK795, a novel, strong ATP-competitive, pan-AKT inhibitor, in patients with platinum resistant ovarian cancer. GSK795 was given to 11 patients in three cohorts, each receiving doses of 25, 50 or 75mg for 2 or 4 weeks, respectively that were escalated to 75 mg in all cohorts following pharmacodynamics assessment, PET evaluation and molecular analysis of paired tumor biopsies (PTB). A pharmacokinetic dose response was observed by positron-emission tomography (PET) between GSK795 plasma levels only for best responding lesions. No clinical response was seen by RECIST v1.1 but evidence of AKT pathway inhibition was observed at the two highest doses; there was direct correlation between best CA125 response, best chemotherapy response and disease stabilization ($P<0.05$). Immunohistochemistry of available PTB from two of three patients receiving 50 or 75mg indicated robust increases in pAKT levels. Decreases in AKT downstream element pPRAS40 and proliferation marker Ki67 levels were seen in four of five patients. Both patients with clear cell cancer had PIK3CA mutations in their original archival samples with one patient experiencing disease stabilization for 50 weeks; however, the other patient did not respond and was shown to also have a Kras mutation. Kras and MET mutations were identified in two other non-responding patients. These data are consistent with the genetic signature associated with PI3K pathway activation and resistance via MAPK pathway activation that characterizes GSK795 sensitivity. Reverse Phase Protein Array on PTB from all 11 patients was performed and identified 15 putative biomarkers. Of these, S6 was predictive with Bid being predictive of response and CCNE1 predictive for resistance to clinical AKT inhibition following GSK795. These results are currently being validated. The treatment was well tolerated with one grade 3 adverse event of hepatotoxicity and

grades 1/2 vomiting reported in 33% of patients. (Gungor, Abstract LBA 24)

Practice point and future research opportunities

Inhibition of AKT using GSK795 shows promise in patients with platinum resistant ovarian cancer; the treatment was tolerable and warrants further testing in large randomized controlled trials. The identification of putative predictive biomarkers of response and resistance may be helpful in patient selection, following validation.

HEMATOLOGICAL MALIGNANCIES

Melphalan/prednisone/lenalidomide versus high-dose melphalan and autologous transplantation in newly diagnosed patients with multiple myeloma

Although new drugs have proven effective in newly diagnosed disease, autologous stem cell transplantation remains the standard of care for multiple myeloma. Cavallo *et al.* reported results from a trial involving 402 patients who underwent induction therapy with lenalidomide and low-dose dexamethasone for four induction-phase cycles; all patients also received cyclophosphamide to mobilize stem cells. Following induction, 202 patients were randomly assigned to receive melphalan, prednisone and lenalidomide (drug therapy treatment arm) while the other 200 patients were assigned to receive tandem melphalan with stem-cell support (transplant arm). While response rates looked similar at 18 months and similar OS rates of 91% were seen with drug therapy and 95% in the transplant group (P=0.073), PFS after 26 months was achieved by just 54% of patients in the drug therapy arm compared to 73% of patients in the transplant arm (P=0.0002), which translates to a relative risk reduction of 49% for patients receiving stem cells. At the same time point, 20% of patients receiving drug therapy achieved a complete remission compared with 25% of the transplant patients. The number of patients discontinuing study was similar in the two treatment groups despite higher toxicity reported in the transplant arm. (Cavallo, Abstract 9200)

Practice point and future research opportunities

The introduction of new drugs has changed the treatment paradigm of multiple myeloma and questioned the role of autologous stem cell transplantation. This is the first report showing a progression-free survival advantage for autologous stem cell transplantation in comparison with chemotherapy combinations including new drugs. At present, no significant overall survival differences between the two arms were detected, and longer follow-up is needed. Autologous stem cell transplantation remains the standard of care for patients newly diagnosed with multiple myeloma who can produce adequate cell number. New drug therapy with lenalidomide shows clinical benefit

and could provide an alternative for patients who do not qualify for transplantation.

Characterizing the biologic basis of efficacy of long-term bisphosphonate treatment in patients with multiple myeloma

Morgan reported findings from an ongoing analysis of results from the Myeloma IX Trial that randomized 1960 patients with multiple myeloma following thalidomide-based chemotherapy to receive either zoledronic acid or clodronate, at least until disease progression. Previously reported Myeloma IX trial results showed greater benefit favoring zoledronic acid with OS improved by 5.5 months (P=0.04) together with a 26% reduction in skeletal-related events (SREs) over clodronate (Morgan et al. *Lancet* 2010). This presentation covered data from an analysis done at follow-up of a median duration of 42 months on clinical outcomes by demographics, disease characteristics, and treatment duration; OS and SRE benefits demonstrated with zoledronic acid compared to clodronate were consistent across all subsets and unaffected by sex, International Staging System (ISS stage), or specific myeloma genotypes. The sole factor affecting outcome was the presence of bone disease (BD+) at baseline; BD+ patients derived superior survival benefit with zoledronic acid that was not seen in patients without baseline bone disease (BD-). Overall, 1401 BD+ patients had significantly shorter median OS of 45.5 months compared with BD- patients who had median OS of 51.6 months (P=0.009). However, following zoledronic acid treatment, patients with bone involvement had a statistically significant 17% improvement in survival (P=0.01), whereas BD- patients experienced similar survival regardless of which bisphosphonate they received. Additionally, zoledronic acid treated patients had a significantly lower rate of SREs (34% versus 43%, P=0.007). Analysis of treatment duration showed therapy of two or more years increased survival benefit with zoledronic acid to a median overall survival of 34 months compared with 27 months for the clodronate arm (P=0.0291). The analysis of SRE showed BD+ patients receiving zoledronic acid had a significantly lower incidence of new bone lesions of 11.4% compared with 5.7% with clodronate (P=0.0002) and 5.8% versus 2.3%, respectively, in BD- patients (P=0.035). The superior effect of zoledronic acid on time to first SRE continued to increase out to one year (P=0.0012) and was maintained for more than three years. Additional efficacy and tolerability analyses are ongoing in the BD+ subset of patients. (Morgan, Abstract 9202)

Practice point and future research opportunities

Overall survival benefit from zoledronic acid treatment of multiple myeloma patients was consistent across all subsets; the only demographic characteristic affecting response to zoledronic acid was the presence of bone disease at baseline. Overall survival improvements with zoledronic acid were most profound in patients receiving bisphosphonates for 2 years, and suggest continued benefits despite disease progression.

Targeting Bcl-2 proteins in hematological malignancies driven by activated mutant JAK2

The JAK2 gene has been implicated in human malignancies; JAK2 mutations and translocations are often seen in myelo- and lympho-proliferative disorders and different activating point mutations of JAK2 have recently been described in pediatric acute pre-B cell lymphoblastic leukemias. In an effort to develop novel treatment strategies for JAK driven malignancies, Waibel *et al.* used a T-cell acute lymphoblastic leukemia (T-ALL) mouse model to identify the critical downstream effectors of oncogenic JAK2 signaling pathways. EμTEL-JAK2-transgenic mice were used to produce a rapid onset T-ALL which was transplanted into C57Bl/6 mice. Cell death assays were performed to elucidate molecular pathways in EμTEL-JAK2 T-ALL cells *ex vivo*. The therapeutic efficacy of the JAK2 inhibitor TG101209, the BH3-mimetic ABT-737, and chemotherapeutic drugs were tested. In cell culture assays, EμTEL-JAK2 T cell leukemic cells were resistant to common apoptotic inducing agents, but were sensitive to the JAK2 inhibitor TG101209. Western Blot analysis showed that these cells expressed high levels of anti-apoptotic Bcl-2 and Bcl-xL proteins, which was confirmed when treatment with theBcl-2/Bcl-xL antagonist ABT-737 induced apoptosis in these cells. The mice transplanted with EμTEL-JAK2 leukemias displayed prolonged survival following treatment with ABT-737 or TG101209 and robust tumor cell apoptosis was also seen *in vivo*. Combinations of ABT-737, TG101209 and etoposide or cyclophosphamide eradicated disease in the mouse model. It was hypothesized that TEL-JAK2 expression induces Bcl-2 and Bcl-xL expression through constitutive activation of STAT5. Bcl-2/Bcl-xL upregulation is common in JAK2-driven hematological malignancies, making them sensitive to therapeutic regimens using ABT-737 in combination with JAK2 inhibitors or standard chemotherapeutic drugs, which may, be a rational approach to treating these diseases. (Waibel, Abstract 9203)

Practice point and future research opportunities

Bcl-2 and Bcl-xL upregulation may be a common feature of JAK2-driven haematological malignancies. Regimens using ABT-737 in combination with JAK2 inhibitors or standard chemotherapeutic drugs may therefore be a rational approach. Ongoing research using a xenotransplantation model with human pre-B acute lymphoblastic leukemia cells expressing constitutively active mutant JAK2 is further testing this hypothesis.

HEAD & NECK

A very accelerated radiotherapy versus concomiitant chemo-radiotherapy in locally advanced head and neck cancer

A very accelerated radiotherapy regimen of 64 Gy delivered within 3.5 weeks was previously reported

to yield superior disease control over conventional radiotherapy for the treatment of patients with locally advanced head and neck cancer (Bourhis JCO 2006), leading Bourhis and the GORTEC Group to further test this regimen against three distinct chemo-radiotherapy regimens in two phase III trials. Long term results from GORTEC 96-01 and GORTEC 99-02 trials involving 949 patients with locally advanced head and neck squamous cell carcinomas were randomized to receive either very accelerated radiotherapy or one of the following three chemo-radiotherapy regimens: conventional, moderately intensified or strongly intensified chemo-radiotherapy. Treatment arms in each trial were well balanced and tumors were mostly located in the oropharynx and hypopharynx. Long term findings at a median follow-up of 5.2 years in GORTEC 99-02 (n=840) and 10.2 years GORTEC 96-01 (n=109) demonstrated significantly superior loco-regional disease control over very accelerated radiotherapy in all three chemo-radiotherapy regimens, with the best results seen in the conventional arm. Patients in the conventional chemo-radiotherapy regimen experienced significantly improved OS compared to very accelerated radiotherapy (P=0.03); no OS benefit was demonstrated with either moderately or strongly intensified chemo-radiotherapy. A nonsignificant trend towards improved PFS with moderately and strongly intensified chemo-radiotherapy (P=0.06 and P=NS, respectively) and significantly improved OS was seen with conventional chemo-radiotherapy compared to very accelerated radiotherapy (P=0.03) A high rate of treatment related deaths observed with strongly intensified chemo-radiotherapy led to discontinuation of this study arm. With these data not included, no difference was seen in long term normal tissues side effects (grade 3-4) among patients in all groups. However long-term feeding tube carriers were more frequent with very accelerated radiotherapy than with conventional chemo-radiotherapy. Chemotherapy inclusion was demonstrated to be a key treatment element but no benefit was seen with increased dose. (Bourhis, Abstract LBA 3)

Practice point and future research opportunities

The long term analysis of these two randomized trials, including updated data on long term side effects allows some conclusions that can impact the daily practice. Conventional chemoradiotherapy remains the standard of care for patients with locally advanced head and neck cancer; loco-regional disease control and overall survival were inferior in very accelerated radiotherapy compared to conventional treatment.

Safety and efficacy of panitumumab in HPV positive and HPV negative recurrent/metastatic squamous cell carcinoma of the head and neck

The phase III SPECTRUM trial evaluated the safety and efficacy of panitumumab, a fully human monoclonal antibody specific to the epidermal growth factor receptor, added to platinum-based chemotherapy compared to sole chemotherapy in patients with recurrent/metastatic squamous cell carcinoma of the head and neck. Findings from a prespecified analysis of SPECTRUM outcomes

stratified by tumor human papillomavirus (HPV) status were presented by Vermorken. Tumor samples were scored positive, negative, or failed (failure rate was <1%) for HPV according to prespecified guidelines and were available for 377 (57%) of 657 patients; of these 83 (22%) tumors were HPV+ and 294 (78%) were HPV-. The rates of HPV+ varied by tumor site with 36% of HPV+ tumors located in the oropharynx, 19% in the larynx, 16% in the oral cavity, and 13% in the hypopharynx. Patients with HPV+ tumors were predominately North American (42%). Non-smokers had 30% HPV+ compared to 14% HPV- tumors; 45% of oropharyngeal primary tumors were HPV+ compared to 23% HPV- and 31% of HPV+ tumors compared to 15% HPV- represented more poorly differentiated tumors. Patients with HPV- tumors experienced improved survival with panitumumab plus chemotherapy compared to sole chemotherapy that was not seen in patients with HPV+ tumors. Overall median PFS was 5.8 compared to 4.6 months; PFS in HPV+ patients was 5.5 versus 5.3 and PFS in HPV- patients was 6.3 versus 5.1 months, with and without panitumumab, respectively (P=0.018). Median OS in HPV+ and HPV- patients was 11.1 versus 9.0, 10.9 versus 12.1 and 11.8 versus 8.7 months with and without panitumumab, respectively (P=0.144). Rates of grade 3 or greater adverse events (AEs) were similar in patients with HPV+ tumors but were 86% and 77% for HPV- patients with and without panitumumab, respectively. However, serious AEs were reported for 51% of panitumumab patients compared to 32% with chemotherapy in the HPV+ arm and by 53% with combination treatment and 41% with chemotherapy in HPV- patients. (Vermorken, Abstract LBA 25)

Practice point and future research opportunities

The addition of panitumumab to chemotherapy improved overall survival and progression-free survival in patients with HPV negative recurrent/metastatic squamous cell carcinoma of the head and neck. It seems that HPV positive and HPV negative tumors have different biological characteristics. The findings should be evaluated in additional studies.

RAD001monotherapy in patients with unresectable adenoid cystic carcinoma

A novel mTOR inhibitor, RAD001, was tested as monotherapy for patients with unresectable adenoid cystic carcinoma by Kim *et al*. in a phase II trial designed to determine efficacy and safety. The study enrolled 34 patients who had at least one measurable lesion and documented disease progression (RECIST criteria) within12 months prior to study entry who were not candidates for curative-intent treatment, had ECOG PS 0 or 1, and adequate organ function. RAD001 was given daily in 4 week cycles for a mean duration of 6.4 months. The primary end-point of 4-month PFS rate improvement from 50% to 65% was met. Of the 34 patients enrolled, 31 were evaluable for response. Partial response was not achieved, although 27 (87.1%) patients experienced stable disease with just 4 (12.9%) patients showing disease progression at four months. The overall disease control rate was 87.1% and 15 (48.4%) patients showed tumor shrinkage. Pre- and post-treatment PET was available

in 18 patients who all showed stable disease by RECIST criteria. Progression free-survival was 11.7 months with RAD001. Dose adjustment was required by 8 (24%) patients. Adverse events consisted of stomatitis (82%), anemia (67%), asthenia (36%), leucopenia (33%) and were reported by 82%, 67%, 36% and 33% of patients, respectively. Major grade 3/4 toxicities of asthenia, infection, and leucopenia were reported by less than 6% of patients. (Kim, Abstract 8502)

Practice point and future research opportunities

RAD001 showed promise as an effective treatment for patients with unresectable adenoid cystic carcinoma and was well tolerated; however these findings were demonstrated in a trail that was not placebo controlled and had a small sample size.

Sentinel lymph node biopsy in oral cancer patients

Lymph node status is the most important prognostic factor in oral cancer and is usually assessed by neck dissection, which is thought to provide the greatest accuracy but is invasive procedure with considerable morbidity. The sentinel lymph node biopsy (SLNB) is accurate in more than 90% of biopsies and could present an alternative staging method. Samaiya *et al.* conducted a retrospective analysis of 130 cases of SLNB in oral cancer patients to assess the accuracy, sensitivity and predictive value of this procedure. The procedure was carried out in patients with oral squamous cell carcinoma and only soft non suspicious lymph nodes. The SLNB was performed either by blue dye or by combined technique and was then validated by neck dissection in 62 patients, with the results of SLNB compared with final histopathology of remaining neck nodes. In the therapeutic phase of this study, 68 patients had SLNB without neck dissection but assessment of SLN was done by intraoperative touch cytology, with these results compared to histopathology. Comparable results were seen with SLNB as validated by both methods; validation by neck dissection showed sensitivity, specificity, negative predictive value and accuracy for SLNB of 81.8%, 100%, 90.4% and 93.3% respectively. With therapeutic SLNB, the identification rate was 100%; sensitivity, specificity, negative predictive valie, positive predictive value and accuracy of touch cytology in therapeutic phase were 88.88%, 98%, 96.07%, 94.11%, and 95.58%, respectively. Neck nodal relapse occurred in two therapeutic phase patents and was determined to be associated with local relapse during the median 10 month follow-up. (Samaiya, Abstract 8506)

Practice point and future research opportunities

Lymph node status is an important prognostic factor in oral cancer. Study findings showed sentinel lymph node biopsy to be accurate, sensitive and predictive for staging lymph node status in oral cancer that avoids neck dissection associated morbidity and high failure rate of observation only.

LUNG/THORACIC ONCOLOGY

Vorinostat in patients with advanced malignant pleural mesothelioma previously treated with pemetrexed and either cisplatin or carboplatin

Vorinostat, a histone deacetylase inhibitor showing promise for the treatment of malignant mesothelioma failed to meet the primary endpoint of lengthening OS) in patients, according to Krug *et al.* who conducted VANTAGE014, a phase III trial that was the largest of its kind in advanced mesothelioma. VANTAGE was carried out in 92 centers, enrolling 660 patients who were randomized to best supportive care plus either vorinostat or placebo. Most patients (72%) had failed standard first-line therapy with pemetrexed plus either cisplatin or carboplatin. The primary endpoints were OS and tolerability; PFS was a secondary endpoint. No clinical benefit was observed with vorinostat; patients had a median OS of 30.7 weeks compared with 27.1 weeks with placebo. A statistically significant advantage for vorinostat that was not clinically meaningful was seen in PFS, which was a median 6.3 weeks with vorinostat compared to 6.1 weeks with placebo ($P<0.001$). No benefit from the treatment was seen in any of the subgroups, nor were there differences in terms of response rate, forced vital capacity, or dyspnea score between the treatment groups. Overall adverse events were comparable between groups but slightly higher with vorinostat, with grade 3-4 adverse events of dyspnoea (11%), fatigue (10%), tumor associated pain (6%), nausea (4%), anemia (3%), decreased appetite (3%), and pneumonia (3%) and six drug-related grade 5 adverse events being reported. It was observed, however, that associated tumor pain was less in the vorinostat group. (Krug, Best Abstract 3)

Practice point and future research opportunities

This is the largest randomized trial to complete enrolment in malignant pleural mesothelioma. It tested a drug with a novel mechanism of action. Unfortunately, the results are negative and urge for a further research in patients with this devastating disease.

MELANOMA AND OTHER SKIN CANCERS

Efficacy and safety of vismodegib in patients with advanced basal cell carcinoma

While basal cell carcinomas are usually managed by surgery, they can become locally advanced or metastatic, conditions which currently have no effective therapies. Mutations in Hedgehog pathway genes, primarily genes encoding patched homologue 1 (*PTCH1*) and smoothened homologue (*SMO*), have been shown to participate in the development of basal-cell carcinoma. Phase I clinical trial results showed that vismodegib (GDC-0449), a first-in-class small-molecule Hedgehog pathway

inhibitor, yielded a 55% response rate in patients with metastatic and locally advanced basal cell carcinoma, leading Dirix *et al*. to conduct this pivotal multicenter, 2-cohort, non-randomized study evaluating vismodegib treatment of 71 patients with locally-asvanced and 33 patients with metastatic basal cell carcinoma, who enrolled at 31 sites throughout the US, Europe and Australia. All patients received 150mg oral vismodegib until progression. Approximately 50% of patients with locally-advanced or metastatic disease had an overall response to vismodegib. Overall response rate (ORR) determined by independent review for patients with locally-advanced disease was 43% (P<0.0001); per investigator review, ORR was 60% following treatment with vismodegib. In patients with metastatic disease who received vismodegib, ORR by independent review was 30% (P=0.0011) and 46% by investigator. Median time to progression was 9.5 months for both groups of patients. Adverse events of muscle spasms, alopecia, taste disturbance, weight loss and fatigue were observed in just over 30% of patients. Serious events were reported by 26 (25%) patients; of these, 4 (4%) patients experienced serious events that were considered to be vismodegib related. Seven fatal events were reportedin patients, with one considered to be treatment related. (Dirix, Best Abstract 1)

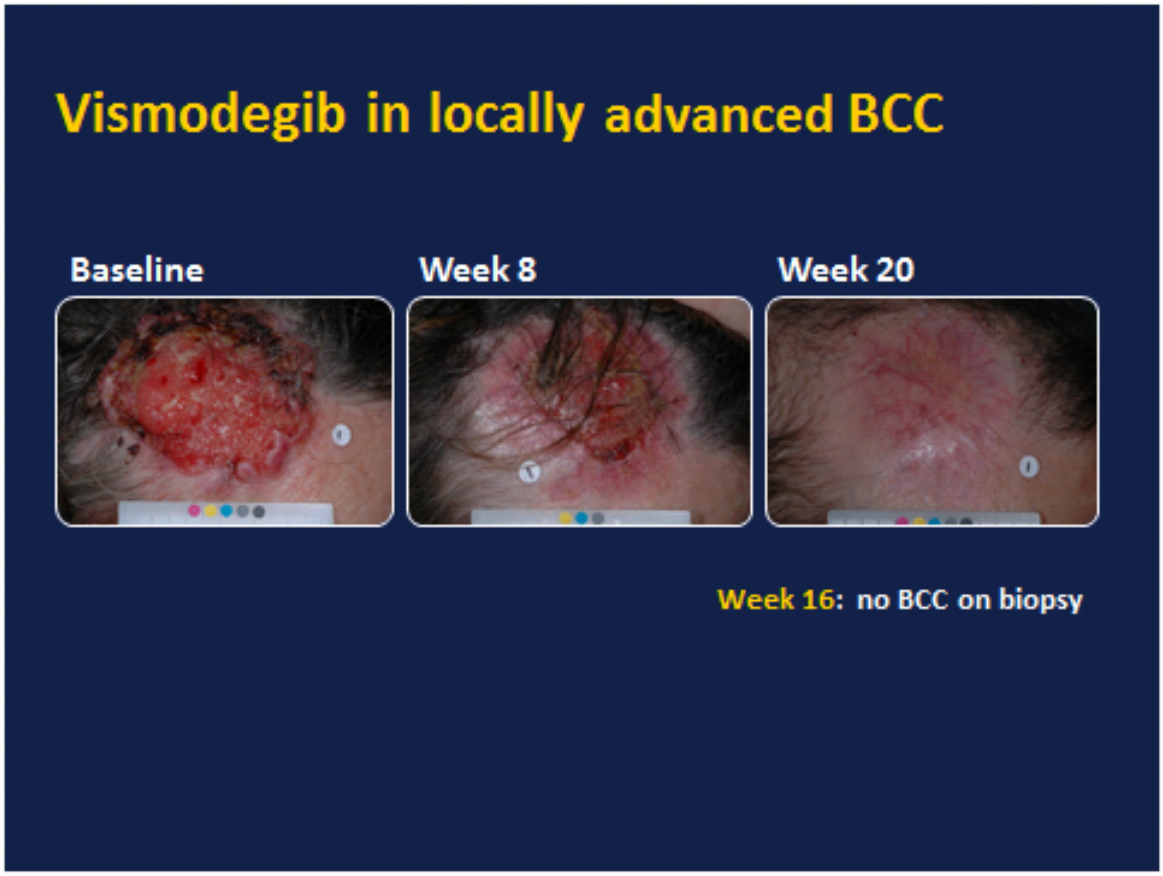

Fig.7. Clinical response to vismodegib observed in responders frequently occurred in matter of weeks, as indicated by these scalp photographs. No residual basal cell carcinoma was seen on the biopsy at week 16 (courtesy of Dr Luc Dirix).

Practice point and future research opportunities

Basal cell carcinoma is the most commonly diagnosed human cancer. Most cases are treated with surgery. However, a small proportion of patients (less than 5%) progress to locally advanced or even metastatic disease, for which there is currently no standard of care. In the pivotal trial, vismodegib provided substantial clinical benefit for patients with advanced basal cell cancer; nearly all patients had some tumor shrinkage, suggesting possible neoadjuvant use to decrease the size of tumors, but surgical resection should always be in the treatment algorithm. Common adverse events were predominantly mild to moderate, targeted inhibition of Hedgehog signalling with vismodegib is a potential, new therapy and approval application has recently been filed for its use in the treatment of inoperable advanced basal cell carcinoma. This novel drug is the first in the class of Hedgehog pathway inhibitors. This pathway is disrupted in about 90% of basal cell carcinomas; it is also affected in several other cancers, including medulloblastoma.

Efficacy of veliparib plus temozolomide versus temozolomide alone in patients with metastatic melanoma

Veliparib has been shown preclinically to augment the antitumor activity of several agents by inhibiting DNA repair enzymes PARP-1 and PARP-2. Middleton *et al.* compared the efficacy of veliparib at two doses plus temozolomide with placebo plus temozolomide in a multicenter, double-blind, placebo controlled trial in patients with metastatic melanoma The trial randomized 346 patients with unresectable stage III or IV metastatic melanoma, and one or more measurable lesions on CT scan (RECIST), with ECOG 0-1, to receive veliparib at 20 or 40 mg plus temozolomide or placebo. Median PFS was nearly doubled in 116 and 115 patients in the 20 and 40 mg veliparib/temozolomide groups compared to the 115 patients who received temozolomide plus placebo, but statistical significance was not reached. Median PFS was 113, 110 and 60 days, respectively, in patients who received temozolomide plus veliparib (20mg), veliparib (40mg) and placebo, respectively. Results for OS also did not reach statistical significance and were similar between the groups. Overall response was observed in 12 (10.3%), 10 (8.7%) and 8 (7.0%) patients treated with temozolomide plus veliparib (20mg), veliparib (40mg) and placebo, respectively. The toxicity profile for temozolomide was as expected but toxicity increased significantly with veliparib; increased incidence of thrombocytopenia, neutropenia and leucopenia occurred. Grade 3/4 hematological adverse events (AEs), were observed in 38% of placebo, 54% veliparib (20 mg), and 57% of veliparib (40 mg) treated patients. Treatment related AEs were reported by 79% to 96% of all treated patients. (Middleton, Abstract LBA 13)

Practice point and future research opportunities

This study represents the first randomized trial of a PARP inhibitor to combine with temozolomide in patients with metastatic melanoma. The study showed that combination therapy numerically improved

median progression-free survival in both the low- and high-dose groups and improved overall survival in the high-dose group, but these differences were not statistically significant. No new toxicity signals were ldentifted. The results of this large phase II study deserve further pursuing of the strategy in this rapidly changing field.

Efficacy of neoadjuvant cisplatin, fluorouracil and cetuximab in locally advanced non resectable epidermoid skin carcinoma

Mateus *et al.* evaluated the efficacy of combination chemotherapy in treating locally advanced non resectable cutaneous squamous cell carcinoma, which currently has no standard therapy. In this study, seven patients were treated prospectively with including combination of cisplatin, fluorouracil and cetuximab, followed by surgery if tumor size was reduced. Adjuvant radiotherapy was administered to three patients because histological signs of aggressiveness were observed at histology. Extensive tumor response was observed; tumor regression that allowed surgical resection was achieved by all seven patients. After a 3-year of follow-up, histology showed a complete sterilization with no active tumoral residue in two patients and complete resection in the remaining five patients. Distant recurrence of pulmonary metastasis occurred in one patient at 18 months after the treatment but no local recurrence was seen after a median follow-up of 31 months. Treatment was well tolerated with manageable toxicity. (Mateus, Abstract 9300)

Practice point and future research opportunities

The combination of cisplatin, fluorouracil and cetuximab is approved for treatment of metastatic head and neck carcinoma but has not been yet evaluated in cutaneous squamous cell carcinoma. The dramatic tumor responses and the long term local control observed in this small group of patients, warrant further evaluation of this association both in the neoadjuvant and in the metastatic settings for patients with non resectable skin squamous cell carcinomas.

Percutaneous hepatic perfusion in patients with melanoma liver metastases

Intra-artherial chemotherapy may slow disease progression in the liver among patients with metastatic uveal melanoma, according to results from Pinkpank *et al.* who tested percutaneous hepatic perfusion (PHP) compared to best alternative care (BAC) in the first phase III multicenter trial of this technique. Melphalan was infused via intra-arterial catheter over a 30 minute period directly into the liver in 44 patients who were randomized to PHP. The outcome of these patients was compared to 49 patients randomized to BAC, which could involve other agents, including interleukin-2, ipilimumab, transcatheter arterial chemoembolization or systemic chemotherapy. The primary endpoint of the study was met; hepatic PFS of median 8.1 in PHP patients compared to 1.6 months in BAC patients ($P<0.0001$) was demonstrated. Similar benefit was seen for overall PFS favoring PHP

patients who experienced a median of 6.1 months versus 1.6 months in patients receiving BAC (P<.001). There was no difference in OS rates at one year, which were 29% with PHP and 26% for BAC (median OS PHP 11.4 months vs. BAC 9.9 months, due to a 51% crossover rate in the trial. Patients who did cross survived for 9.2 months without their disease progressing in the liver and 6.5 months without any overall progression. Side effects of grade 3 or 4 neutropenia and thrombocytopenia occurred, but most patients were able to undergo multiple PHP treatments, as toxicity resolved. (Pingpank, Abstract 9304)

Practice point and future research opportunities

This is the first treatment to show a clinical benefit in patients with liver metastases from uveal melanoma and the first trial to show a benefit of regional treatment for liver metastases in this disease. Given the current lack of targeted drugs in uveal melanoma - in contrast to the emerging treatments in cutaneous melanoma - the clinically relevant benefit achieved with melphalan perfusion could provide a new reference treatment for patients with hepatic metastases of uveal melanoma. Most patients retain 80% or more of their daily functional status, and return to full performance once therapy is completed. If subsequent recurrence is noted in the liver, retreatment is possible and effective. Fifty percent of melanoma patients with metastatic liver disease die of liver failure, and there is unmet medical need for a frontline therapy. There is always controversy surrounding the application of regional therapy to patients with metastatic disease, especially when there is a high risk for metastases elsewhere in the body. However, at present, the dearth of options for these patients renders this a moot point, and this therapy could be an early choice for patients with liver-only disease. Therefore, percutaneous hepatic perfusion offers a treatment option in patients with unresectable liver-dominant metastatic melanoma, which currently has no chance of a cure. Percutaneous hepatic perfusion could be used in other cancers that have spread to the liver. The device is currently approved in Europe for all malignant liver tumors and approval is pending in the U.S. for liver metastases from melanoma only.

SARCOMA

Prognostic and predictive factors in advanced soft tissue sarcoma patients treated with pazopanib

Findings from the randomized double-blind, placebo-controlled phase III PALETTE trial were previously reported showing pazopanib, a multi targeted angiogenesis inhibitor, increased median PFS by 13 weeks in patients pre-treated for advanced non-adipocytic soft tissue sarcoma (P<0.0001). A subsequent analysis of these data from 369 patients (123 placebo, 246 pazopanib) was done by Van der Graaf et *al.* to identify prognostic and predictive values for PFS from principal baseline

characteristics, including age, sex, WHO performance status, number of lines of prior systemic therapy for advanced disease, grade, presence of locoregional disease and presence of liver metastases. Upon univariate analysis randomized treatment, performance status and the number of lines of prior therapy had a statistically significant prognostic value, with multivariate analysis showing significant association only between randomized treatment and the number of lines of prior therapy and pazopanib efficacy. No other factors showed significant predictive value for pazopanib efficacy, which remained significant across all explored subgroups. (Van der Graaf, Abstract 9400)

Practice point and future research opportunities

Pazopanib is an active drug showing a prolongation of progression-free survival of more than 3 months in patients with metastatic non-adipocytic soft tissue sarcomas, who have been pretreated with chemotherapy. This treatment effect is present independent from age, sex, tumour grade, performance status, histological subtypes, localization of metastases and the number of lines of prior chemotherapy.

Adjuvant chemotherapy in localized uterine sarcomas

Pautier *et al*. examined a combined chemotherapy approach to treat patients with uterine sarcoma, using adjuvant doxorubicin, ifosfamide and cisplatin (API) followed by radiotherapy in a phase III multicenter study. The objective was to detect an increase of 20% or greater in 3 year PFS with API. The study was halted due to lack of recruitment; however, results of 81 patients with FIGO stage III uterine sarcoma after complete surgery, normal thoracic, abdominal and pelvic CT scan who enrolled were presented. Chemotherapy consisting of 4 cycles of API and additional radiotherapy was administered to 39 patients, while radiotherapy only to 42 patients; vaginal brachytherapy was optional. At median follow-up of 4.3 years, 15 (38%) API and 26 (62%) radiotherapy patients experienced disease recurrence at a median time of 13 months (range 5-43 months). Median overall disease free-survival was 33 months, with 3 year disease free-survival rates favoring API plus radiotherapy; 55% of patients in this treatment arm compared to 41% of patients receiving radiotherapy remained disease free at 3 years (P=0.048). Overall survival rates at 3 years were 81% with API and 69% with radiotherapy. Dose reduction was required by 28% of API patients; toxicity during API of grades 3 and 4 occurred in 31% and 68% of patients, respectively. Febrile neutropenia was seen in 22% of patients with two cases resulting in toxic deaths; renal toxicity of grade 4 was seen in one patient, and nausea and /or vomiting of grades 3 /4 occurred in 24% of patients. (Pautier, Abstract LBA 30)

Practice point and future research opportunities

Adjuvant chemotherapy with doxorubicin, ifosfamide and cisplatin followed by radiotherapy

statistically improved the 3 year disease free- and overall- survival in patients with uterine sarcoma over radiotherapy alone, but with high toxicity during treatment. These results are affected by a small sample size and should be confirmed with a larger trial and longer follow-up to see a real impact on overall-survival.

Imatinib rechallenge in patients with recurring GIST after completion of adjuvant imatinib treatment

Previously reported results from the SSGXVIII/AIO trial of patients with KIT-positive gastrointestinal stromal tumors (GIST) showed that 199 and 198 patients who had been randomly assigned to receive imatinib for either 12 or 36 months had clinical benefit from imatinib. It was significantly greater in patients who had longer treatment. Reichardt *et al.* evaluated the efficacy of imatinib rechallenge within the 81 patients who had GIST recurrence at follow-up done at a median 54.4 months. In the imatinib rechallenged patients overall, complete response (CR) was achieved by 15 (32.6%), partial response (PR) by 14 (30.4%) patients, stable disease (SD) was seen in 10 (21.7%) patients and progressive disease (PD) occurred in 7 (15.2%) patients. The overall clinical benefit rate was 84.8%. Of these patients, 54 patients were in the one year group and 27 patients were in the three year group. In the former group, 11 and 12 patients achieved CR and PR, respectively with 8 patients showing SD and PD occurring in 5 patients. In 27 patients who received imatinib for 3 years with recurrent GIST, 5 and 4 patients achieved CR and PR, respectively with 3 showing SD and PD occurring in 4 patients. The clinical benefit rates of 86% of patients with 1 year and 75% of patients with 3 year treatment were also comparable. The median time to progression rates are not yet mature, since the majority of patients in the 3 year group are still on treatment. Upon mutational analysis, exon 9 mutations were higher in patients with recurrent GIST and associated with a higher risk of recurrence. (Reichardt, Abstract LBA 31)

Practice point and future research opportunities

Significant clinical benefit with high complete response rate was seen following imatinib therapy in patients with recurrent GIST who had previously received adjuvant imatinib, with time to disease progression similar to that of patients who have not been exposed to imatinib in the adjuvant setting. The quality of response may also be attributed to early detection of recurrent disease during follow-up. The data from the analyses are not mature yet.

OTHER ADVANCES IN CANCER - EPIDEMIOLOGY

Blood pressure and risk of incident and fatal cancer in the Metabolic Syndrome and Cancer Project

A statistically significantly association between hypertension and a 10-20% higher risk for men of developing cancer and a higher risk of dying from the disease in both men and women was shown. This study by Van Hemelrijck *et al.* was part of the Metabolic syndrome and Cancer project (Me-Can) that was conducted in Norway, Austria, and Sweden, including 289454 men and 288345 women which sought to reconcile contradictory results reported by several observational studies. From the second year of an average 12 years of follow-up, 22184 male and 14744 female study participants were diagnosed with cancer, with 8724 men and 4525 women dying from their disease. Hazard ratios of incident and fatal cancer were calculated using mid-blood pressure figures, which represent systolic plus diastolic blood pressure divided by two. Average mid-blood pressure was 107 mmHg for men and 102 mmHG for women; results were given by mid-blood pressure quintiles and 10 mmHg increments. Models were stratified by cohort, sex, and birth year, and adjusted for baseline age, body mass index, and smoking status; adjustment for random error in blood pressure measurement or variation within the individual was also incorporated. The incident risk of cancer in men was determined as HR 1.07 per 10 mmHg increment in blood pressure; overall risk of developing any cancer increased by 29% between men in the lowest quintile and highest quintiles. As blood pressure rose, the risk of oral cancers, and cancer of the colon, rectum, lung, bladder, renal cell, and melanoma and non-melanoma skin cancer increased. In women, blood pressure did not significantly associate with overall incident cancer, but did associate with an increased risk of melanoma and cancers of the liver, pancreas, cervix and endometrium. A positive trend by quintiles and 10 mmHg increments of blood pressure was also found for fatal cancer, HR 1.19 and HR 1.12 per 10 mmHg increment in men and women, respectively. Increased risk of dying from cancer was shown for both men and women with elevated blood pressure; men and women in the fifth quintile had a 49% and 24%, respectively, increased risk of dying compared to those in the first quintile. The study was not designed to show a causal link between high blood pressure and cancer risk and did not include treatment for hypertension data. (Van Hemelrijck, Best Abstract 4)

Practice point and future research opportunities

There is increasing evidence that metabolic syndrome is associated with a higher risk of developing cancer as well as other chronic diseases. As an unhealthy lifestyle is a major determinant of hypertension, these results add to the evidence that lifestyles affect both the risk and prognosis of cancer. This extensive, population-based study of the role of concomitant hypertension shows that it has a modest effect on the risk of certain cancers, especially of the kidney and colorectum. This is the largest and the first study to take into account random error, which showed that the association between hypertension and incident or fatal cancer is stronger for men than for women. In contrast, the second largest study previously found a higher cancer risk for women than for men. The differences in findings might be explained due to the larger sample size, slightly older population, adjustment for random error, or lack of information on anti-hypertensive treatment. An association between elevated blood pressure and the risk of developing and dying from cancer has a large public

health implication due to the increasing, already large, hypertensive population.

Chemotherapy during pregnancy: Large study on cognitive and cardiac outcome in children with prenatal exposure to chemotherapy

Amant *et al*. investigated the cardiac and neurodevelopmental outcomes in children prenatally exposed to chemotherapy in a prospective multicenter study. Seventy children ranging from 18 months to 18 years were examined at birth and at the ages of 18 months, between 5 to 6, 8 to 9, 11 to 12, 15 to 16 and at 18 years; their health was monitored for an average of nearly two years, with some for as long as 18 years. In all, 236 chemotherapy cycles, some in combination with radiotherapy, were administered during 68 pregnancies for a variety of cancer types with breast cancer being the most common, occurring in 35 women. The children's general health, school performance, behavioural or emotional problems and other parameters were recorded by questionnaires completed by the parents. Development of the children's mental processes was gauged by testing intelligence, verbal and non-verbal memory, attention, working memory and executive functions. Cardiac function was assessed by electrocardiography and echocardiography. The children were born at a median gestational age of 35.7 weeks; incidence and type of congenital malformations were similar to the general population, as were growth, general health and development. Cognitive development was also in the normal range for the majority of the children; most children falling below the normal Intelligence Quotient (IQ) range had been born preterm. One of the two sets of twins showed significant neurodevelopmental delay; they had been born at 32.5 weeks, but prenatal chemotherapy exposure could not be ruled out. Preterm birth associated with far more developmental difficulties than *in utero* chemotherapy exposure; IQ scores were found to be decreased by about 2.5 points per each week of gestation less than 37 weeks, with a dramatic decrease in children born around 27 weeks. Current practices of delaying treatment of the mother until birth or inducing preterm birth prior to beginning treatment can not be recommended. (Amant, Abstract LBA 12)

Practice point and future research opportunities

The study data suggest that delay of cancer treatment during the second or third trimester of pregnancy or termination of pregnancy in that stage is not necessary. Fetal exposure to chemotherapy is not associated with increased morbidity at the level of the central nervous system, cardiac and auditory functions, as well as general health and growth. However, prematurity was frequently encountered, and associated with impaired cognitive development. International collaboration on longer follow-up will be continued, because at this stage the full, long-term consequences of prenatal chemotherapy, including its effect on the children's fertility and likelihood of developing cancers when they are older are unknown.

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AFFILIATIONS AND DISCLOSURE

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