3. Is it useful to identify more advanced disease in order to be able to restrict invasive / toxic treatments to those patients who can benefit?

We can use stage in clinical practice as a guide to planning the multidisciplinary approach to therapy. The concept of systemic treatment intensification for poorer prognosis patients is unproven, at least in solid tumours, has been discredited in breast cancer and is still under investigation for Ewing's family tumours. This is most likely due to the very narrow therapeutic index of cytotoxic chemotherapy relative to many-fold levels of resistance of cancer cells. However, defining the presence and sites of metastatic disease can be vital to the choice of treatment, e.g. by indicating a need for systemic therapy, lymph node dissection, radiotherapy, etc.

19-FDG-PET and PET-CT are being used increasingly in routine clinical practice. PET can be used to define the treatment volume for radiotherapy and identify which patients are responding or not. PET-CT is becoming an integral part of staging prior to surgery for NSCLC. Although false positives may occur, it is possible to identify occult mediastinal nodal involvement and prevent pneumonectomy from being performed inappropriately. PET is also used to identify residual active disease after systemic treatment of Hodgkin's lymphoma and testicular tumours, requiring local therapy. MRI, including whole body STIR, can be used to identify metastatic bone disease not visible on isotope bone scan, e.g. in Ewing's. MRI may be the only means of detecting bone disease in metastatic myxoid liposarcoma. Cancer may often be a systemic disease, but local therapy is often the only curative modality. To apply it appropriately requires an accurate knowledge of the disease.

Finally, modern imaging tools are capable of telling us about the biology of a cancer and its response to molecularly targeted therapy. This is put to good use in the management of GIST with imatinib and sunitinib, where FDG-PET can be used to define response or progression within a matter of days and is used to plan local therapies such as radiofrequency ablation of liver metastases. In conclusion, improved whole body imaging techniques are capable of helping deliver genuine improvements in cancer control and should be welcomed.

13 INVITED

Whole-body MRI

H. Schlemmer. *University of Tübingen, Radiologische Diagnostik, Tübingen, Germany*

A malignant tumor is in per se a potential systemic disease. Imaging is of fundamental importance for initial and follow-up staging as serum tumor markers cannot provide information about the localization of tumor tissue and secondary complications related to possibly harmed surrounding anatomic structures. Precise staging and accurate therapy monitoring in individual patients are essential for assessing prognosis and achieving best patient outcome in terms of survival and quality of life.

High-resolution whole-body MRI is a novel and promising technique and its medical and economic is of considerable importance. Due to the provided high soft tissue contrast it is the modality of choice for local staging in a variety of tumors. The method plays particularly an important part for evaluating metastatic disease and for estimating the individual total tumor burden. Compared to CT and PET/CT it has been proven as the most accurate method for detecting metastases in the brain, abdominal organs and bone marrow. Regarding bone metastases, it is particularly more sensitive than conventional bone scintigraphy, X-ray, CT and PET/CT for different tumor types. One major drawback of MRI remains the limited accuracy for an early detection of lymph node metastases. Novel contrast media containing lymphotropic paramagnetic nanoparticles (USPIO) may help to increase the specificity. There is a need of more representative studies evaluating teh benefits of whole-body MRI versus whole-body CT end PET/CT with respect to specific tumor types and stages.

Whole-body imaging significantly increases the number of acquired images per patient. One examination comprises up to 1000 images, which all have carefully to be reviewed for the presence or absence of suspicious mass lesions consuming a notable amount of time and concentration. The time required for reading, documentation and discussion of the high number of images vary substantially, and 15−60 minutes are needed, particularly if additional images, e.g. from follow-up and/or multimodal diagnostic approaches with CT, PET or PET/CT have to be evaluated. Finally, a small number of essential images showing all relevant findings have to be sorted out and demonstrated in a fast and comprehensive manner as therapeutic decisions are increasingly based on recommendations by multidisciplinary conferences. The involved Radiologists will accordingly be faced with heavier workload, in particular as referring clinicians are getting more and more aware of a comprehensive whole-body approach probably cutting down the total time demand for imaging. Logistical implications for work flow optimization have therefore increasingly to be considered to minimize the time demand not only of the patient examination but also of the reading and reporting process. Novel ideas for redesigning the department's workflow concepts are challenging but a reasonable prerequisite for utilizing the potential of whole-body imaging technology.

14 INVITED

PET/CT: improved sensitivity and specificity in staging and therapy monitoring

G. von Schulthess. *University Hospital Zürich, Department medical radiology Clinic for nuclear medicine, Zurich, Switzerland*

Since its first worldwide introduction into clinical practice at our institution in March 2001, PET-CT has been the most rapidly growing imaging modality worldwide, developping into an annual market of over 1 billion US$. There are very good reasons for this, which have been amply documented in the last 6 years:

1. PET is well known to be highly sensitive in detecting tumor manifestations.
2. PET as most Nuclear Medicine procedures, lacks sensitivity in many settings.
3. Adding CT to PET improves – above all – examination specificity.
4. PET-CT is a more accurate examination than either PET, CT or PET and CT read side-by-side.

The purpose of this presentation is to familiarize the participant with the key indications for PET-CT in tumor staging (e.g. NSCLC) and therapy monitoring (e.g. lymphoma). As the CT portion of PET-CT can be run mainly for anatomic localization as a low dose CT, but also as full scale, contrast enhanced multi-phase CT, it is critical for the referring physician to understand, that frequently when the diagnosis is clear and staging with a cross-sectional imaging exam is to follow, referral directly to PET-CT can be made with the advantage that the resulting data are comprehensive, integrated and the patient only needs a single appointment. If CT or MR data exist from a very recent examination, a repetition of a full scale CT within PET-CT frequently is unnecessary.

While deeper insights into reading PET scans is beyond the scope of this presentation, it is a second aim to familiarize the referring physician with some important pitfalls in PET imaging. It is well known that inexperienced PET readers and particularly radiologists who have little formal PET training, are too sensitive in PET image interpretation which in turn leads to too many false positive diagnoses.

In summary, PET-CT has proven to be the staging modality of choice in many important tumors and due to its unique feature of depicting molecular processes rather than just anatomy, is rapidly gaining acceptance as excellent imaging procedure to monitor therapy

Special session (Mon, 24 Sep, 13:30−14:30)
Biosimilars in oncology and hematology – what should a physician know

15 INVITED

Open questions about biosimilars – pharmacovigilance, substitution, labelling, naming and economy

H. Mellstedt[1], H. Ludwig[2], D. Niederwieser[3]. *[1]Karolinska Institute, Dept of Oncology, Stockholm, Sweden; [2]Wilhelminenspital, Dept of Medicine, Vienna, Austria; [3]University of Leipzig, Dept of Hematology and Oncology, Leipzig, Germany*

Biosimilars are new, non-innovative biopharmaceutical agents that are "similar", but not identical to reference biopharmaceutical products. Biosimilars should provide cost savings and greater access to biopharmaceuticals; however, they are unique molecules and should not be considered generic versions of reference products. Characteristics of any biopharmaceutical are closely related to its manufacturing processes (eg, cellular expression system, extraction/purification process), many of which are proprietary information. Thus, biosimilar manufacturers cannot duplicate a reference product. Moreover, small differences between biopharmaceutical products may produce clinical differences with respect to efficacy, safety, and immunogenicity. Because of these issues, the approval process required for biosimilars is not as straightforward as that for small molecule generics. The EMEA has developed a general regulatory pathway for the approval of biosimilars. The approval process will vary according to the product category. For example, specific guidelines have been developed for biosimilar epoetins and biosimilar granulocyte colony-stimulating factors (G-CSFs). In general, the approval of biosimilars will be based on the demonstration of comparable efficacy and safety to an innovator reference product in a relevant patient population. Because clinical data for biosimilars will be limited at the time of approval, regulatory guidelines also require post-approval monitoring (ie, pharmacovigilance) to establish

a more accurate and comprehensive clinical database and to ensure that any unexpected treatment issues are identified promptly. The EMEA guidelines will permit the use biosimilars for indications for which they have not been formally studied (ie, extrapolation) when proper justification is provided. While the EMEA guidelines are scientifically rigorous and provide a pathway for the approval of biosimilars, they do not fully address some important post-approval issues relevant to physicians, particularly in the oncology setting. These include automatic substitution with biosimilars, labeling so that physicians can make informed decisions, and nonproprietary naming for accurate prescribing and dispensing practices. Currently, the EMEA cannot guarantee the interchangeability of biosimilars with reference products, and because of the potential for differential clinical response it would appear prudent that automatic substitution should not be allowed for any biopharmaceutical – biosimilars or innovator products. Also, the use of biosimilars for indications based on extrapolation of data must be weighed against the possibility for differences in safety and efficacy. Such issues underscore the need for full disclosure in the product labeling of biosimilars so that physicians and patients can make informed decisions regarding product selection. A thorough knowledge of the issues surrounding biosimilars will ensure the appropriate use of biopharmaceuticals.

16 INVITED

Follow-on erythropoietins – Pros and cons

H. Ludwig. *Wilhelminenspital, Medizinische Abteilung mit Onkologie, Vienna, Austria*

Background: Erythropoietin biosimilars are not generic equivalents of the innovator product and are likely to be approved in Europe soon.
Material and Methods: This report presents a review of present literature on biosimilar erythropoietins. Literature search included Medline and abstracts from ASCO, ESMO, ASH, EHA and ECCO meetings (2000-2007).
Results: Amino acid sequences of biosimilars of erythropoietin will most likely be similar to that of endogenous erythropoietin, but glycosylation patterns will differ. Differences in glycosylation may have a significant impact on the rate of plasma clearance, on receptor binding, and importantly on biological and on clinical activity. A recent study comparing 11 erythropoietin products from 4 different countries (Korea, Argentina, China, India), revealed significant variations in the distribution of erythropoietin isoforms. Further, in vivo bioactivity ranged from 71% to 226%, with 5 products failing to meet their own specifications.
Due to the differences in carbohydrate moiety and possibly immunogenicity and clinical activity, appropriate labelling of the drugs as unique molecules is mandatory. This is particularly important for identification of eventual late adverse effects during pharmacovigilance studies. Hence, switching or substitution between innovator products and biosimilars should not be enforced automatically, and must be viewed as a change in clinical management. Rigorous pharmacovigilance programs are needed to capture possible side effects and to build a database establishing the clinical use of each product.
On the positive side, biosimilars will increase the usage of drugs and benefit more patients. The introduction of biosimilars will motivate industry to increase its research efforts even further in order to develop new drugs, which will be protected by patent rights for a defined period.
Conclusion: Biosimilars are not identical to the innovator drug, cannot automatically be substituted and need careful pharmacovigilance programs. Their introduction will allow a greater number of patients to actually receive treatment, and will drive industry to further enhance its research efforts.

17 INVITED

G-CSF biosimilars – approval process, substitution and extrapolation

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Two G-CSF products differing with respect to biological characteristics and approved indications are currently available in Europe. Comparative studies have demonstrated differences between these two products with regard to pharmacological properties and clinical outcomes and are not considered interchangeable. According to EMEA guidelines, G-CSF biosimilars have to demonstrate comparability in efficacy and safety to one of the two G-CSF products in the prophylaxis of severe cytotoxic chemotherapy-induced neutropenia. While a two-arm comparability study is recommended for chemotherapy regimens with known frequency and duration of severe neutropenia, a 3-arm study (including placebo arm) is required for other chemotherapy regimens.
Since limited clinical experience will be available at approval of biosimilars, substitution represents a major challenge. Automatic substitution may lead to the administration of multiple products and events would not be able to be linked to a specific product. Furthermore, the identification of biopharmaceutical products might not be possible if multiple products share one International Nonproprietary Name (INN).
Although data extrapolation has a rational basis, the process by which indications for a product were approved should be known. A potential concern with the concept of data extrapolation arises in particular for G-CSF biosimilars, since efficacy and risks may differ in patient populations depending on age, on disease (malignant or non-malignant) and immunosuppression. As an example non-immunosuppressed patients with chronic neutropenia may be more likely to develop antibodies to biopharmaceutical agents than immunosuppressed patients. Especially the use of G-CSF biosimilars for stem cell mobilization from healthy donors in allografting presents an ethical dilemma. Since healthy donors receive no therapeutic benefit from the receipt of CSFs for stem cell mobilization, ethical concerns dictate that drug safety be of paramount concern. Sufficient experience with the biosimilar product and adequate follow up should be required.
In summary, information is the key to mitigating the potential concerns regarding the use of biosimilars. Any change from one product to another should be considered as a change in clinical management. Extrapolation should be avoided for use of biosimilars in healthy stem cell donors as long as sufficient data from stem cell mobilization in patients are available.

Special session (Mon, 24 Sep, 13:30−14:30)
Retroperitoneal sarcoma

18 INVITED

Surgical standards of treatment

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The specific problems of retroperitoneal soft tissue sarcoma relate to the proof of malignancy by biopsy and the heterogeneity of huge tumors with sometimes low grade and high grade compartments. Biopsy needs to prove that lymphoma, extragonadal germ cell tumors and lymph-node metastasis of tumors of the testicles do not hide behind a sarcomatous appearance. The future of defining molecular targets might also offer preoperative targeted therapy with new substances, for example in myxoid or round-cell liposarcoma.
The primary goal of surgery is an R0 resection – adjuvant chemotherapy has not proven to be of value. Thus, planning of the operative treatment must be made not to leave viable tumor tissue behind. At the first stage, an adequate imaging of the whole abdomen starting from the diaphragm down to the lower pelvis is required not to miss an extension of the tumor to the thorax, the lower pelvis, the adductors or paravertebrally. Usually retroperitoneal sarcoma is in close contact to one of the kidneys. If there is any risk that the kidney or the ureter will be involved in the resection, assessment of the function of the contralateral kidney is mandatory.
Concerning resectability the limits of resection are the spine, the neuroforamen, major involvement of the aorta, invasion or extension to the root of the mesentery with major small bowel resection as a consequence, bony structures as the ileo-sacral joint and extraabdominal extension. The retroperitoneal compartment, sarcoma usually originates in, offers a unique possibility for a radical resection. However, this means that tumor removal is a multivisceral resection by principle. Dissection of the aorta or vena cava, resection of the psoas muscle, removal of the internal oblique muscle, as well as keeping the sarcoma covered by large bowel resection and nephrectomy are the crucial steps. Extended resections include removal of parts of the vena cava and graft reconstruction, as well as partial resection of the aorta with graft or patch plasty and finally also autotransplantation of the kidney in case of involvement of the fatty capsule of the kidney only. Resection and reconstruction by diaphragm with a synthetic graft may complete the approach.
It must be born in mind that after removal of a huge retroperitoneal mass the small bowel will move to the former tumor bed and by this way makes postoperative adjuvant radiotherapy inefficient due to the limit of tissue radiation tolerability. Consequently, radiotherapy should be used prior to the operation. In high-grade soft tissue sarcoma, preoperative radio-/chemotherapy could be useful. Recently, in a randomized prospective trial, systemic chemotherapy combined with deep wave hyperthermia has proven effective, not only in the down-staging of tumors, but also in improving survival. This methodology might not be available at any center, but an experienced sarcoma center is required to offer the patient an optimum standard of care. A multistep explanation of the therapeutic