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Editorial

It is with pleasure that the team of the headoffice of the Central European Cooperative Group (CECOG) and I present to you the third CECOG newsletter which continues the relatively young tradition of distribution of information about important developments in international oncology as well as within CECOG. The recent year has rather quietly brought very major advances to the arena of clinical oncology: Taking advanced breast cancer as an example, we have witnessed not only the emergence of new aromatase inhibitors and a shift in the recommended time point of their use, but also of therapeutic modalities harboring the potential of inducing impressive responses via the use of innovative combinations of cytotoxic drugs in a very considerable number and percentage of patients, impressively outshining previous data obtained with traditional cytotoxics and their combinations. These results have impressively documented the persisting vast potential of novel cytotoxic drugs and their combinations in the control of advanced breast cancer without reducing the justly tremendous expectations connected with the highly promising results obtained in first large-scale studies testing for the efficacy of biological agents including the administration of specific antibodies in clearly defined patient populations. CECOG is happy to be at the forefront of this development by running the very well accepted randomized phase III study comparing the efficacy of the highly promising combination of gemcitabine, epirubicin and paclitaxel (GET) with the traditional regimen containing fluorouracil, epirubicin and cyclophosphamide (FEC) in its area. The trial has recruited more than 130 patients with advanced breast cancer who received either regimen as first-line cytotoxic treatment since the inclusion of the first patient 18 months ago and is fulfilling all criteria of a successful clinical study in any possible aspect. A first interim toxicity analysis has corroborated our initial expectations of an acceptable side-effect profile of GET as compared to the FEC regimen. Not only the progress of the latter trial, but also excellent and swift recruitment into another randomized prospective CECOG study which tests for the efficacy of maintenance chemotherapy with gemcitabine following induction treatment with gemcitabine and cisplatin in patients with advanced Non Small Cell Lung Cancer (NSCLC) allow for optimism to position the area covered by CECOG as independent point of gravitation in the field of clinical oncology

in the near future. In order to document CECOG's devotion in the pursuit of this goal, we are glad to present to you portraits of our most successful partners in the recruitment of patients into either protocol in this issue of the CECOG newsletter. The satisfactory development of our trials has given CECOG the opportunity to sponsor yet another trial comparing the efficacy of GET with epirubicin and paclitaxel (ET) in a prospective, randomized phase III trial which will be conducted on a global scale. This study conducted in cooperation with Professor PierFranco Conte from Santa Chiara Hospital in Pisa who acts as Principle Investigator has been the subject of vast recent efforts at the CECOG headoffice and has finally led to the recruitment of the first patient in March 2001. Of course, all of the mentioned developments would not have been possible without a major expansion of our headoffice. As you can read in the section on CECOG News in the current issue, not only administrative personnel and CRAs have been hired, but also a re-definition of tasks and structures has been performed. Thus, the CECOG headoffice is happy to welcome Dr. Thomas Brodowicz as Co-Coordinator, and several other highly qualified collaborators mentioned in this issue under CECOG News have joined our team. While additional protocols for clinical studies on pancreatic, bladder or NSCLC are being designed or finalized currently, one of the major additional tasks of CECOG lies in the establishment of quality guidelines in the treatment of cancer: Thus, CECOG's educational committee chaired by Prof. Michael Krainer acting in cooperation with the European School of Oncology is preparing for a Consensus Development Conference on the Treatment of Non Small Lung Cancer which will convene opinion leaders in the field and define minimal treatment standards for NSCLC in November 2001 in Vienna. Recommendations of this Conference will be published and serve as guidance for appropriate and quality-oriented care of patients with NSCLC within CECOG's area of activities. While continuing our academic, clinical and educational efforts, we are constantly updating our homepage www.cecog.org which you are very warmly invited to visit in order to pick up all of the exciting news of this dynamic group. We would be happy to have you participating in our endeavour.

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Adjuvant therapy of breast cancer St. Gallen Consensus 2001

The St. Gallen Breast Cancer Meeting, which takes place every three years, is one of the major highlights in the congress calendar of oncologists. The consensus statement related to the adjuvant treatment of breast cancer originating from this meeting will serve as a guideline for many doctors throughout the world. The interdisciplinary discussion on the 2001 consensus was again very interesting and thrilling. It should be emphasized that the following report is not the consensus statement per se. It is rather a summary of the discussions and presentations during this conference.

Antihormonal therapy

Risk stratification is one of the most important issues that influence therapeutic strategies in early breast cancer patients. The actual St. Gallen consensus statement differentiates between low and high risk patients, but does not refer to intermediate risk patients anymore. „Low risk“ comprises breast cancer patients without lymph node metastases, with a primary tumor size ≤ 2 cm, hormone receptor positive tumours, a low grading (1–2) and an age ≥ 35 years. „High risk“ applies for node negative breast cancer patients in case of a tumour size > 2 cm, hormone receptor negativity, grading 3 and age < 35 years. In addition, patients with hormone receptor positive tumours are considered as „high risk“, if one of the high risk criteria is present.

According to the 2001 statement, adjuvant therapy of choice in low risk breast cancer patients is tamoxifen. In addition the St. Gallen statement also offers the option to refrain from adjuvant treatment. Thus the decision in favour of or against a therapy with tamoxifen is always based on the individual situation of the patient. This de-

cision often represents a challenging issue due to the lack of clear cut criteria which could help to define a rationale for the treatment strategy. One of the key questions would be to outweigh the risks and benefits of a long term therapy with tamoxifen, usually scheduled for five years.

In high risk patients the adjuvant treatment strategies depend on the menopausal status: Premenopausal women with hormone receptor positive tumours have several options including the combination of ovarian ablation/LHRH analogues + tamoxifen, the combination of antihormonal therapy and chemotherapy and chemotherapy alone. However, a clear cut advantage for one or another therapy regimen has not emerged from prospective randomized trials so far. Therefore the selection of the optimal adjuvant therapy is a matter of an individual decision making process. In postmenopausal hormone receptor positive breast cancer patients tamoxifen has to be regarded as drug of choice, either as monotherapy or in combination with chemotherapy. However, exact prediction of the patient subset who experience a substantial benefit from combining tamoxifen and chemotherapy regimens is still representing a matter of research.

Treatment strategies in lymph node positive breast cancer patients are also based on menopausal- and hormone receptor status. Premenopausal hormone receptor positive patients should receive the combination of ovarian ablation/LHRH analogues + ta-

moxifen ± chemotherapy. In postmenopausal women a tamoxifen based adjuvant therapy (either alone or in combination with chemotherapy) is regarded to represent the preferred strategy.

Chemotherapy

High risk patients with hormone receptor negative tumours should receive adjuvant chemotherapy. Several prognostic and predictive factors might be used for the definition of suitable patients. However, the clinical relevance of these factors has not been established in prospective studies.

With respect to the selection of a treatment approach there has been no doubt that anthracyclines play a major role. These drugs have been shown to improve relapse free survival and overall survival. Incorporation of anthracyclines in adjuvant therapeutic regimens yielded a 3% survival improvement as compared to CMF. Given that CMF therapy resulted in an 8–12% improvement compared to a control group, it was reasonable to state that implementation of anthracyclines in the adjuvant treatment approach represented a major progress. According to the 2001 consensus statement 4 cycles of an anthracycline containing adjuvant regimen should be administered as first line therapy (AC, EC, FAC, FEC). Due to the widespread use of different CMF schedules it was clearly stated and recommended to administer the classic CMF schedule according to Bonadonna in case of any pre-existing contraindications for anthracycline application.

Risk stratification of NO patients

Tumour size	≤ 2 cm	> 2 cm
ER/PR status	positive	negative
Grading	1–2	3
Age	≥ 35	< 35

Table 1: Definition of low and high risk patients (lymph node negative).

Within an interim analysis of an adjuvant breast cancer study, where 4 cycles AC followed by taxanes were administered, a 3% improvement of overall- and relapse-free survival as compared to the control arm occurred. However, a second analysis of this trial has shown that the previously reported benefit of the taxane containing regimen was restricted to the subgroup of premenopausal patients. Nevertheless, the 2001 consensus statement will probably include this regimen as a therapeutic option for lymph

node positive breast cancer patients. By contrast, the NIH consensus (November 2000) does not consider this combination regimen as a recommended treatment option. In order to define the definite role of taxanes in the adjuvant treatment set-

Summary on chemotherapy

- HER2 status should not be used for treatment decisions
- If chemotherapy, use anthracycline containing regimens
- If CMF, use the original Bonadonna regimen
- The role of taxanes needs to be defined

Table 2: Summary of the discussion on adjuvant chemotherapy

ting of breast cancer patients further studies are warranted. ◆

Gemcitabine in locally advanced and/or metastatic bladder cancer

Introduction

It is estimated that there are 261.000 new cases of bladder cancer worldwide with 115.000 deaths reported annually (1). Bladder cancer is the fifth most common cancer in men and the seventh in women, with an occurrence of three males to one female (2). In Europe, bladder cancer is the fourth most common cancer in men, accounting for 4% of all cancer deaths in men, and it is the fifth most common cause of cancer death overall (3).

Bladder cancer is predominantly the disease of the elderly and despite the continuous increase in incidence, the mortality has been fairly stable over the last two decades (2).

The most common histological type in bladder cancer is transitional cell carcinoma (TCC). Approximately 70-80% of tumours are detected and diagnosed at an early, curable stage. However, 20-30% of tumours infiltrate the bladder wall, and one-half of muscle-invasive tumours will become metastatic (2). Radical cystectomy is the recommended

treatment in most cases of infiltrating, non-metastatic, bladder cancer. Systemic chemotherapy is the only current modality for long-term survival in patients with advanced or metastatic TCC. These include methotr-

exate, doxorubicin (Adriamycin®), vinblastine, cisplatin, ifosfamide and the taxanes. These compounds have yielded overall response rates on the order of 23-42%. (4)

In the 1980s, cisplatin-based combinations were developed for the treatment of patients with advanced and metastatic urothelial cancer. The most commonly used regimens in Europe have been CM (cisplatin and methotrexate), CISCA/CAP (cyclophosphamide, adriamycin, and cisplatin) and M-VAC (methotrexate, vinblastine, doxorubicin, and cisplatin). The CMV and M-VAC combinations have been considered the most active for treatment of advanced and metastatic TCC, showing the highest complete and partial response rates (5-7). No study comparing M-VAC with CMV has been performed to answer whether the inclusion of adriamycin to CMV increases efficacy. However, M-VAC used to be the most common regimen in the treatment of advanced and metastatic bladder cancer (8).

The M-VAC regimen was developed at the Memorial Sloan Kettering Cancer Centre (MSKCC) in 1983. Published data indicate an overall response rate as to M-VAC of 72%, with a complete response rate of 36% in 121 evaluable patients (5). The median survival for all patients (n= 133) was 13 months. In a further update by the MSKCC in 203 pati-

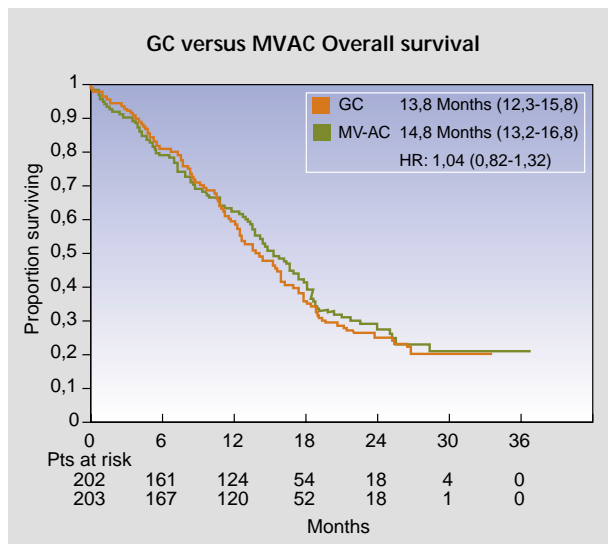


Figure 1: Overall survival curves for the gemcitabine/cisplatin (GC) combination versus M-VAC in a large, multi-national, phase III study in bladder cancer (25)

ents, the 5-year survival rate for the 46 complete responders was 41% at a median follow-up of 47 months (9). In four phase II trials (10 - 13), M-VAC yielded somewhat lower responses. The overall response rate was about 50%, with a complete remission rate of about 15%. In a phase III randomised setting, M-VAC was compared with cisplatin in an Intergroup study (14), and compared with CISCA in a study conducted by the MD Anderson Cancer Centre (15). Both trials proved the superiority of M-VAC over reference arms. Overall response rates in the M-VAC arms were 39% and 65% and median survival durations were 12.5 and 11.2 months, respectively. A recent follow-up study of an Intergroup trial demonstrated that only 3.7% of patients randomised to M-VAC were alive and continuously disease-free at 6 years (16). The M-VAC regimen was also associated with significant treatment-related toxicities, including myelosuppression, neutropenic fever and sepsis, mucositis, nephrotoxicity, and peripheral neuropathy, and a toxic death rate of 4% (6, 14).

The current chemotherapy has demonstrated a modest survival benefit in patients with advanced bladder cancer, with small numbers of patients achieving long-term control of their disease, and significant toxicity associated with M-VAC. In addition, bladder cancer is predominantly a disease of the elderly, who frequently present with concomitant chronic diseases and challenging medical problems. Thus, it is of the utmost importance to develop less toxic drug regimens with greater efficacy.

Gemcitabine as a single-agent and in a combination with cisplatin

Gemcitabine (2'-difluorodeoxycytidine, dFdC), is highly active in the treatment of bladder cancer. After one phase I study (17), gemcitabine was tested in four phase II studies (18, 19, 20, 21) in patients with locally advanced or metastatic TCC. Single-agent gemcitabine, given weekly for 3 weeks (on days 1, 8, and 15), produced response rates ranging from 23% to 29%. Responses were

seen in lymph nodes, liver, lung, and bone. Toxicities, particularly myelosuppression, were modest and transient, with only two patients experiencing febrile neutropenia. The favourable tolerability and antitumour activity of gemcitabine in chemonaive as well as pre-treated patients, led to further exploration of this compound in the treatment of TCC of the urothelium.

The gemcitabine and cisplatin combination was studied in three phase II trials (22-24). Efficacy and toxicity data are summarised in Table 1. These studies demonstrated that the combination of gemcitabine and cisplatin has high, durable activity in advanced or metastatic TCC of the urothelium, with complete response rates of 18% to 28%, overall response rates of 41% to 57%, and median overall survival durations of 12.5 to 14.3 months. These results compare favourably with those of other cisplatin-based regimens.

Gemcitabine plus cisplatin versus M-VAC, in randomised phase III trial

Phase II studies of gemcitabine plus cisplatin in bladder cancer

Study	Gemcitabine Dose	Concomitant Drug Dose	No. Pts	RR (CR)	Median/Overall Survival	Grade 3/4 Toxicity
von der Maase (22)	1.000 mg/m ² Days 1, 8, 15 q 28 days	Cisplatin 35 mg/m ² Days 1, 8, 15 q 28 days	38	42% (7)	12,5 months	Grade 3/4 neutropenia (25/33%), thrombocytopenia (29/49%), anemia (29%/0), leukopenia (44/17%), nausea/vomiting (29%), pulmonary toxicity (7%)
Moore (23)	1.000 mg/m ² Days 1, 8, 15 q 28 days	Cisplatin 70 mg/m ² Day 2 q 28 days	29	57% (6)	13,2 months	Grade 3/4 neutropenia (32%), granulocytopenia (39%), thrombocytopenia (55%), anemia (32%), and nausea (13%)
Kaufman (24)	1.000 mg/m ² Days 1, 8, 15 q 28 days	Cisplatin 75-100 mg/m ² Day 1 q 28 days	46	41% (10)	14,3 months	Grade 3/4 neutropenia (38/36%), thrombocytopenia (36/29%), anemia (27/4%), leukopenia (40/13%), nausea/vomiting (18%/0), infection (9%/0)

Table 1

The next step was to directly compare the two-drug combination of gemcitabine and cisplatin with the four-drug combination of M-VAC in a randomised phase III trial (25). A multinational, multicentre, randomised trial was initiated late in 1996. Final data were presented during the thirty-sixth ASCO meeting and published in JCO in September 2000. In this largest ever randomised trial, which included 99 investigators from 19 countries, the planned recruitment of 405 patients was reached after 22 months (end of October 1998). Patients with stage IV TCC and no prior systemic chemotherapy were randomised to the gemcitabine and cisplatin arm (gem-

citabine 1.000 mg/m² on days 1, 8, and 15; cisplatin 70 mg/m² on day 2) or to the reference arm consisting of standard M-VAC, administered every 28 days for a maximum of six cycles. A total of 203 patients were randomised to the gemcitabine and cisplatin arm and 202 to the M-VAC arm. The groups were well balanced with respect to prognostic factors. Final results demonstrated that both arms were similar in the terms of survival. The median overall survival of the gemcitabine plus cisplatin arm was 13.8 months versus 14.8 months for M-VAC. There was no statistical significant difference between these two arms in overall survival (p=0.75). Figure 1 provides

Kaplan-Meier survival curves for each treatment arm.

There were also no statistically significant differences between arms as to other efficacy parameters. Time to progressive disease was the same for both arms (7.4 months), and time to treatment failure was 5.8 months for the gemcitabine plus cisplatin arm and 4.6 months for the M-VAC arm (p=0.27). The overall response rates (independently reviewed) were 49.4% for the gemcitabine plus cisplatin arm and 45.7% for the M-VAC arm, with 12.2% and 11.9% complete response rates on respective arms.

The most important toxicities were myelosuppression, neutropenic fever/sep-

New gemcitabine combination regimes in phase II studies of bladder cancer

Investigator (reference)	Dose and schedule	Prior chemotherapy	Evaluable patients (n)	CR/PR	RR% (CR%)
Bruni et al. 1998 (26)	Gem: 1.000 mg/m ² Vin: 12 mg/m ² days 1 and 8 Every 21 days	M-VAC or CMV	10	0/4	40% (0%)
Perez et al. 1999 (27)	Gem: 1.000 mg/m ² days 1 and 8 Carbo: AUC 5 day 1 every 21 days	Systemic chemotherapy	13	1/4	38% (8%)
Marini et al. 1999 (28)	Gem: 2.500–3.000 mg/m ² Pac: 150 mg/m ² every 2 weeks plus GCSF support	M-VAC	21	5/8	62% (24%)
Meluch et al. 1999 (29)	Gem: 1.000 mg/m ² days 1, 8, 15 Pac: 200 mg/m ² day 1 every 21 days	One systemic chemotherapy regimen	25	2/13	60% (8%)
Bellmunt et al. 1999 (30)	Gem: 1.000 mg/m ² Pac: 80 mg/m ² days 1 and 8 Cis: 70 mg/m ² day 1 every 21 days	Adjuvant > 1 year prior to study entry	58	16/29	77% (27%)
Vaishampayan et al. 1999 (31)	Gem: 800 mg/m ² days 1 and 8 Pac: 200 mg/m ² Carbo: AUC 5 day 1 every 21 days	Adjuvant > 6 months prior to study entry	19	5/6	58% (26%)

Gem = gemcitabine; Vin = vinorelbine; Pac = paclitaxel; Carbo = carboplatin; CR = complete response; PR = partial response; RR = overall response rate; M-VAC = methotrexate, vinblastine, adriamycin, cisplatin; CMV = cisplatin, methotrexate, vinblastine

Table 2

sis, and mucositis. Patients on the gemcitabine plus cisplatin arm experienced more WHO grade 3-4 anemia (GC 27%, M-VAC 18%); however, the rates of red blood cell transfusions were the same on each arm (13 patients per 100 cycles of treatment). Grade 3-4 thrombocytopenia was seen more often on the gemcitabine plus cisplatin arm (GC 57%, M-VAC 21%), but grade 3 bleeding was the same on both arms (2% of patients). No grade 4 bleeding was reported on either arm. Rates of platelet transfusions were low on both arms (GC 4 per 100 cycles, M-VAC 2 per 100 cycles). Grade 3-4 neutropenia was seen more often on the M-VAC arm (MVAC 82%, GC 71%), as well as neutropenic fever (M-VAC 14%, GC 2%) and neutropenic sepsis (M-VAC 12% versus GC 1%; $p < 0.001$). Also, grade 3-4 mucositis was significantly more common on the M-VAC arm (M-VAC 22% versus GC 1%; $p < 0.001$). The drug toxicity-related mortality rate on the M-VAC arm was 3% compared with 1% on the gemcitabine plus cisplatin arm.

This study demonstrated that gemcitabine plus cisplatin has comparable activity with M-VAC in the treatment of advanced and metastatic TCC. The gemcitabine plus cisplatin arm was better tolerated with lower toxicity-related mortality and significantly lower rates of neutropenic sepsis/fever and grade 3 or 4 mucositis. In addition, patients treated with gemcitabine plus cisplatin used fewer resources for managing adverse events and supportive care compared with the M-VAC regimen. Finally, more patients treated with gemcitabine plus cisplatin fared better with respect to weight, performance status, and fatigue. Only anemia and thrombocytopenia were seen more frequently with gemcitabine plus cisplatin; however, there were few clinical sequelae from these toxicities, which did not exceed those appearing on the M-VAC arm.

Based on the above-mentioned results, the gemcitabine plus cisplatin combination was approved for the treatment of advanced and metastatic bladder carcinoma in many countries around the world. By April 2001, registration approval had been obtained in the following European countries: Belgium,

Bosnia, Bulgaria, the Czech Republic, Denmark, Estonia, Finland, France, Hungary, Latvia, Luxembourg, Slovakia, Spain, Sweden, Switzerland and the United Kingdom. In addition to these European countries, registration approval has been obtained from South Africa, Israel, and Egypt.

Non-platinum and three-drug combination regimens

Bladder cancer is predominantly the disease of elderly patients. Many of them are not able to tolerate full doses of chemotherapy, or any cisplatin-based chemotherapy due to renal failure. Thus, it is important to develop less toxic regimens for these patients; however, new highly active regimens are also needed for "fit" patients (good performance status patients) better suited for aggressive chemotherapy. Preliminary results of six phase II studies (26-31) using new gemcitabine combinations are summarised in Table 2.

In one such study (26), the gemcitabine plus vinorelbine combination was tested in elderly patients (median age 71 years, range 42-48) refractory to platinum-based regimens such as M-VAC or CMV. Patients received gemcitabine 1.000 mg/m² plus vinorelbine 25 mg/m² on days 1 and 8, every 3 weeks, for 4 cycles. Ten patients with a median Karnofsky performance status score of 80 (range 60-90) have been evaluated so far. Four patients had a partial response and two had stable disease. The regimen was well tolerated, with grade 3 neutropenia reported in two patients, and grade 3 thrombocytopenia and anemia reported in one patient each, respectively. No grade 4 toxicities were reported.

Another alternative is the combination of gemcitabine and taxanes. Published preliminary data from one such phase II trial (28) that used the gemcitabine plus paclitaxel combination, showed interesting efficacy with manageable toxicity. Gemcitabine 2.500-3.000 mg/m² and paclitaxel 150 mg/m² were given every 2 weeks to patients pre-treated with M-VAC. The median age of the 24 enrolled patients was 67 years (range 54-76). The overall response rate for the 21 evaluable patients was 62%, with 5 (24%)

complete and 8 (38%) partial responders. Median duration of response was 6+ months (range 2-27+ months). Grade 3-4 neutropenia was observed in 8 (37%) patients and grade 3-4 neurotoxicity in 1 (5%) patient. There was no grade 3-4 thrombocytopenia.

The three-drug combination and gemcitabine, paclitaxel, and cisplatin or carboplatin (30, 31) were developed for "fit" patients. One such study by Bellmunt et al. (30) used gemcitabine 1.000 mg/m² and paclitaxel 80 mg/m², both given on days 1 and 8, plus cisplatin 70 mg/m² given on day 1, every 21 days. A total of 58 evaluable patients, with median age of 63 years (range 36-77) and a median ECOG performance status of 1 (range 0-2), were retrospectively analysed. The overall response rate was 77%, with a 27% complete response rate. The overall median survival was 19.2 months after a 10.8-month follow-up. The main grade 3-4 toxicities reported were granulocytopenia in 38%, thrombocytopenia in 22%, anemia in 13.5%, infection in 11%, and febrile neutropenia in 11% of patients. Grade 2 asthenia occurred in 51% of patients.

Up-coming international trials

Favourable results of a phase III, multinational, multicentre trial comparing the two-drug combination of gemcitabine plus cisplatin with the four-drug combination of M-VAC, definitely integrated gemcitabine into the chemotherapeutic arsenal for patients with TCC (25). Previously published trials testing non-platinum doublet regimens using new drugs in patients with poor performance status ("unfit patients") as well as triplet regimens in patients with good performance status ("fit patients"), led to the initiation of a series of international trials coordinated by EORTC. The first trial in "fit" patients is comparing gemcitabine plus cisplatin (GC) versus the three-drug combination of gemcitabine, cisplatin, and paclitaxel (GCT). A total of 620 patients are planned to detect a 4-month improvement in median survival (GC= 14 months, GCT= 18 months). The second study is designed to test gemcitabine plus carboplatin (GCb) versus carboplatin, methotrexate, and

vinblastine (CbMV) in „unfit“ patients. A total of 225 patients are expected to be enrolled to demonstrate a 4.5-month improvement in median survival (GCb= 9 months, CbMV= 13.5 months). The final results of these trials are expected in 2005 („fit“ patients trial) and 2004 („unfit“ patients trial), respectively.

Conclusions

For nearly two decades, the M-VAC combination was the most frequently used treatment for advanced and metastatic bladder cancer. In many countries around the world this multi-drug combination was considered a „gold standard“. In the 1990s, new compounds such as gemcitabine and the taxanes, have shown promising activity with mild toxicity profiles and raised the interest for further exploration. In the last 2 years, the gemcitabine/cisplatin combination has been one of the most frequently studied combinations in the treatment of bladder cancer. A large, phase III randomised study has definitively confirmed the activity of gemcitabine plus cisplatin in bladder cancer, and has demonstrated a superior risk-benefit ratio for GC compared with M-VAC (25). Thus, gemcitabine plus cisplatin is a safer treatment alternative for patients with advanced and metastatic bladder cancer and should be considered a standard of care for these patients. The better toxicity profile of new compounds also offers alternative options for „unfit“ patients, who cannot receive cisplatin-based regimens. Molecular targeting agents are possible future alternative in the treatment of bladder cancer. Those new compounds, for example, anti-vascular endothelial growth factor (VEGF) antibody, anti-HER2 receptor antibody and epidermal growth factor receptor ZD1839 are widely tested in different diagnoses, including bladder cancer. ◆

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Clinical Protocols

Three protocols are open for recruitment of patients (see also our homepage www.cecog.org):

1. GET vs. FEC Trial in Advanced Breast Cancer (prospective, randomized, parallel, multicenter phase III study; Study Number: CECOG-BCM1):

Background information: This trial recruits patients with advanced breast cancer who are prospectively randomized to receive either gemcitabine, epirubicin and paclitaxel (GET) or fluorouracil, epirubicin, cyclophosphamide (FEC) as first-line cytotoxic treatment of histologically proven metastatic breast carcinoma. This trial is being performed in Austria, Bosnia, Bulgaria, Croatia, Czech Republic, Hungary, Israel, Poland, Romania, Slovakia, Slovenia and Turkey.

Number of patients: Currently, 130 patients have been recruited at a projected total number of 260 patients.

2. GET vs. ET Trial in Advanced Breast Cancer (prospective, randomized, parallel, multicenter phase III study; Study Number: GET-IT/CECOG-BCM2):

Background information: This trial recruits patients with advanced breast cancer who are prospectively randomized to receive either gemcitabine, epirubicin and paclitaxel (GET) or epirubicin, and paclitaxel (ET) as first-line cytotoxic treatment of histologically proven metastatic breast carcinoma. This trial is being performed within countries of the European Union, in North and South America and in India.

The trial has been opened for recruitment in March, 2001.

Principle Investigator: Professor PierFranco Conte, Ospedale Santa Chiara, Pisa, Italy.

Projected total number of patients: 630.

3. Maintenance chemotherapy in NSCLC (prospective, randomized, parallel, multicenter phase III study; Study Number: CECOG-LCM1):

Background information: This trial recruits patients with advanced Non Small Cell Lung Cancer (NSCLC) who are treated with gemcitabine and cisplatin as first-line cytotoxic treatment and are prospectively randomized to receive therapy with gemcitabine for maintenance or undergo observation only. This trial is being performed in Austria, Bulgaria, Croatia, Czech Republic, Hungary, Poland, Romania, Slovakia, Slovenia and Turkey.

Number of patients: Currently, 170 patients have been recruited at a projected total number of 240 patients.

4. Protocols for the following entities are currently being prepared:

Advanced pancreatic cancer, metastatic transitional cell carcinoma, NSCLC.

CECOG is proud to cooperate with IEM and CATO for on-site monitoring (CRO) and with Innopharm and BETA for data analysis.

Best Recruiters for Protocols CECOG-BCM1 + CECOG-LCM1 (in alphabetic order)

Semir Beslija

Semir Beslija, MD, is Deputy Head of the Medical Oncology Department at the Institute of Oncology, Clinical Center of Sarajevo University and senior teaching assistant in oncology at Sarajevo Medical School.

He was born in 1964 in Sarajevo, Bosnia and Herzegovina. He has studied medicine in Sarajevo, completing his education in 1988. He has specialized in internal medicine at the Clinical Center of Sarajevo University. After that he has spent two years at the Institute of Oncology in Ljubljana, Slovenia, as the ESMO fellow in medical oncology. He moved back in 1997 to Sarajevo and took the position of medical oncologist – junior teaching assistant at the Institute in Sarajevo. He has organized the unit for the outpatients' chemotherapy, networking of the Institute and modern multimedia teaching space for the student and residents. With his colleagues, he has engaged the newly equipped Institute of Oncology in Sarajevo, which is the only comprehensive Cancer Center in Bosnia and Herzegovina, to several international projects. He is a member of several professional societies including the American Society of Clinical Oncology and European Society for Medical Oncology. He plays an active role in a Society of Oncologists in Bosnia and Herzegovina as the President of the Executive Board.

One of Dr. Beslija's main interests is breast cancer and currently he is the principal investigator in five various international trials in primary and advanced disease.

He has published several articles on national and international level.

Josipina Ana Cervek

Josipina Ana Cervek is a Medical Oncologist, Consultant of Medical Oncology at the Onkološki Institut Ljubljana Slovenia. The institute was founded in 1938 and is one of the oldest comprehensive oncology centers in Europe.

After residency and board examination in Internal Medicine in 1974 she started to work in the field of medical oncology and is one of the pioneers (in introducing, establishing and affirming the principles) of medical oncology in Slovenia. As responsible investigator she has taken part in many national and international multicenter studies particularly concerning breast cancer, sarcoma and bladder cancer, her special interest being organ sparing treatments. She was one of the first to study the use of aromatase inhibitors in the treatment of breast cancer.

Dr. Cervek is a member of the Ludwig Breast Cancer Study Group in the European Society of Medical Oncology (ESMO) and Member of the Central European Cooperative Oncology Group (CECOG) and many others.

One of Dr. Cervek's current aspirations is the introduction and development of a palliative care team and a palliative care unit at the Oncology Institute in Ljubljana.

Ciuleanu

CV was not received in sufficient time.

Jacek Jassem

Jacek Jassem, MD, PhD, Professor of Radiotherapy and Clinical Oncology, Head, Dept. of Oncology and Radiotherapy, Medical University of Gdansk, Poland.

Fellowships: 1977: Radiuhemmet, Stockholm, 1989/1990 and 1994: The Netherlands Cancer Institute, Amsterdam
 Author of over 180 publications in peer-reviewed international and Polish journals. Main scientific interests: lung cancer, breast cancer, head and neck cancer, molecular biology of cancer. Author and co-author of textbooks: Lung Cancer (PZWL), Multimodality Treatment of Head and Neck Cancer (Georg Thieme Verlag), Oxford Textbook of Oncology (Oxford University Press), Breast Cancer (Springer-PWN), Molecular Aspects of Cancer and its Therapy (Birkhauser Verlag) and others.

Member of the editorial boards of six international and eight Polish medical journals.

Member of a number of international scientific societies, advisory boards and co-operative groups. Chairman, EORTC Breast Cancer Co-operative Group. Board member, European Society of Therapeutic Radiology and Oncology, Lecturer, European Society of Therapeutic Radiology and Oncology, European School of Oncology, University of Antwerp. Chairman, Polish Lung Cancer Co-operative Group (1981-1990), Chairman, Oncology Section, Polish Phtisiopneumonological Society, Vice-president, Polish Society of Radiation Oncology. Member, Scientific Board, National Cancer Institute - Marie Curie Memorial Hospital in Warsaw. Married, three children. Hobby: classical music, basketball, wind-surfing.

Zsuzsanna Kahán

Name: Zsuzsanna Kahán, MD

Date of birth: 24 December 1953

Place of birth: Budapest, Hungary

Office address: Albert Szent-Györgyi Medical University School, Department of Oncotherapy

Phone:(36)62-545-406, **Fax:** (36)36-545-922

E-mail: kahan@onko.szote.u-szeged.hu

and special end-examination on the topic, Szeged, Hungary

1989: Six-month fellowship at the National Institute of Oncology, Budapest, Hungary, and special end-examination on Clinical Oncology

1983: Special examination on Internal Medicine, Szeged, Hungary

1972-78: Medical University of Szeged, graduated „summa cum laude“

Education:

- 1995:** Special examination on Radiotherapy, Budapest, Hungary
- 1994:** Brachytherapy, Tübingen, Germany (ESTRO Course)
- 1993:** Radiobiology, Tours, France (ESTRO Course)
- 1993:** Radiophysics, Leuven, Belgium (ESTRO Course)
- 1990:** Controversies in Breast Cancer Treatment, Jerusalem, Israel (ESO Course)
- 1989:** Breast Cancer: new developments in Biology, Diagnosis, and Treatment, London, U.K. (British Council Course)
- 1989:** Course on application of isotope-techniques

Professional experiences

- 1998:** Assistant Professor at the Department of Oncotherapy, A. Szent-Györgyi Medical University School.
- 1997-1998:** Research Associate Professor, 18-month fellowship at the Endocrine, Polypeptide and Cancer Institute, Tulane University, New Orleans, USA.
- 1996-1997:** Consultant at the Department of Oncoradiology, Markusovszky Teaching Hospital, Szombathely.
- 1994-1996:** Professor's assistant at the Department of Oncotherapy, A. Szent-Györgyi Medical University School. General clinical onco-

logy: examination, medical and radiotherapy, follow-up of in- and out-patients. The main topic of medical practice and interest is the hormonal treatment and prognostic factors in breast cancer disease. Lecturing, teaching students of the Medical University in Hungarian and English languages.

1994: Ph. D. thesis (submitted to the Hungarian Academy of Sciences).

1993: One-month fellowship at the Institute of Biochemistry, Georg-August University, Göttingen, Germany

1992: One-year fellowship at „INSERM, Unite 148, Labo de Biologie Cellulaire et Hormonale, Montpellier, France“ granted by Association pour la Recherche sur le Cancer“. Study of mannose-6-phosphate receptors in human breast cancer.

1989–1991: Fellowship of the Hungarian Academy of Sciences, research work on „EGF-like activity and EGF-receptors in human breast cancer“.

1986-1994: Professor's assistant at the Department of Radiology. General clinical oncology: examination, medical and radiotherapy, follow-up of in- and out-patients. The main topic of medical practice and interest is the hormonal treatment of breast cancer patients. Lecturing, teaching students of the

Medical University in Hungarian and English languages.

1978–85: Resident and assistant lecturer at the 1st Department of Medicine, Medical University, Szeged. Practising general internal medicine; lecturing, teaching and examining medical students. Research work on the measurement of gastric blood circulation.

Knowledge of Languages:

English, written and spoken, good
 French, written and spoken, medium
 (English and French language state examinations of medium grade have been passed)

Membership

The Society of Hungarian Oncologists
 The Hungarian Society of Senology

Awards

„I. Cserhádi award“ for junior scientists, 1988 and 1990, Szeged
 „K. Waltner award“ for young internists, 1985, Szeged
 „SZAB (Regional Commission of the Hungarian Academy of Sciences) award“ 1993, Szeged

Personal status

Married since 1974, Two daughters, age 16 and 26

Maciej/Jerzy Krzakowski

Family name: Krzakowski
First/second name: Maciej/Jerzy
Date of birth: 28. 07. 1951
Place of work: Oncology Centre-Institute, M. Sklodowska-Curie Memorial, 5, Roentgen Street, 02-781 Warsaw, Poland
Phone: (48-22) 644-76-25, **Fax:** (48-22) 644-76-25,
E-Mail: maciekk@coi.waw.pl.

Education:

1969-1975: Medical Academy /Warsaw/Poland
 Diploma of Physician

1978: Postgraduate Medical Centre/Warsaw/Poland
 1st degree specialty – radiotherapy

1980: Postgraduate Medical Centre/ Warsaw /Poland
 Ph Dissertation

1981: Postgraduate Medical Centre/Warsaw/Poland
 1st degree specialty – internal medicine

1982: Postgraduate Medical Centre/Warsaw/Poland
 2nd degree specialty – radiotherapy

1992: Postgraduate Medical Centre/Warsaw/Poland
 2nd degree specialty – medical oncology

1999: The Maria Sklodowska-Curie Memorial Cancer Center and Institute of Oncology - Warsaw/Poland
 Associate Professor

Postgraduate medical practices:

1988: Institute Jules Bordet – Brussels/Belgium
1989: Free University Hospital – Amsterdam/The Netherlands
1992: Royal Marsden Hospital – London/United Kingdom

Employment and positions held:

1975–1983: Postgraduate Medical Centre/Warsaw/Poland
 Oncology Department – senior registrar

1984–1986: Kuwait Cancer Control Centre – consultant

1987: The Maria Sklodowska-Curie Memorial

Cancer Center and Institute of Oncology –
Warsaw/Poland
Lung & Thoracic Tumours Department –
head of department

1998: National Consultant in Oncology - Poland

Publications:

63 papers published in local and international medical journals (full list included if needed)

Past experience in clinical trials:

Participation in numerous clinical trials international and local

single- and multiinstitutional
phase II and III
testing antineoplastic and supportive therapy

Membership:

Polish Society of Oncology
European Society of Radiotherapeutic Oncology
Multinational Association for Supportive Care in Cancer
Polish Society of Clinical Oncology
European Organisation for Research and Treatment of
Cancer – EORTC Lung Cancer Group

I do declare the above to be a full and true statement.

Rodryg Ramlau

Rodryg Ramlau, MD, born on 28th January 1961 in **Pozna, Poland**.

In 1981 I became a student at the Faculty of Medicine of Medical University in Pozna and graduated in 1987, obtaining a Diploma of Physician. In 1991 I concluded my First Degree of Specialisation in Radiotherapy and started the Second Degree of Specialisation in Medical Oncology, which was successfully finished in 1994. In the meantime, in 1993 I achieved a Medicine Doctor Degree (Ph.D.).

Concerning my professional experience, in the years 1987–1991 I worked as a young assistant in the Cancer Centre in Pozna and since 1989, additionally as an assistant in Palliative Care Service at Medical Academy in Pozna. In 1989 I started a part time job in the Oncology Clinic at the Medical Academy. In the years 1991–1995 I was an assistant in the Cancer Centre, Department of Medical Oncology. Since 1995 I have been working as a Head of the Oncology Department at the Wielkopolska Lung Diseases Centre.

Memberships: Polish Oncological Society, Polish Phtisiopneumonological Society, EORTC Lung Cancer Co-operative Group, IASLC, and ESMO.

Author and co-author of 30 publications in Polish and foreign medical journals („Nowotwory“-quarterly of Polish Oncological Society, „Nowiny Lekarskie“, „European Journal of Cancer Prevention“, „Journal of Clinical Oncology“, „Lung Cancer“) and two brochures for patients concerning treatment in oncology clinic.

Stanislav Spanik

Stanislav Spanik, MD, PhD, Associate Professor

Born 1959, **Bratislava, Czechoslovakia**

Medical Education: School of medicine, Charles University, Prague, School of Medicine, Comenius University, Bratislava.

Doctor of Medicine: 1984

Professional Training: Department of Internal Medicine, Institute of Clinical Oncology, Bratislava, Department of Internal Medicine and Department of Hematology and Blood Transfusion, National Cancer Institute, Bratislava,

1993: 6 months Department of Medicine, Memorial Sloan – Kettering Cancer Center, New York

1995: 2 months Department of Medicine and Department of Oncology and Department of Hematology, Mayo Clinic, Rochester Postgraduate Examinations

1987: Internal Medicine Board Examination

1991: Hematology and Blood Transfusion Board Examination

1994: Clinical Oncology Board Examination

1995: Ph. D.

Position: Department of Medicine and Medical Oncology St. Elisabeth Cancer Institute, Bratislava, Slovakia, Head of Department

Status: married, 4 children

Valentina Ilieva Tzekova

Name: Valentina Ilieva Tzekova

Born: January 28, 1951

Place of birth: Sofia, Bulgaria

Marital status: Married with 2 children

Education: Faculty of Medicine, Medical University, Sofia, 1975

Degree and titles:

- Physician – Department of Internal Medicine, Gotze Delchev, 1975–1977
- Performing doctors thesis – Laboratory of Carcino genesis – National Oncological Center, 1977–1981
- Ph.D. – „Cell proliferation of human bladder cancer”, National Oncological Center, Sofia, 1982;
- Assistant – Clinic of Chemotherapy, National Oncological Center, 1981
- Speciality in Internal Medicine – 1986
- Chief assistant - Clinic of Chemotherapy, National Oncological Center, 1995

- Head of Clinic of Chemotherapy, University Hospital „Queen Joanna”, Sofia, 1992–1999

- Associate Professor - Faculty of Medicine, Medical University, Sofia, 1995

Present position: Head of Department of Chemotherapy, Clinic of Oncology, University Hospital “Queen Joanna”, Sofia

Speaking engagements: Lectures in training courses

Membership in professional societies:

- Bulgarian Oncological Scientific Society
- European Association for Cancer Research
- The Balkan Union of Oncology
- Central European Cooperative Oncology Group-member of Scientific Committee
- Central and Eastern Oncology Group – member of Scientific Committee
- American Society of Clinical Oncology

Scientific publications: 50 published works

Ernst Christian Ulsperger

Dr. med. Ernst Christian Ulsperger, born: 8. 3. 1959 in Vienna

June 1977	Completion of High School
7. 3. 1985	Graduation M.D.
15. 4.–30. 9. 85	Guest-doctor at the Ludwig Boltzmann Inst. f. Clin. Oncology, Lainz
1. 10. 85–31. 5. 86	Civil-Service
1. 6.–31. 12. 1986	M.D. in an oncologic praxis
20. 4. 85–28. 2. 88	Institut for Epidemiology of Neoplasms University Vienna as University-Assistant (Prof. Dr. K. Karrer)
1. 3. 88–30. 11. 89	M.D. at the 5th Med. Dep., Oncology, Lainz
23. 4.–13. 5. 1989	Education at the Medical Research Inst. f. Oncology, Petrow, Leningrad, UdSSR
1. 12. 89–30. 11. 94	Special Education Internal Medicine at 5th Med. Dep. Oncology, Lainz
1. 1. 1995	Head Physician at the 5th Med. Dep. Oncology, Lainz
21. 2. 1997	Completion of education as specialist for „Hematology-Oncology“
17. 11. 1998	Completion of education Diving-Medicine
October 1999	Private Praxis in Eggenburg, and consilary oncologist in Waldviertelklinikum Horn (Lower Austria)
May 2000	Completion of the course „Medicine and Management“
since 1986	Coordinator and Principle Investigator in several oncologic multicenter trials

Damir Vrbanec

Name and surname: Prof. Dr. Damir Vrbanec

Address: Department of Pathophysiology
Clinical Hospital Centre Rebro
Medical Faculty
Kispaticeva ul. 12, 10000 Zagreb, Croatia

Phone:+ 385 1 2421848

Fax : + 385 1 2421969

E-Mail: dvrbanec@rebro.mef.hr
damir.vrbanec@zg.tel.hr

Born: 19. 07. 1955 in Zagreb, Croatia

Present Position: Head of Clinical Department, Department of Pathophysiology

Education

M.D. Faculty of Medicine, University of Zagreb, 1978
 Specialization in Internal Medicine („Sisters of Mercy“ University Hospital, Zagreb, 1980–1984)
 M.S. in Experimental Biology and Medicine, Faculty of Natural Sciences and Mathematics, University of Zagreb 1980.
 Ph.D. in Medicine, Faculty of Medicine University of Zagreb, 1982.
 Fellowship from Alexander von Humboldt Stiftung 1987/1989 and 1994 (University of Hamburg, UK Eppendorf, Germany)

Employment

Junior assistant, Dept. of Internal Medicine, Sisters of Mercy, University Hospital Zagreb, 1980-1984
 Cancer Research Assistant, Nuclear Medicine and Oncology Department, Sisters of Mercy University Hospital, 1985–1989

Assistant Lecturer, Dept. of Pathophysiology, University Hospital Rebro, 1989-1993.
 Assistant Professor 1993–1998, and Professor of Medicine 1998-present

Certification

Board of Internal Medicine 1984
 Board of Medical Oncology 1997

Memberships

Vicepresident of the Croatian Association of Oncology
 Member of the European Association of Medical Oncology (ESMO)
 EORTC Breast Cancer Group
 Member of the Croatian Association of Internal Medicine and Croatian Medical Association

Research interest: chemo-hormonal therapy, clinical and experimental oncology, breast cancer, oncogenes and growth factors

Miklós Wenczl

Miklós Wenczl was born on 16th January 1940 in **Kisnyárád, Hungary**. After leaving secondary school in Mohács, he was awarded an MD in 1964 by the University of Pécs. Since then he has been employed by the **Markusovszky Teaching Hospital, Markusovszky u. 3., 9700 Szombathely, Hungary, Phone: 36.94.311542, Fax: 36.94.327873**. After initially undergoing 4 years training in hematology, he subsequently worked for 20 years in internal medicine. He received his qualifications in Internal Medicine/1970/, in Hematology/1987/ and in Medical Oncology /1988/. He speaks English, French, German and Hungarian fluently. He was appointed consultant physician in 1979 and in 1988 he assumed his current position at the Dept. of Radiation Oncology. His clinical interests moved increasingly to the medical treatment of cancer, and since 1995 he has been local investigator of 14 international trials in the field of ovarian, breast, pancreatic, colorectal, gastric and lung cancer. **He is member of ASCO, DGHO, ESMO, FFOM, ÖGHO and several Hungarian societies.** His wife and 3 children are also physicians.

Matjaz Zwitter

Matjaz Zwitter, MD, PhD, is Head of the Department of Radiation Oncology at the Institute of Oncology in Ljubljana, Slovenia, and Associate Professor for Radiotherapy and Oncology at the University of Ljubljana Medical School.

He is a graduate of the Ljubljana University where he also completed his training in radiotherapy and oncology. After fellowships in London and Stanford, he returned to Ljubljana and conducted a number of clinical trials in the fields of malignant lymphomas, pediatric oncology, brain tumors, and lung cancer. In 1997, Drs. Antonella Surbone and Matjaz Zwitter co-edited a book on Communication with the cancer patient: information and truth which was published in the Annals of the New York Academy of Sciences. His current research interests include ethical issues in oncology, treatment for lung cancer, and biology of Hodgkin's disease.

Education

Under the chairmanship of Prof. Michael Krainer and assisted by Ms. Ursula Fischer, CECOG has successfully fulfilled a series of educational activities and is currently expanding into the field of quality control in clinical oncology.

Past tasks, year 2000:

Seminars organized under the participation of national and international faculty were held on Colorectal Cancer (Prague), Lung Cancer (Wroclaw), Urogenital Cancer (Vienna) and Breast Cancer (Budapest). CECOG wants to pay particular tribute to seminar organisers Professors Petruzella, Scheithauer, Jassem, Marberger and Bösze, all speakers and supporting companies Aventis, Bristol Myers-Squibb, Eli Lilly, Novartis, Roche and Sanofi which contributed by providing educational grants. All seminars were attended by 40

to 80 participants and – according to analyses of questionnaires - were well perceived and received high rating.

Educational activities in 2001:

- CECOG Consensus Development Conference on the Treatment of Non Small Cell Lung Cancer. Participation by invitation only. November 2001, Vienna.
- CECOG's Guidelines for the Medical Treatment of Malignant Disorders. A Publication for Clinicians.

CECOG is proud to be partner of the European School of Oncology in its educational activities.

People at CECOG

- Effective February 2001, Dr. Thomas Brodowicz has been named Co-Coordinator of CECOG. Dr. Thomas Brodowicz has done his training in internal medicine and clinical oncology at Vienna University Hospital and been with CECOG since its founding in 1999.
- In its meeting in Hamburg in October 2000, CECOG's Scientific Committee has unanimously agreed on the nomination of Prof. Heinz Zwierzina as CECOG's liaison officer to other international cooperative groups. Prof. Zwierzina is Professor of Medicine at Innsbruck University Hospital and chairs the EORTC-BTDG.
- Effective April, 2000, Ms. Margit Landsgesell has been named Chief Administrator of the CECOG headoffice. Ms. Landsgesell has been with CECOG since its very beginning and successfully developed its administrative structures. Ms. Landsgesell continues to be responsible for clinical trials performed in Central and Southeastern Europe and Israel.
- Effective April 2000, Ms. Dagmar Just has joined the CECOG headoffice team. Ms. Just is responsible for the administration of the GET-IT/CECOG-BCM2 trial.
- Effective April 2000, Ms. Petra Schlösser has been recruited as consultant for clinical-administrative affairs.
- Effective February 2001, CECOG has recruited Dr. Irmgard Resch as CRA into the headoffice team.

We welcome all new collaborators to our team.

The CECOG headoffice and all of our collaborators can be reached under our e-mail address cecog@akh-wien.ac.at.

For constantly updated information, please visit our homepage www.cecog.org.

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