for 5 –6 weeks for a total dose of 50–60 Gy. Chemotherapy with Temozolomide was delivered concomitant with radiotherapy (75 mg/sqm/d × 7 d/wk) followed by six cycles of adjuvant temozolomide (200 mg/sqm/d × 5 days, every 28 days) in 21 patients. Adjuvant Temozolomide (200 mg/sqm/d × 5 days, every 28 days) was delivered after three weeks from the radiotherapy to 30 patients and to 9 patients with relapse after radiotherapy with curative intent.
Results: Concomitant Temozolomide with RT+ adjuvant TMZ was followed by 5 partial responses, 8 stable diseases, 14 patients were free of disease three month after completion of treatment and 3 patients with progressive disease. For patients with Temozolomide adjuvant to RT we obtained 3 partial responses, 12 stable disease, 1 patient with progressive disease and 5 patients were free of disease. Median survival was 13 months for patients with concomitant treatment, and 6.5 months for patients with adjuvant treatment. The main toxicities were: grade 1 and 2 nausea and vomiting in 12 patients, grade 2 trombocytopenia in 6 patients, grade 3 skin toxicity in 2 patients and obstipation in 7 patients.
Conclusion: Combined radiotherapy and Temozolomide, for high-grade gliomas, concomitant or adjuvant, is feasible with acceptable toxicities and good compliance. This protocol may prolong the disease free interval and possible the survival of patients with high-grade gliomas.

524 PUBLICATION

Concomitant radio-chemotherapy with temozolomide in malignant gliomas

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Background: Malignant gliomas are highly aggressive tumors with frequent relapse after surgery and no effective treatment at this time. In our study we assess the efficacy of concomitant radiotherapy and temozolomide in multiform glioblastoma treatment.
Patients and methods: Between June 2002-June 2003 12 patients have been treated after optimal surgery for glioblastoma multiforme. Median age was 48 years (range 39–60 years). Sex ratio male/female was 2:1. Treatment schedule was: external radiotherapy up to 60 Gy, in the target volume, conventional fractionation 30 × 200 cGy 6 weeks and Temozolomide: 150 mg/m^2/day, days 8–12 and 36–40, concomitant with RT followed by 6 more cycles with Temozolomide 200 mg/m^2/day, days 1–5, repeated at 28 days.
Results: Haematological toxicity was grade 3 leucopenia 2 patients, grade 3 anemia 1 patient and grade 3 trombocitopenia 1 patient, no grade 4 toxicity. Nonhaematological toxicity: fatigability grade 1–2 in 4 patients, grade 3–4 in 1 patient, rash grade 1–2 in 2 patients, grade 3–4 in 1 patient, nausea grade 1–2 in 4 patients, grade 3–4 in 1 patient. Median survival was 16.5 months; 8 patients are alive after 1 year (6 of them free of disease) and free of disease median survival was 7.8 months.
Conclusions: The treatment scheme has been well tolerated. Results are slightly better than those with postoperative RT alone and are similar to those reported in other studies or with daily administration (50–75 mg/m^2/day for 6 weeks). Further investigation is required.

525 PUBLICATION

The effect of a tumour board on the prognosis of patients with brain metastases treated using radiosurgery

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Purpose: To analyse prognostic factors and classification schemes for patients with brain metastases selected by a tumour board for stereotactic radiosurgery (SRS).
Materials and methods: From June 1997 to December 2004, 69 patients with 1–3 brain metastases received SRS, most as a boost after 30 Gy/10 whole brain radiotherapy (WBRT), and some as salvage after craniotomy and/or 20 Gy/5 WBRT. Twenty-six patients had lung, 17 had breast, and 26 had other histologies. The largest lesion per patient had a median diameter of 20 mm (3–31). The patients had a median age of 56 (35–78) and a median ECOG-PS of 1 (0–3). A median dose of 18 Gy (13.5–24) was prescribed to the 80% isodose surface. For each patient, the RTOG recursive partitioning analysis class (RPA), score index for radiosurgery in brain metastasis (SIR), and the basic score for brain metastasis (BS-BM) were determined.
Results: For the entire cohort, the median survival was 12.0 months, and univariate Cox regression of age, KPS, ECOG-PS, Lesion Number, Lesion Volume, Primary Control, Extra-cranial Metastases, Histology, RPA, SIR, and BS-BM determined that only younger Age ($p = 0.003$) predicted for better survival. For the subset that excluded the 3 outlying patients with survival >36 months, the median survival was also 12.0 months. In this subset, univariate Cox regression demonstrated that younger Age ($p = 0.009$), better ECOG-PS ($p = 0.001$) and, unexpectedly, higher Lesion Number ($p = 0.01$) predicted for better survival. Multivariate Cox regression determined that younger Age ($p = 0.045$) and better ECOG-PS ($p = 0.01$) predicted for better survival.
Conclusions: For this cohort of patients with brain metastases, selected for radiosurgery by a tumour board, the median survival compared favourably with other reports; however, RPA class, BS-BM and SIR did not predict for patient survival. Patients with fewer lesions had a significantly poorer survival than those with more lesions, suggesting that the tumour board exerted selection pressure, altering the usual influence of known prognostic factors in this cohort.

526 PUBLICATION

The role of age for survival in high grade glial tumors

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Purpose: In this retrospective study we analyzed the results of radiotherapy in patients with surgically removed high grade brain tumors treated with postoperative radiotherapy (RT).
Materials and methods: Between July 1999 and December 2004, 53 patients (28 male, 25 female) were treated in our department. Median age of the patients was 52 (18–75) years. Seven patients had a total surgical resection, 30 near total resection, and 14 subtotal resection. In 2 patients, diagnosis was based upon clinical and radiological data. The pathology was consistent with grade III astrocytoma in 12 (22.6%) and glioblastoma multiforme in 41 (77.4%) patients. At the time of diagnosis 21 (39.6%) patients had ⩽ 70 karnofsky performance status and 10 (19%) had history of seizure. Adjuvant RT was given with a single daily fraction of 1.8 Gy to a total dose of 63 Gy. The median interval between surgery and radiotherapy (RT) was 37 days and RT was completed in median 49 days. Twenty-eight (52.8%) patients received chemotherapy after completion of RT for this study, the prognostic importance of age, sex, performance status, a history of seizure at diagnosis, extent of surgery for overall survival were analyzed. Mean follow-up period was 15 (2–64) months.
Results: The median overall survival was 25 months. Fourteen patients are alive without any recurrence. More than 50 years of age was the only significant factor in univariate analysis and there were no significant factors in multivariate analysis for overall survival.
Conclusion: This study concluded that more than 50 years of age was a poor prognostic factor in glioblastoma multiforme.

Clinical Trials Methodology and Ethics

Poster presentations (Wed, 2 Nov)
Clinical trials methodology and ethics

527 POSTER

Impact of the new European regulation on the authorisation of new oncology drugs in the European Union (EU)

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On 20 November 2005, new European pharmaceutical legislation will enter into force. Thereafter, all oncology drugs seeking approval in the EU will be evaluated *via* the European Medicines Agency (EMEA) leading to an EU-wide approval. This review focuses on the main regulatory changes related to the centralized procedure and the new concepts for approval that may affect applications for oncology products.
Regulation (EC) No. 726/2004 introduces new tools and procedures allowing early access to new drugs, including anticancer drugs. One of theses measures is the 150 days accelerated procedure (instead of 210 days) for drugs that are of major public health interest, particularly in terms of therapeutic innovation. Moreover, renewable conditional authorisations may be granted for certain products pending completion of further studies (detailed implementing legislation is expected to be adopted by the time of reporting). The existing mechanism of approval under exceptional circumstances when the rarity of the indication, the state of the scientific knowledge or the principles of medical ethic do not allow to provide

comprehensive data on the efficacy and safety of such products, is retained. In addition, opinions for cohort compassionate use of products eligible to the centralised procedure may be given by the EMEA to treat patients with chronically or seriously debilitating disease, considered life-threatening, when no other authorised alternative exists.
The new European pharmaceutical legislation contains a number of new tools to provide early access to medicinal products of public health interest. The new approval mechanisms and the impact on the authorisation of oncology drugs are reviewed based on EMEA guidance.
Disclaimer: The views presented in this abstract are those of the authors and should not be understood or quoted as being made on behalf of the EMEA or its scientific committees

528 POSTER

Conduct of international multi-centre Investigator-Initiated Trials (IIT) in Europe after the transposition of the Clinical Trials Directive in national Member States law

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Background: Due to the mandatory implementation of the Clinical Trials Directive, Member States (MS) of the European Union (EU) have adapted their existing legislation to the new requirements for the conduct of clinical trials into humans. The Directive is aimed to harmonise legal acts for the set-up, conduct and reporting of clinical trials, to implement GCP-principles European-wide and to enforce patient protection. For non-commercial trials, the Directive is seen to impede the realization of future trials, as requirements, obligations and costs for clinical research projects are considerably increasing.
Methods: The comparative analysis carried out is aimed to investigate differences, obstacles and pitfalls for the conduct of future multi-centre trials in MS. The legislation of 8 MS has been revised, major differences and alleviations allowed for non-commercial trials are tabulated. 3 IIT case studies in oncology are presented; the feasibility to conduct each trial throughout the EU will be discussed.
Results: Major differences are noticed regarding the scope of revised legislations in the MS. Differences also apply to sponsorship and liability issues. Until now, only a few MS have expressively added provisions for non-commercial trials into their legislation. These specify e.g. the use of commercially available products and address reimbursement issues, simplified or exempted submissions of an Investigational Medicinal Product Dossier to competent authorities, or allow for exemptions from fees for IRB/dossier approval. No common definitions are available throughout the EU neither for the so-called 'Phase IV' studies, nor for the terms 'IIT' or 'non-interventional studies'.
Conclusion: The new legal framework for clinical trials renders the realization especially of future pan-European multi-centre trials much more difficult. In having harmonised organisational requirements for trials throughout the EU, the Directive has failed to simplify the conduct of academic clinical trials in the European trial space. Radiotherapy studies, trials investigating surgical techniques and some multi-modal trial concepts remain in some, but not all MS out of the scope of the revised legislative texts. Apart from 'interventional' trials, non-interventional trials allow – although heavily restricted to small Phase I/II case series within or in close proximity to the approved prescription window given by drug labelling – in some MS limited research in form of observational studies outside of the new legal framework. 12 months after implementation, the new EU legislation results in a harsh drop-down of the number of new clinical trials and promotes primarily the conduct of nation-wide research projects.

529 POSTER

Study participation improves treatment strategies and individual patient care in participating centers

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The ADEBAR study is a prospective multicenter Phase III trial to examine whether high-risk breast cancer patients (> 4 involved axillary lymph nodes) benefit from a sequential anthracycline-docetaxel regimen (E90C-D: 4 cycles epirubicin [E] 90 mg/m^2 BSA plus cyclophosphamide [C] 600 mg/m^2 BSA q21d, followed by 4 cycles docetaxel [D] 100 mg/m^2 BSA q21d) compared to standard chemotherapy with anthracyclines (FE120C: 6 cycles E60 mg/m^2 BSA d1+8, 5-FU 500 mg/m^2 BSA d1+8 and C 75 mg/m^2 BSA d1–14, q28days). The ADEBAR study was the best recruiting study in Germany in this indication group until the end of the trial.
Methods: A standardized questionnaire was sent to all participating centers in order to find out the extent to which treatment strategies and patient care are affected by participation in the ADEBAR study. The questionnaire comprised 5 questions: previous inclusion of patients at the same tumor stage in studies, the type of chemotherapy received by comparable patients previously outside the study, change in the intensity of medical care since participating in the ADEBAR study, the increase in knowledge acquired through participation in the study, and changes in the overall quality of medical care.
Results: In the year preceding the ADEBAR study, 63.2% of participating centers had not entered their high-risk patients into a clinical trial. Before participating in the ADEBAR protocol, 44.2% of patients with the same indication had received inadequate therapy by today's standard of knowledge, such as CMF, EC/CMF, or 4 × EC. 59.0% of the centers noted an increase in the intensity of patient care as a result of participating in the study – independent from the care given to patients purely as a result of participating in the study. By being part of an investigators' network, with a regular flow of information via newsletters, study meetings, etc., 80.0% noted an improvement in their professional knowledge in the field of breast cancer. Moreover, 31.6% of the centers reported an improvement in the overall quality of their patient care since the start of the trial.
Conclusion: The results of the questionnaire demonstrate that both medical doctors and patients benefit from participation in clinical trials.

530 POSTER

The influence of mentorship on research productivity in oncology

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Background: Mentoring is the process by which an experienced person provides guidance, support and encouragement to a less experienced person. This project evaluates whether the availability and support of mentors are associated with research productivity in oncology.
Methods: Two electronic mailings of an on-line survey were sent out to 1,009 oncologists who have previously attended one of two educational workshops between 1996 and 2004. The two workshops, located in Vail and Flims, have been sponsored by AACR/ASCO/FECS with the goal of training oncologists in the methods of clinical cancer research.
Results: 322 oncologists (32%) responded to the survey with the following demographics: Vail/Flims (56%:44%); m/f (63%:37%); median age = 37; median year of graduation = 2001; medical oncology/radiation oncology/surgical oncology/others (63%: 11%: 9%: 17%); USA/EU/Canada/others (51%: 35%: 6%: 8%); 65% have other academic degrees besides MD. Of all respondents, 88% currently are engaged in academic research, 47% and 45% have been principal investigators on grants supported by academic/governmental agencies, and by the pharmaceutical industries, respectively. About one-third of respondents currently spend over half of their time on academic research. The self-reported median number of peer-reviewed papers published as main or co-author since graduation from medical school was 8 (range 0–150). In day-to-day work life and career development thus far, 81% of respondents have had the support of at least one mentor, while 19% did not have any mentors. All respondents who did not have any mentors indicated that their career would have benefited from having a mentor, and 94% of those who had a mentor indicated that mentorship was important in their career development. For all respondents, the greatest perceived benefits of having mentors are: to discuss research work and projects, to provide career advice, and to generate networking opportunities. Respondents with mentors are more likely to be currently engaged in academic research than those without mentors. However, having mentors or not did not influence respondents' self-reported Publication onlyn record, or in their success of becoming principal investigators on academic or pharmaceutical grants, even when respondents' year of graduation are taken into account.
Conclusions: Mentorship is considered valuable to oncologists in enhancing their research and networking experiences. In this selected group of oncologists, mentorship has effects on their current involvement in academic research, but not on self-reported Publication onlyn or grant records.