The 6th Belgian symposium on the integration of molecular biology advances into oncology clinical practice

Highlights from the 6th Belgian symposium on the integration of molecular biology advances into oncology clinical practice, 23-24 November 2012, Diegem, Belgium

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On the 23rd and 24th of November 2012, the Jules Bordet Institute and the Belgian Society of Medical Oncology (BSMO) hosted the 6th Belgian symposium on the integration of molecular biology advances into oncology clinical practice. The aim of this meeting once more was to translate the major advances made in molecular and biological understanding in cancer into clear messages for daily oncological, clinical practice. Over the two days, a plethora of Belgian and international key opinion leaders discussed the clinical impact of molecular advances in several tumour types. Given the high quality of the different lectures, it was not surprising to see that the meeting again obtained the ESMO label.
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Bringing personalised oncology to clinical practice (J. De Grève, VUB)

The 6th symposium on the integration of molecular biology advances into clinical practice kicked off with a summary of a white paper that aims to sensitize all health stakeholders in Belgium to the potential advances of personalized medicine and the current hurdles faced when implementing this in clinical practice. Personalized medicine has the potential to predict responsiveness, improve patient outcomes and lead to a more cost-effective health care. However, budgetary constraints form a great threat in implementing personalized medicine into daily practice and currently the patient access to new drugs is too slow (4-5 years between phase I/II and general patient access). To improve on this, the task force pleads for a synchronized reimbursement system for both drugs and diagnostic tests, quick adoption of new cost-effective pharmacodynamic technologies or validated biomarkers into hospitals, regular communication between all stakeholders in early stages of drug development and early conditional marketing approval (reversible drug approval for high impact agents based on early data when a companion diagnostic is available). Furthermore, an education system for all healthcare professionals who are in contact with patients that are candidates for stratified medicine is needed to increase awareness. Similarly, workshops for government personnel involved in reimbursement issues on clinical and pharmaco-economic aspects are warranted.

A complete version of this consensus text will be published in the next issue of the Belgian Journal of Medical Oncology.

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New targeted therapies in solid cancers

New agents in melanoma (J-F. Baurain, UCL)

Until recently, patients with advanced melanoma had very few treatment options and were faced with a six month progression-free survival (PFS) of 15% and a one year overall survival (OS) of 25%. However, recent insights into the molecular biology underlying melanoma have led to the introduction of the BRAFV600E inhibitor vemurafenib in the treatment arsenal of melanoma. The clinical benefit of vemurafenib in BRAFV600 mutated advanced melanoma patients was demonstrated in the phase III BRIM-2 and BRIM-3 studies. However, 50% of patients do not respond to vemurafenib and the duration of response to BRAF inhibitors is relatively short (six months). To circumvent this, a BRAF inhibitor can be combined with a MEK inhibitor (trametinib). This combination was shown to increase PFS with an impressive 75% response rate. Furthermore, this combination did not lead to extra toxicity. Currently MEK inhibitors are also evaluated in NRAS mutated melanoma and the combination of vemurafenib and trametinib will be assessed in the adjuvant setting. In addition to this, combining BRAF inhibitors with immunotherapy (ipilimumab) will also be evaluated.

New agents in renal cell carcinoma (S. Rottey, Ghent University Hospital)

A whole range of new treatments has dramatically changed clinical outcomes for patients with metastatic renal cell carcinoma (RCC). However, therapy is non-curative, treatment is chronic and has a significant impact on quality of life (QoL). Several multi-targeted TKIs with high affinity for VEGF receptors are currently under evaluation in RCC. Despite incremental improvements in PFS, these TKIs (axitinib, cediranib, dovitinib, tivozanib, regorafenib, etc.) have not led to an improved OS raising the question whether this is the way to follow. As such, research currently focuses on other strategies including the combination of agents with different, potentially complimentary, mechanisms of action (e.g. MEK inhibitor tivantinib plus sorafenib: ORR 15%, PFS: 12.7 months, well tolerated). In addition to this several immunotherapeutic treatment strategies are under evaluation in RCC. This encompasses dendritic cell vaccination, CTLA4 inhibition, T-cell modulation with PD-1 blocking antibodies.

New agents in prostate cancer (T. Gil, Jules Bordet Institute)

Over the last two years, six new compounds were shown to improve survival in patients with metastatic castration-resistant prostate cancer (mCRPC). Currently, docetaxel monotherapy remains the standard first-line treatment option for patients with mCRPC although several combination studies are underway. Cabazitaxel is available in 2nd line treatment under restrictive conditions (progression on docetaxel or within 5 months). Abiraterone acetate improves OS with 4 months compared with placebo in post-docetaxel mCRPC and has a positive influence on skeletal related events (SRE) and PSA levels. As such, abiraterone acetate is available in Belgium under restrictive conditions after docetaxel (progression on docetaxel or within 5 months).

With respect to bone-targeted therapies, denosumab was shown to significantly prolong the time to first SRE compared with zoledronic acid (20.7 vs. 17.1 months, p=0.008). Alpharadin also prolongs the time to first SRE compared to placebo (12.2 vs. 6.7 months). Moreover, alphardin is the first bone-targeted therapy shown to prolong OS in mCRPC. It is currently available in Belgium in the context of an ongoing trial after chemotherapy or for docetaxel-unfit patients.

New agents in NSCLC (G. Berchem, CH Luxembourg)

About 50% of all NSCLC patients harbour potentially actionable genetic alterations in their genome. Unfortunately today many patients are still treated according in a one-size-fits-all manner. Nevertheless, EGFR TKIs are the preferred first-line treatment in metastatic NSCLC patients whose tumor harbors an activating EGFR mutation and EGFR mutation testing has more and more become standard of care in the management of NSCLC.

New phase III data presented at ESMO 2012 show that crizotinib is more effective than standard chemotherapy in patients with advanced, ALK-positive NSCLC, who were previously treated with first-line, platinum-based chemotherapy. These results establish crizotinib as the standard of care for patients with advanced, previously treated, ALK-positive NSCLC. Results of the phase III LUX-Lung 3 study comparing afatinib with chemotherapy in EGFR mutated NSCLC patients show an improved PFS, an improved response rate and a better QoL for patients treated with afatinib. A phase II study evaluating the addition

of the MET inhibitor onartuzumab to erlotinib in patients with NSCLC show a positive effect of the combination on PFS and OS in the subgroup of patients with a high MET expression. This promising combination will now be tested in a larger phase III study (MetLUNG).

Geriatric Oncology: reality and perspectives (H. Wildiers, KUL)

Geriatric assessment of cancer patients can have prognostic information, have a predictive value for morbidity or QoL, can help to detect multiple problems that can influence treatment choice and can possibly direct interventions that can lead to better QoL and survival. A reduced cognition of patients, for example, was shown to have a significant impact on OS in cancer patients. Similarly, malnutrition was shown to be associated with a significantly higher mortality rate in cancer patients aged 75 years.

The current view on personalized medicine mainly focusses on tumour characteristics. When dealing with geriatric patients it is however also important to focus on aspects of the host (comorbidities, functionality, cognition, etc.). The international society of geriatric oncology (SIOG) has formulated guidelines on geriatric assessment. In addition to this, more specific guidelines have been formulated for breast cancer, colorectal cancer, prostate cancer, etc. In Belgium, the cancer plan 2012-15 supports several projects focussing on geriatric interventions. Furthermore, a scientific committee has been set up to review the literature on geriatric assessment, summarize finished projects, coordinate the ongoing projects and to establish national recommendations for further implementation of geriatric oncology after 2015.

Implications of HPV testing in head and neck cancer (A. Psyrri, Attikon University of Athens)

HPV status in combination with p16 expression is useful in classifying oropharyngeal squamous cell carcinomas (OSCC) into distinct subgroups. Interestingly, these subgroups have very distinct molecular phenotypes. Moreover, high p16 expression levels were shown to be associated with an improved prognosis for survival and local recurrence. As such, clinical trials in OSCC should stratify by p16 expression or HPV DNA status or at least include them as a prognostic variable. Evaluating the OS data by HPV status in prospective clinical trials indicates that the relative survival of HPV+ patients is independent of therapy as long as this therapy is the standard of care. Furthermore, the absolute survival difference between HPV+ and HPV-patients is consistently higher than 30% in favor of HPV+ patients.

In recent years discussion has risen over the fact whether HPV+ patients benefit from cetuximab therapy. In the Bonner study, the clinical phenotype that benefited most from cetuximab treatment was consistent with HPV+ disease. However, a trend towards a worse survival with cetuximab was seen for p16+ patients in the RTOG0522 study. To clarify this issue an HPV analysis of the EXTREME study, evaluating the safety and efficacy of cisplatin plus 5-FU and cetuximab in HPV- and HPV+ patients with metastatic squamous HNC, was performed. This analysis illustrated that both p16+ and p16- patients seem to benefit from cetuximab therapy (both for PFS and OS). As such, HPV+ patients should be treated similarly to stage-matched HPV- patients. However, HPV+ patients need to be enrolled in clinical trials to shed more light on these issues.

Immune checkpoint inhibitors in cancer immunotherapy (P. Coulie, UCL)

Cancer immunotherapy means using the patient's adaptive immune system to treat cancer. In passive immunotherapy, tumor-specific T cells or antibodies are transferred into the patient. Active immunotherapy consists of inducing or boosting tumor-specific B or T cell responses in patients. This can be done by using therapeutic vaccination against tumor-specific antigens or by inducing a general increase in the activity of T lymphocytes.

CTLA-4 has an important role in T-cell homeostasis by limiting T-cell activation and preventing too strong T-cell responses. Preclinical studies in mice demonstrated that blocking CTLA-4 results in a significant enhancement of the antitumor immunity. Furthermore, the initial rejection of tumor cells in mice, mediated by CTLA-4 blockage, resulted in immunological memory. These data led to the design of clinical trials with anti-CTLA4 antibodies (Pfizer with tremelimumab and Medarex with ipilimumab).

A second important breakthrough came with the discovery of PD-1, a membrane protein on the surface of activated T, B and NK cells. Interestingly, expression of PD-1 ligand (PD-L1) on the surface of immunogenic cells leads to immune escape. As such, blocking the interaction between PD-1 and PD-L1 forms an interesting antitumoral strategy. Moreover, as PD-1 is a weaker inhibitor than CTLA-4, autoimmune toxicity with this apporach should be milder than for anti-CTLA-4. Many clinical trials are currently underway evaluating immune checkpoint inhibitors in different tumor types.

Tumor heterogeneity: biological phenomenon, or clinical problem? (J. Foekens, Erasmus MC)

Natural selection in tumors takes place through competition for space and resources. Selective pressure leads to the fact that some mutant subclones expand while others become extinct or remain dormant. In that view, tumors are evolving ecosystems of malignant cells and follow Darwin's branching evolutionary tree. Through this evolution, tumors vary in their mutational/clonal composition over time and space. As such, mutations detected in a bulk population will not all co-occur in the same cells. However, most diagnostic tests and drug development completely ignore clonality and many tumors are treated as if they were a single disease entity.

Therapeutic interventions may destroy cancer clones and erode their habitats, but it can also unintentionally provide a selection pressure for the expansion of resisitant clones. A such, repeated sampling of the tumor at different time points might be needed for a more effective targeted treatment strategy. Single cell analysis of circulating tumor cells can be helpfull to gain insight into clonal genotypes and into the overall intra-tumor heterogeneity over time. Characterization of the genetic alterations can identify targets for therapy and can give. insight into treatment efficacy during therapy.

Management of ovarian cancer

Should bevacizumab be used in ovarian cancer?
(J. Kerger, Institut Jules Bordet)

The AURELIA study evaluated the addition of bevacizumab to chemotherapy in platinum-resistant ovarian cancer (OC). This study showed that adding bevacizmuab resulted in a doubling of the PFS compared to chemotherapy alone (3.4 vs. 6.7 months; $p<0.001$). The OCEANS trial on the other hand evaluated the addition of bevacizumab to carboplatin and gemcitabine in platinum-sensitive recurrent OC. Again, adding bevacizumab resulted in a significant prolongation of PFS (8.4 vs. 2.4; $p<0.0001$).

In the supportive GOG-0218 study, carboplatin plus paclitaxel (CP) was compared with CP plus bevacizumab (CPB) and CP plus bevacizumab followed by bevacizumab maintenance (CPB-B) as front-line therapy in newly diagnosed OC. The PFS was shown to be significantly longer for the CPB-B arm compared to CP (10.6 vs. 14.7 months; $p<0.0001$; PFS for CPB 11.6 months) while maintainging QoL. The efficacy of continuing bevacizumab beyond chemotherapy was further confirmed in the ICON-7 study. In all these trials, the safety analyses confirms the toxicity profile of bevacizumab with no new safety concerns and reassuring data regarding gastrointestinal events.

Ongoing trials have been designed to address the optimal duration of bevacizumab, the combination of bevacizumab with weekly paclitaxel, the combination with intraperitoneal therapy, the use of bevacizumab in the neoadjuvant setting and the use of bevacizumab following progression after front-line bevacizumab. In addition to bevacizumab, the angiogenesis antibody aflibercept is also under evaluation in OC as are cabozantinib and trebananib.

Indications of intraperitoneal aproach in OC
(J. Vermorken, UZ Antwerp)

As the peritoneal cavity is the principle site of disease in OC, intraperitoneal chemotherapy (IPCT) seems an attractive treatment strategy for these patients. However, limited penetration, poor exposure to extraperitoneal disease and toxicity remain limitations for IPCT. Due to a lack of randomized data, IPCT should not be used in relapsed OC. With respect to consolidation, only one IPCT is available which was inconclusive. Combined use of intravenous and intraperitoneal chemotherapy was however shown to lead to a significant survival benefit in women with optimally debulked early OC (median about 12 months). Based on the most recent trials, strong consideration should be given to a regimen with intraperitoneal cisplatin.

Hyperthermic intraperitoneal chemotherapy (HIPEC) is not used in routine clinical practice. Literature

data are in support of its efficacy in particular after failure of primary treatment but, unfortunately no randomized trials are available and participation trials are warrranted.

Perspectives in breast cancer (M. Piccart, Institut Jules Bordet)

Over the last decade many new treatment strategies have emerged in the management of breast cancer. With respect to HER2 positive breast cancer, the antibody-drug conjugate T-DM1 was shown to be superior to gemcitabine plus lapatinib in terms of PFS with a strong trend towards improved OS. Pertuzumab, an antibody directed against the external domain of HER2, will soon enter clinical practice. In CLEOPTARA it was shown that adding pertuzumab to docetaxel plus trastuzumab in women with advanced HER2 positive breast cancer results in an impressive improvement in PFS (OS data to be presented at SABCS 2012). Currently a trial is underway evaluating the combination of T-DM1 with pertuzumab in women with advanced HER2 positive breast cancer (*MARIANNE).*

Several other intersting pathways are being targeted in breast cancer. Amplifications of FGFR1 are found in 10% of all breast cancers. As a result, inhibitors of this pathway are under evaluation in breast cancer. An interesting study of dovitinib in patients with HER2 negative metastatic breast cancer who received up to 3 lines of chemotherapy showed that the activity of dovitinib was restricted to patients harboring FGFR1 amplifications (mostly hormone receptor positive cancers).

cMET overexpression is observed in 70% of patients and is associated with a worse prognosis. Moreover, more than 90% of breast cancers show overexpression of the hepatocyte growth factor, a ligand of the cMET receptor. As such, the cMET pathway forms an interesting target in breast cancer. Currently several antibodies directed against components of the cMET pathway are under investigation in clinical trials. In addition tot this, several inhibitors of the PI3K pathway and agents blocking intranuclear cyclin dependent kinases are being studied.

Last but not least, efforts are no longer solely focussed on targets in the tumor, but also take the tumoral microenvironment into account. Furthermore, the Breast International Group (BIG) recently set up an immune task force aiming at evaluating vaccinations and PD-1 inhibition in breast cancers.