CONFERENCE SCENE

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Neuro-oncology insights from European Society of Medical Oncology 2012

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European Society of Medical Oncology (ESMO), the annual conference of the ESMO, has become one of the leading oncological meetings worldwide. This year's ESMO was held in Vienna, Austria, from 28 September to 2 October, attracted more than 16,000 attendees from around the world and was dedicated to the implementation of personalized medicine in all oncologic subdisciplines, including neuro-oncology.

This year's European Society of Medical Oncology (ESMO) reported and discussed the outcomes of more than 90,000 patients treated in trials, and attracted 1240 abstract submissions, and has succeeded in becoming one of the major oncological conventions worldwide. In 2012, an oncologic meeting without a track for CNS tumors would be perceived as incomplete; ESMO 2012 provided attractive sessions summarizing all topics covered by neuro-oncology, designed for dedicated neuro-oncologists as well as for interested attendants from other disciplines. The main theme for this conference was the initiation of personalized therapy in all subdisciplines of oncological practice, including all tumor entities treated in neuro-oncology.

Moreover, the meeting offered a comprehensive overview about the actual state-of-the-art antiangiogenic treatments, which was highly interesting for neuro-oncologists awaiting the results of the trials treating glioblastoma (GBM) patients with bevacizumab-containing regimens as first-line treatment. Michal Neeman (Rehovot, Israel) discussed physiological and pathophysiological angiogenic

pathways and the appropriate molecular MRI imaging methods permitting their visualization *in vivo*. She reminded us that neoangiogenesis in cancer is composed of complex and tightly regulated processes that offer greater possibilities for intervention than simply blocking VEGF. In fact, bevacizumab blocks the sprouting of new capillaries and might become less effective when endothelial cells become stabilized by pericytes, leading to highly permeable 'tumor vessels' that leak proteins and other macromolecules and that are responsible for the typical phenomenon of contrast-enhancing tumors with high oncotic pressure and limited perfusion. Neeman presented potential strategies for intervening at this stage; her experimental data were subsequently placed into a clinical perspective by the breast cancer specialist David Miles (Northwood, UK), calling for a more rational and less 'watering can-like' use of antiangiogenic agents, taking into account clinico-pharmacological knowledge and thorough subanalyses of previous studies in order to improve clinical outcomes, even in times of budget restrictions. Other topics covered

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were supportive care options, adequate oncological management of elderly patients and the positioning of European universities and study groups versus US primacy in the development of new drugs.

The CNS track dealt with almost 50 submitted abstracts presented as posters, late-breaking abstracts selected for oral presentations, four dedicated oral sessions and an educational session on new aspects of decision-making and clinical management of patients with malignant glioma, such that almost all subjects of neuro-oncology were covered.

Brain metastases from solid tumors are up to ten-times more frequent than primary brain tumors and are a common cause of treatment failure in patients with malignancy. At ESMO 2012, brain metastases moved to the center stage as news of innovation for this difficult topic was presented. Michael Brada (Royal Marsden, London, UK) analysed strategies in the treatment of brain metastases of solid tumors. He emphasized the crucial role of study design, choosing suitable patients for testing novel treatment strategies and choosing the right end points – avoiding pitfalls caused by early systemic progress of the malignancy. In the joint meeting of ESMO and the European Society for Therapeutic Radiology and Oncology, first experiences with radiotherapy techniques allowing preservation of the neurocognitive function of patients by hippocampus-sparing radiation were reported by Klaus Belka (Munich, Germany). He showed that, in a series of 272 patients with brain metastases, 86% occurred in locations at least 15 mm distant from the hippocampus, allowing hippocampal-sparing radiation with tomotherapy, intensity-modulated radiation therapy and volumetric-modulated arc therapy. He demonstrated that sparing the hippocampus with whole-brain radiotherapy is feasible by any of the abovementioned techniques, but emphasized that there are still no outcome data on the impact on neurocognition and recurrence rates for treatment with the new techniques, and referred to the awaited data from the Radiation Therapy Oncology Group 0933.

Thomas Bachelot (Lyon, France) reported the results of the multicenter, French

LANDSCAPE trial, a Phase II study in which 45 patients with brain metastases from HER-2-positive breast cancer were treated with oral lapatinib 1250 mg once daily and oral capecitabine 2000 mg/m² from day 1 to 14, every 21 days, showing that with this regimen whole-brain radiotherapy can be delayed for a median of 8 months. The response rate in brain was 67%. When these results can be confirmed, this regimen will probably change the sequence of treatments in women with HER-2-positive breast cancer and brain metastases.

Delaying radiotherapy in selected patients with brain metastases from non-small-cell lung cancer was the subject of the talk by Toshihiko Iuchi (Chiba, Japan). He reported on a Phase II trial for patients with brain metastases from EGF receptor-mutated non-small-cell lung cancer, that received first gefitinib and then erlotinib, in order to delay brain radiation. Thirty-seven patients were enrolled; the median time to radiotherapy as salvation treatment was 14.3 months; the median progression-free survival (PFS) and overall survival times were 8.9 and 28.3 months, respectively. Of note, response to tyrosine kinase inhibitor was superior in exon 19-deleted cases ($p < 0.03$). In patients with exon 19 deletion, PFS and time to radiotherapy were also more favorable than in the other patients, at 14.5 and 18 months, respectively. Both contributions substantiate that personalized care has been initiated for patients with brain metastases.

Evaluations of the impact of molecular markers for diagnosis and treatment decisions were also the main topic for the sessions dealing with glioma therapy. In the session on 'Molecular neuro-oncology: new avenues in diagnosis', Martin van den Bent (Rotterdam, Belgium) outlined that, in patients with WHO grade III malignant gliomas, the molecular markers available should over-rule histological diagnosis in decision-making. He demonstrated that the data of the EORTC study 26951 show that patients with 1p19q codeletion benefit from combined therapy with radiation and chemotherapy – in this study the regimen given was procarbazine, lomustine and vincristine – to an unprecedented extent as median survival has not been reached after 14 years, whereas patients treated

with radiotherapy alone had a median survival of 9.3 years. van den Bent detailed that 1p19q codeletion, *MGMT* promoter methylation and *IDH1* mutation show a significant but not complete overlap in their occurrence in glial tumors, and that their impact is that they all predict response to alkylating chemotherapies – favoring combined treatment regimes. The question as to whether temozolomide could replace the more toxic regimen of procarbazine, lomustine and vincristine cannot be answered at the moment, but will potentially be investigated within the global CODEL trial (which has stopped recruitment due to ethical concerns of undertreating patients that would be randomized to receive radiotherapy only).

One of the major highlights of ESMO was that one could listen to key experts developing their insights about the current impact of the available molecular markers – namely *IDH1* mutation, *MGMT* promoter methylation and 1p19q codeletion – for decision-making in patients with gliomas. Marc Sanson (Paris, France) introduced this topic in an educational session showing a comprehensive overview of the occurrence of the markers, diagnostic methods and impact on survival, detailing their significance for decision-making at different time points in a patient's disease course. In the same session, Roger Stupp showed how evidence from trials should be translated into every day's practice, as “gliomas are not all the same,” giving actual state-of-the-art opinions on the treatment of newly diagnosed and recurrent GBMs, anaplastic oligodendrogliomas and anaplastic astrocytomas, focusing also on the duration of therapy and emphasizing that actual evidence does not support adjuvant therapy in GBM beyond six adjuvant cycles. He also reviewed the results of two European trials on the treatment of GBM in elderly patients, namely the NOA08 trial from the German glioma network and the Nordic glioma trial, showing that in both trials the responsiveness to temozolomide clearly depends on the *MGMT* promoter methylation status and that omitting radiotherapy in the elderly can only be done safely in elderly patients with methylated *MGMT*.

Michael Weller (Zürich, Switzerland) detailed his thoughts on stratified care for the management of patients with malignant gliomas based on age, performance status and molecular markers: so far, with the exception of GBM, patients bearing tumors with *IDH1* mutation can safely be treated with temozolomide alone, whereas patients with wild-type *IDH1* require treatment by radiotherapy. The possibility to diagnose a *IDH1*-mutated glioma by detecting 2-hydroxyglutarate in plasma or urine was presented by Guiseppe Lombard (Padua, Italy). Exciting first hints on the potential impact of high plasma levels of matrix metalloproteinase-2 as a predictive marker for response to bevacizumab were presented by Emmeline Tabouret (Marseille, France).

For the difficult subgroup of patients with unresectable GBM, Bruno Chauffert (Amiens, France) presented data from the TEMAVIR ANOCEF study on 120 patients, randomized either to standard chemoradiotherapy with temozolomide or to upfront treatment with bevacizumab plus irinotecan. This study just missed the end point of 66% 6-month PFS but yielded remarkable and randomized outcome data on this worst prognosis subgroup of GBM patients.

A brilliant and inspiring insight into the genetically defined subgroups and their implications for tailored therapy for children with medulloblastomas was given by Stefan Pfister (Heidelberg, Germany) who demonstrated that performing adequate treatment for each subgroup significantly improved the outcome for the whole cohort, allowing neuro-oncologists for adult patients to hope that some day we could reach the level already achieved by our pediatric colleagues.

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