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Meeting Report

42nd Annual Meeting of the American Society of Clinical Oncology (ASCO) (June 2-6, Atlanta) 2006

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Introduction

During the 42nd Annual Meeting of the American Society of Clinical Oncology (ASCO), which was held in Atlanta, Georgia on June 2-6, 2006, several novelties in the field of cancer treatment and prevention were presented. Here we report what we believe were the most interesting talks regarding the present and near-future daily management of solid tumors by clinical oncologists.

Breast and ovarian cancer

A number of trials on breast cancer were presented, describing therapeutic results obtained with new drugs or with a more skilled use of "old" drugs. The specific prognostic impact of *BRCA1/BRCA2* mutations on breast and ovarian cancers was also highlighted.

A phase III study conducted by Dr. C.E. Geyer, Director of Breast Medical Oncology at the Allegheny General Hospital (Pittsburgh, PA), tested the efficacy of a new drug, lapatinib (Tyberb®), when added to capecitabine in patients with breast cancer progressing after therapy with trastuzumab. In this disease, *HER2/neu* expression is associated with a worse prognosis. Trastuzumab (Herceptin) is an antibody that targets the extracellular part of the HER2/neu protein and represents a useful therapy in these patients. Lapatinib (Tykerb) is an oral drug that inhibits tyrosine kinases on the internal domain of two receptors, erbB1 (EGFR) and erbB2 (HER2). This phase III study enrolled 321 patients who were assessed between March 2004 and November 2005. Half of them received lapatinib + capecitabine and the other half capecitabine alone. Advantages were reported for the combination group regarding disease-free survival (37 weeks *vs.* 20 weeks) and the incidence of brain metastases (4 cases *vs.* 11 cases), although data on overall survival are still not complete. The side effects related to the new drug were mild (58% diarrhea, 30% rash). In conclusion, lapatinib appears to be an alternative treatment for patients whose cancer becomes resistant to trastuzumab.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) released results of the STAR (Study of Tamoxifen and Raloxifene) study comparing tamoxifen and raloxifene (Evista®) for the prevention of new and recurrent breast cancer in high-risk patients. The results were presented by Dr. L. Wickerham, Associate Chairman of the NSABP from Pittsburgh, PA. Tamoxifen is a partial estrogen receptor (ER) antagonist and is active against ER^+ and/or progesterone receptor-positive (PR^+) breast cancers in pre- and postmenopausal women. Its main side effects are an increased risk of thrombosis and uterine cancers. Raloxifene reduces breast cancer risk in postmenopausal women and prevents osteoporosis, with a moderately increased risk of uterine cancer and thrombosis. Both drugs are taken orally. The STAR study, starting in 1999, included 19,747 postmenopausal women at increased risk of breast cancer who were randomized to receive tamoxifen (20 mg/day) or raloxifene (60 mg/day) for 5 years. After 4 years of treatment, the number of invasive carcinomas occurring in the two groups was similar (163 cases *vs.* 167 cases), while more noninvasive tumors were found in the raloxifene group (57 cases *vs*. 81 cases). The toxicity profile slightly favored raloxifene, with a 36% lower risk of uterine cancer (which was considered not statistically significant), a 29% lower risk of venous thrombosis and fewer patients experiencing pulmonary embolism

(0.9/year *vs*. 1.4/year), while no difference was found in the risk of reduced heart function or bone fractures. A substudy assessing the quality of life of patients enrolled in the STAR study pointed out that in the tamoxifen subgroup, hot flashes, vaginal bleeding, bladder incontinence and cramps were more common, while in the raloxifene arm, joint pain and vaginal dryness were reported more frequently. The study concluded that both drugs reduce by roughly 50% the risk of invasive breast cancer in high-risk postmenopausal women, while only tamoxifen prevents noninvasive cancers as well. On the other hand, the well-known risks related to tamoxifen in terms of side effects may be important in choosing the appropriate drug in selected cases.

Results from the Intergroup Exemestane Study (IES) were discussed by Dr. J. Bliss (Institute of Cancer Research, Sutton, UK). The study aimed to evaluate the effect of switching to exemestane (Aromasin®) after 2-3 years of adjuvant therapy with tamoxifen in postmenopausal women treated for early hormone-sensitive breast cancer. This study enrolled 4,724 patients, half of whom were randomly switched to exemestane after 2 or 3 years of tamoxifen and the other half were kept on tamoxifen for the entire 5 years. The switch to exemestane provided a 15-17% reduction in the risk of death (210 deaths *vs.* 251 deaths) and a 24% reduction in the recurrence rate at a median follow-up of 4.8 years. Patients receiving the combined adjuvant therapy also obtained constant results in the last 2 years of treatment, in contrast to patients who were treated with tamoxifen alone. Musculoskeletal side effects were reported more frequently in the combination group, while a lower rate of thrombosis and uterine tumors was reported in this group. No difference in cardiac events was found between the two treatment groups. In conclusion, switching to exemestane after 2 or 3 years of adjuvant treatment with tamoxifene reduces the risk of death, the recurrence rate and the expected side effects typical of tamoxifen.

Data from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial on the effects of anastrozole (Arimidex®) on bone loss were presented by Dr. Coleman. Anastrozole inhibits the ability of aromatases to convert androgens to estrogens in the subcutaneous fat and other extraovarian tissues. It is widely used in patients with hormone-sensitive breast cancer, and the ATAC study itself has previously demonstrated that this drug lowers the recurrence rates when used as adjuvant therapy. Since anastrozole also reduces the beneficial effects that estrogens have on continuous bone remodeling, its main expected side effect is increased bone resorption. Conversely, tamoxifen, as a partial ER agonist/antagonist, has a protective effect on bone resorption. The ATAC study compared 5 years of adjuvant treatment with anastrozole *vs*. tamoxifen in women who underwent radical surgery for breast cancer. During the trial, data were collected to study the effects of the two drugs on bone resorption in postmenopausal patients. Eighty-one women received anastrozole and 86 tamoxifen. In the first group, the average loss in bone mineral density (BMD) was 6.1% in the lumbar spine and 7.2% in the hip, compared to 2.8% and 0.7%, respectively, in the tamoxifen group. In conclusion, anastrozole induced a greater loss of BMD than tamoxifen, although it has not been proven to induce osteoporosis (15-20% loss in bone mass). Overall, it appears that anastrozole is associated with an overall safer profile than tamoxifen in the treatment of breast cancer and in the prevention of recurrence, given the low rates of thrombosis and uterine cancer. Nevertheless, it is recommended that it be used with vitamin D and other strategies to increase calcium intake, and that an annual follow-up of the patients' BMD be performed.

An interesting study was performed at the M.D. Anderson Cancer Center (Houston, TX) and the Swami Vivekananda Yoga Anusandhana Samsthana yoga center in Bangalore, India, to assess if yoga can improve the quality of life of women receiving radiotherapy for breast cancer. The study included 61 patients receiving radiotherapy, divided by stage groups, who were randomly assigned to yoga or to the control arm, which consisted of no programmed alternative activity. The yoga arm performed physical and relaxation exercises twice per week for the entire duration of radiotherapy. The quality-of-life questionnaires showed that patients with the same disease stage felt better physically and psychologically, and in general had a better quality of life, if they practiced yoga during the cancer treatment. This may suggest that yoga improves the condition of patients receiving treatment for breast cancer, but the researchers also pointed out that the patients in the yoga arm may have felt better because of the psychological help deriving from a group activity more than from the yoga itself. Moreover, the perception that the hospital was taking better care of them may also have played a role in this result. The same group is in fact preparing a new study comparing patients attending yoga classes with patients attending regular stretching classes.

A study was conducted to further evaluate the advantage of prophylactic oophorectomy in women with *BRCA1/BRCA2* mutations, a well-known risk factor for breast and ovarian cancer. The study, led by Dr. N. Kauff from Memorial Sloan-Kettering Cancer Center in New York, was concluded in November 2005, with an average follow-up of 40 months. A total of 886 women over 30 years of age with a *BRCA1/BRCA2* mutation were divided into two groups depending on whether they underwent surgery (561 cases) or not (325 cases). The analysis of the data showed that the overall risk reduction was 47% for breast cancer and 89% for ovarian cancer. Results were even more interesting when subjects were stratified by the type of mutation. In women with *BRCA1* mutations, surgery decreased the risk of ovarian cancer by 87%, and the risk of breast cancer was reduced by 39%. In women with a *BRCA2* mutation, the risk of breast cancer was reduced by 72% and no ovarian cancer was seen after surgery, although it did occur in 2 women who did not undergo surgery. *BRCA1/BRCA2* mutations are well-known and extensively studied risk factors for both breast

and ovarian cancers. The choice of receiving prophylactic surgery is taken by the patient advised by physicians on the basis of the risk of cancer associated with the mutation. This study not only further confirms this association, but also points out the difference between the two mutations regarding the relative risk of breast and ovarian cancer. In light of these results, it might be worthwhile to study the advantage of combined prophylactic oophorectomy and bilateral mastectomy for women with mutations in the *BRCA2* gene.

Lung cancer

Two phase II clinical trials in previously treated patients with advanced non-small cell lung cancer (NSCLC) investigating the response to sorafenib (Nexavar®) and sunitinib (Sutent®) were presented. Interesting talks were also held on the effect of adjuvant treatment in early-stage NSCLC, with data partially contradicting previously reported results.

Sorafenib is a multikinase inhibitor that interferes with the cell cycle by blocking the Raf kinase pathway (which is downstream from the *RAS* gene and the epidermal growth factor receptor [EGFR]) and interrupting angiogenesis via inhibition of vascular endothelial growth factor receptors VEGFR-1, -2 and -3, platelet-derived growth factor receptor α (PDGFRα), c-Kit and Flt-3. Fifty-two patients were enrolled in a clinical trial to receive oral sorafenib 400 mg twice daily until disease progression. The results showed a partial remission (PR) in 7.7% of the cases, stable disease (SD) in 58% (29% with an initial objective response) and progressive disease (PD) in 35%. The median progression-free survival was particularly interesting for the patients who achieved SD (23.7 weeks), while the global progression-free survival was 11.9 weeks. The median overall survival was 29.3 weeks, with 2 patients currently on treatment after more than 2 years. Grade 3 adverse events were rare (hand-foot skin reaction, 10%; hypertension, 4%; diarrhea, 2%). Biomarker data also showed that both patients with high initial circulating VEGF levels and those with a large decrease in circulating VEGF levels had a shorter survival. Among the patients classified with SD, several cases were reported to have a clear tumor cavitation on CT scan, highlighting that the responses to certain new biologicals should be evaluated with different systems than that currently used, which only measures disease diameters. Objective responses were at least as frequent as with gefitinib (Iressa®) and erlotinib (Tarceva®), two compounds extensively tested as single-drug therapies for this disease.

Sunitinib is a tyrosine kinase inhibitor that acts on VEGFR-1, -2 and -3, PDGFRα and PDGFRα, Ret, Flt-3 and c-Kit. A study which enrolled 63 patients not responding to other therapies, who took sunitinib orally at a dose of 50 mg/day with a 2-week pause every 4 weeks until evidence of disease progression, was discussed. About 40% had SD and 10% achieved objective responses, with an average progression-free survival of 11.3 weeks. One patient died of treatment-related pulmonary hemorrhage.

J.P. Pignon presented a meta-analysis of trials with adjuvant chemotherapy in lung cancer, performed at the Institut Gustave-Roussy in Villejuif, France. The trials analyzed were ALPI, ANITA, BLT, IALT and JBR10, all of which were randomized and included at least 300 patients who underwent complete surgical resection. The studies compared cisplatin with or without radiotherapy *versus* no chemotherapy with or without radiotherapy and excluded concurrent chemo/radiotherapy. All the trials were terminated after 1995 with a median follow-up of 5.1 years (3.1-5.9 years). According to this analysis, the chemotherapy arms gave a 3.9% advantage in 3-year survival (61% *vs*. 57.1%) and a 5.3% advantage at 5 years (48.8% *vs.* 43.5%), as well as a major disease-free survival. The most interesting results emerged when patients were stratified by stage; the main benefits were associated with stage II and III, while patients with stage IB showed no benefit of chemotherapy and stage IA patients even showed a detrimental effect of the treatment. These results support the use of adjuvant chemotherapy in stage II-III NSCLC and provide more details than a previous meta-analysis published in 1995 in the *British Medical Journal*, which did not give results stratified by stage. The authors also demonstrated that the combination of cisplatin and vinorelbine was associated with better results than other combinations, although this could be attributed to the higher doses of cisplatin used in this scheme rather than the addition of vinorelbine.

The update on the Cancer and Leukemia Group B (CALGB) trial for the evaluation of long-term survival in patients treated with adjuvant chemotherapy for stage IB NSCLC was presented at the ASCO conference by Dr. G.M. Strauss. Patients in the study were randomized to a control and a chemotherapy arm, where they received 4 cycles of carboplatin (AUC6) and paclitaxel (200 mg/m^2) 4-8 weeks after complete surgical resection consisting of lobectomy/pneumonectomy and node sampling. Trial enrollment was interrupted at 384 patients because of the significant survival advantage seen in the chemotherapy arm. Initial results obtained at a median follow-up of 34 months were presented at the 2004 ASCO meeting, with an 8% overall survival benefit in the chemotherapy arm (79% *vs*. 71%). Nevertheless, this benefit was not confirmed at the 54-month follow-up presented at this year's meeting. The updated overall survival data were similar in the chemotherapy and control arms: 59% *vs*. 57%, with major benefits associated with tumors > 4 cm. Side effects other than grade 3/4 neutropenia (35% of cases) were infrequent. In conclusion, a small percentage of patients obtained a longer progression-free survival, but at 5-year follow-up the advantage in overall survival was not evident, at least for patients receiving carboplatin and paclitaxel, and especially for tumors < 4 cm.

A retrospective analysis was performed on patients included in the National Cancer Institute of Canada Trials Group and Intergroup study BR.10, and the findings were presented by Dr. C. Pepe, from Princess Margaret Hospital in Toronto, Canada. The analysis assessed the

feasibility and advantage of adjuvant chemotherapy in elderly patients with early-stage NSCLC. In this study, 482 patients with complete resection of stage IB and II NSCLC were randomly assigned to a chemotherapy arm with 4 cycles of cisplatin (50 mg/m^2 on days 1 and 8 every 4 weeks) plus 6 weeks of vinorelbine (25 mg/m^2/week) or to a control arm. Of these, 155 were considered elderly (over 65 years of age) and were divided equally in the two treatment arms. Elderly patients presented less frequently with an optimal performance status (PS0: 41% *vs*. 53%) and with adenocarcinoma (43% *vs*. 58%) than younger patients. The overall survival at 5 years was longer in the chemotherapy arm (69% *vs*. 54%). Elderly patients received lower doses of drugs, even if treatment-related toxicities were similar between the groups, probably due to the concern of both patients and physicians of even mild side effects. Nevertheless, while differences in 5-year overall survival between treatment arms in younger patients were not statistically significant, 5-year overall survival for elderly patients receiving chemotherapy was significantly higher than in the control group (66% *vs*. 46%; $p = 0.04$). Although not yet confirmed by phase III trials, the combination of cisplatin and vinorelbine has been suggested to be the most effective treatment for such patients. Moreover, the results from this study have not been stratified by stage and tumor dimensions, and according to other recent studies, the larger size of the tumors and the inclusion of stage II patients may have positively influenced the results. In conclusion, on the one hand, this study coincides with other results presented at this year's ASCO meeting insofar as it shows no advantage for adjuvant therapy in stage I NSCLC patients. On the other hand, it also demonstrates that even low doses of adjuvant cisplatin-based chemotherapy are able to improve survival in elderly stage IB/II NSCLC patients.

Kidney cancer

Four promising targeted drugs have provided good results in renal cell carcinoma (RCC), a cancer in which no significant improvement has been achieved in more than a decade.

A multicenter phase III study was performed and presented by Dr. R.J. Motzer, from Memorial Sloan-Kettering Cancer Center (MSKCC) in New York, to assess the efficacy of sunitinib malate as first-line therapy in metastatic RCC. Through October 2005, 750 patients were enrolled and randomized to receive interferon alfa (IFN-α; escalated doses of 3, 6 and 9 MU/week s.c.) or sunitinib (50 mg/day p.o. for 4 weeks followed by a 2-week rest period) until disease progression. Approximately 90% of patients from both treatment groups underwent nephrectomy. The results of this multicenter phase III trial significantly favored the sunitinib arm, with a progression-free survival of 47 weeks compared to 25 weeks, irrespective of the MSKCC risk group the patients were included in, and an objective response rate of 35.7% *versus* 8.8%, including 1 complete response (CR). Quality-of-life (QoL) questionnaires also favored the sunitinib arm, the most common side effect being asthenia; patients receiving the new drug showed lower rates of withdrawal from the trial than those given IFN-α. The objective response rate, progression-free survival and QoL results confirm data obtained in preliminary phase II trials. However, the median overall survival has not yet been reached and no differences in overall survival have been found between the two arms to date. It remains to be seen what advantage this first-line therapy entails for metastatic RCC.

A randomized phase III trial compared temsirolimus, IFN-α or the combination of temsirolimus and IFN-α as first-line therapy in advanced, high-risk RCC. Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin) kinase, which regulates cell growth and angiogenesis downstream of the phosphatidylinositol 3-kinase (PI3K)/Akt cascade. The trial accrued through April 2005 a total of 626 patients, who were randomized into three treatment arms consisting of weekly temsirolimus alone (25 mg i.v.), IFN-α alone (up to 18 MU/week) or the combination of temsirolimus (15 mg/week) and IFN-α (6 MU/week). The results from the second interim analysis, presented by Dr. G. Hudes, from the Fox Chase Cancer Center in Philadelphia, PA, significantly favored monotherapy with temsirolimus over the combination. Monotherapy with temsirolimus gave a median overall survival of 10.9 months compared to 8.4 months for the combination and 7.3 months for IFN-α alone. A similar advantage compared to IFN-α monotherapy was obtained for progression-free survival (3.7 months with temsirolimus, 3.7 months with the combination and 1.9 months with IFN-α) and objective response rates (9% with temsirolimus, 11% with the combination and 7% with IFN-α). Tolerability also favored treatment with temsirolimus alone; the most common side effects were asthenia (grade 3 in 12% of cases), anemia (grade 3 in 21% of cases) and dyspnea (grade 3 in 9% of cases). Thus, first-line treatment with temsirolimus alone appears to be an attractive choice in patients with RCC, and this trial indicates that combination therapies are not always the best option, perhaps because of the necessary dose reductions.

A phase III study was conducted in refractory metastatic RCC patients to assess the efficacy of lapatinib, and the results were presented by Dr. A. Ravaud from the University Hospital in Bordeaux, France. This new tyrosine kinase inhibitor blocks the receptors erbB1 (EGFR) and erbB2 (HER2). The 416 patients included in the study from December 2002 were randomized to receive either oral lapatinib or hormone therapy (megestrol acetate or tamoxifen). Improved overall survival (46 weeks *vs.* 37.9 weeks) and progression-free survival (15.1 weeks *vs.* 10.9 weeks) were obtained with lapatinib in patients with high EGFR expression. On the other hand, no difference between the treatment arms was found in the analysis patients with low or negative EGFR expression, due to the mechanisms of action of the drug. Side effects were tolerable, the most common event associated with lapatinib being diarrhea in 40% of cases; a reduced left ventricular ejection fraction was detected in

5% of patients treated with lapatinib. As the EGFR is highly expressed in roughly 60% of RCC, lapatinib can be considered an interesting treatment option in this group of patients.

A phase II and a phase III trial were conducted to assess the efficacy of sorafenib as first- and second-line treatment, respectively, in patients with metastatic RCC, and preliminary data were presented at the ASCO meeting. The phase II trial accrued, until September 2005, 188 previously untreated patients who were randomized to receive sorafenib as first-line treatment (400 mg b.i.d. p.o.) or IFN (9 million units weekly s.c.) until disease progression, with the option to switch to sorafenib after progression on IFN or to escalate to a sorafenib dose of 600 mg twice daily. Patients were stratified into two groups according to an MSKCC risk score: low (59% of the patients who received sorafenib and 57% of those receiving IFN) or intermediate (40% of the patients who received sorafenib and 42% of those receiving IFN). Over 90% of patients from both groups underwent a prior nephrectomy. Sorafenib was in general better tolerated than IFN; the main grade 3 events associated with the drug were hand-foot syndrome (10%), rash (5%), diarrhea (4%) and fatigue (3%), and fewer patients on sorafenib discontinued treatment due to side effects. At a median follow-up of 5.3 months, among 51 evaluable patients receiving sorafenib, SD was reported in 13 cases and PD in 38. In the phase III trial, 903 patients with metastatic RCC who failed prior systemic therapy were included and randomized to receive second-line therapy with sorafenib or placebo until disease progression. Based on data obtained from another phase III study that showed a 39% improvement in survival for patients taking sorafenib, patients in this trial were allowed to cross over to sorafenib after disease progression on placebo. At the time of analysis in November 2005, 216 placebo patients had already crossed over. The median overall survival was 19.3 months for sorafenib *versus* 15.9 months for placebo, with an improvement in survival of 30%.

Data presented on sorafenib at this meeting do not yet allow us to draw definitive conclusions. Nevertheless, sorafenib has been approved by the FDA for the treatment of advanced RCC, and the promising initial results discussed above confirm its efficacy and its putative role in the first- and second-line treatment of RCC.

Head and neck cancer

Induction chemotherapy with docetaxel (Taxol®), cisplatin (Platamine®) and 5-fluorouracil (5-FU) (TPF) was compared to the standard combination of cisplatin and 5-FU (PF) in patients with advanced squamous cell cancer of the head and neck (SCCHN). In this phase III study, presented by Dr. R. Posner from the Dana-Farber Cancer Institute in Boston, 494 patients with stage III-IV tumors of the oral cavity, oropharynx, larynx and hypopharynx were treated, with a median follow-up of 42 months. They were randomized to receive one of the two induction treatments for 3 cycles every 3 weeks, and then received chemo/radiotherapy with weekly carboplatin and eventually debulking surgery. The overall survival at 3 years was improved in the TPF arm (62% *vs*. 48%), with a median overall survival of 70.6 months *vs.* 30.1 months, and the death rate was reduced by 30%. Treatments were equally well tolerated except for increased neutropenia and alopecia in the TPF arm. Toxicity was mainly due to the radiation part of the sequential therapy, and more patients in the PF arm died within 30 days from the treatment (12 patients *vs.* 4 patients). Adding docetaxel to the standard induction therapy with cisplatin and 5-FU therefore improves 3-year survival and is not associated with relevant additional toxicity; further studies are required to clearly prove the superiority of this sequential therapy over the standard chemo/radiotherapy treatment.

Esophageal cancer

Results from the CALGB 9781 study were presented comparing trimodality treatment (induction, chemoradiation and surgery) with surgery alone in esophageal cancer. This randomized phase III study was closed in March 2000 after 3 years due to poor accrual. Patients included presented with stage I-III disease, tumors > 2 cm from the gastroesophageal junction, no distant node metastases, 75% with adenocarcinoma and a median follow-up of 6 years. Of the expected 500 patients, only 56 were enrolled and randomized into two groups with equal risk factors. Thirty patients received the combination treatment (cisplatin 100 mg/m^2 on day 1 + 5-FU 1000 mg/m^2 on days 1-4 on weeks 1 and 5 + radiotherapy 50.4 Gy over 5.6 weeks) followed by esophagectomy with node dissection after 3-8 weeks. Response was assessable in only 25 patients; 40% of the patients in the trimodality arm achieved a complete pathological response (pCR) and 40% a partial pathological response (pPR). The trimodality treatment caused mainly grade 3-4 hematopoietic toxicity (54%), dysphagia (40%) and anastomotic leak in 2 patients (6.7%). More patients treated with surgery alone suffered from complications related to the surgery (17 *vs.* 14), and 2 of them died within 30 days after the procedure. Survival rates at 5 years were higher in the trimodality arm (39% *vs.* 16%), as were the overall survival (4.5 years *vs.* 1.8 years; p = 0.02) and the recurrence rate (9 relapses *vs*. 14 relapses, mainly distant). Thus, although accrual was notably reduced and the numbers presented are very small, clear statistically significant advantages were proven for the trimodality treatment.

Anal canal cancer

A phase III multicenter, randomized study was conducted to compare the standard combination treatment of 5-FU, mitomycin (MMC) and radiotherapy (RT) with an induction treatment based on 5-FU and cisplatin followed by combination of 5-FU, cisplatin and radiotherapy, in patients with squamous cell carcinoma of the anal canal.

The study, presented by Dr. J.A. Ajani from the M.D. Anderson Cancer Center (Houston, TX), aimed to assess whether induction therapy with cisplatin prior to radiation would improve the outcome of these patients. The two treatment arms consisted of the standard 5-FU (1000 mg/m^2 on days 1-4 and 29-32), MMC (10 mg/m^2 on days 1 and 29) and concurrent RT (45-59 Gy), or 5-FU (1000 mg/m^2 on days 1-4, 29-32, 57-60 and 85-88), cisplatin (75 mg/m^2 on days 1, 29, 57 and 85) and RT (45-59 Gy starting at day 57). The trial accrued 598 evaluable patients (682 total) with a median age of 55 years; 69% of evaluable patients were women, 28% had tumors > 5 cm and 26% presented with clinical lymphadenopathy. Both disease-free survival (56% *vs.* 48%) and overall survival (69% in both) at 5 years did not show any significant differences between the groups, nor did local control rate. Although hematological toxicity was more frequent in the standard treatment arm (67% *vs.* 47%), the rate of colostomy at 5 years was clearly higher in the induction therapy arm (20% *vs*. 10%). Therefore, the use of induction therapy based on cisplatin not only does not represent a more effective therapy for patients with squamous cell anal cancer, but it also increases the late toxicity of radiotherapy, resulting in more patients remaining on colostomy after 5 years. Therefore, the standard therapy based on 5-FU, MMC and concurrent RT remains the best option for these patients.

Pancreatic cancer

A phase III trial (RTOG 9704) compared the efficacy of gemcitabine (GEM) and 5-FU as induction and adjuvant therapy in patients treated with chemoradiation (CRT) with 5-FU for resected pancreatic carcinoma. The study accrued through July 2002 442 evaluable patients (538 total) with T1-4, N0-1, nonmetastatic, completely resected adenocarcinomas. Patients were stratified by nodal and margin status and by tumor size. The standard treatment arm consisted of 3 weeks' induction with 5-FU (250 mg/m^2/day by continuous infusion), CRT with 5-FU (250 mg/m^2/day by continuous infusion) and RT (50.4 Gy over 28 days) and then the same dose of 5-FU for 12 weeks. The second arm consisted of 3 weeks' induction with GEM (1000 mg/m^2/week) followed by CRT with 5-FU (same dose as the standard arm) and 12 weeks of GEM (1000 mg/m^2/week). Results did not show any significant differences between the arms when the entire population was analyzed; however, a significant advantage in terms of survival (median: 18.8 months *vs.* 16.7 months; 3-year survival: 31% *vs*. 21%) emerged for patients whose tumor was localized to the head of the pancreas. No significant difference in toxicity was observed between the two treatments other than a higher rate of grade 4 hematological toxicity for patients receiving GEM (14% *vs*. 2%). In particular, 90% of patients in the GEM arm and 86% of those in the 5-FU arm were able to receive all the programmed chemotherapy, and radiotherapy could be completed in 88% of the patients in the GEM arm and 85% in the 5-FU arm. It was concluded that the most effective treatment for patients with complete resection of adenocarcinoma of the pancreatic head is GEM + 5-FU/RT + GEM.

Gastric cancer

A large, randomized phase III trial compared the use of oral capecitabine (Xeloda®) with intravenous (i.v.) cisplatin (XP) and continuous infusion of 5-FU in association with cisplatin (FP) for the treatment of advanced gastric cancer. The study was presented by Dr. Y. Kang, from the Asian Medical Center in Seoul, Korea. The trial enrolled 316 patients with previously untreated advanced or metastatic cancer, who received either capecitabine (1000 mg/m^2 b.i.d. on days 1-4) and i.v. bolus cisplatin (80 mg/m^2 on day 1) every 3 weeks, or continuous i.v. infusion of 5-FU (800 mg/m^2 on days 1-5) plus cisplatin until disease progression. The two treatments showed similar overall survival (median XP: 10.5 months; median FP: 9.3 months), with the XP arm showing a trend for better progression-free survival and higher response rates (41% *vs.* 29%). Minimal differences in toxicities were found in favor of the FP group for hand-foot syndrome (5% *vs*. 0%) and stomatitis (6% *vs.* 2%). Thus, the XP regimen provides similar overall and progression-free survival, higher response rate and similar toxicity compared to the standard FP regimen, sparing the need for setting up a central line. Therefore, in compliant patients, the higher costs of this regimen may overcome the costs of hospitalization for procedures and complications of the intravenous infusions.

Prostate cancer

A large trial was conducted to assess the efficacy and tolerability of intermittent androgen deprivation therapy (iADT) compared to the standard continuous androgen deprivation therapy (cADT). The results were presented by Dr. F.M. Calais Da Silva, from the Hospital Desterro in Lisbon, Portugal. The 766 patients enrolled presented with locally advanced (T3-4, M0) or metastatic disease and no previous therapy. They first received induction therapy with cyproterone acetate (200 mg for 2 weeks) and a luteinizing hormone-releasing hormone (LHRH) analogue (1 injection/month for 3 months). Then, patients with an 80% decrease in their prostate-specific antigen (PSA) or with a PSA < 4 ng/ml were randomized to one of the subsequent treatment arms with ADT. In patients in the iADT group, the time off therapy ended at symptomatic PSA levels > 10 ng/ml, asymptomatic PSA > 20 ng/ml or a PSA increase of > 20%. A total of 626 patients were randomized in groups equally balanced by median PSA (1.2 ng/ml in the iADT and 1.3 ng/ml in the cADT), with 22% showing a PSA > 4 ng/ml and 31% a PSA < 2 ng/ml. PSA was monitored every 3 months. The median time off therapy was 52 weeks, 74 weeks (82% of the treatment time) for patients whose PSA at randomization was < 2 ng/ml and 16 weeks if the PSA at randomization was > 4 ng/ml. Overall, half of the patients in the iADT group were off therapy for at least 52 weeks, 29% of them

for at least 36 months. Independently of the PSA values at randomization, the median duration of the second treatment “cycle” was 14 weeks, and the median duration of the subsequent time off therapy was 70 weeks. There was no significant difference between the two arms in terms of overall survival. During the follow-up period, 110 patients from the iADT group and 99 from the cADT group showed PD. Side effects clearly favored the iADT arm, where fewer patients complained of at least 1 episode of hot flashes (20% *vs.* 30%) and more reported significantly improved sexual activity. Intermittent androgen deprivation therapy is not curative but provides similar results to continuous therapy, with a significantly better quality of life. Therefore, this treatment option should be considered in daily practice, especially for patients with metastatic disease.