The 5th Belgian symposium on the integration of molecular biology advances into oncology clinical practice

Highlights from the 5th Belgian symposium on the integration of molecular biology advances into oncology clinical practice (Diegem, November 25-26, 2011)

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On the 25th and 26th of November 2011, the Jules Bordet Institute and the Belgian Society of Medical Oncology (BSMO) hosted the 5th 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 2 days, a plethora of Belgian and international key opinion leaders discussed the clinical impact of molecular advances in several tumour types.

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Introduction

This report offers a brief overview of the most important data presented at the 5th Belgian symposium on the integration of molecular biology advances into oncology clinical practice.

Early response to chemotherapy in solid tumours

In a presentation by Dr. Hendlisz (*Jules Bordet, Belgium*) the assessment of early responses to chemotherapy in solid tumours was discussed. The early assessment of response is important to avoid needless toxicity with an ineffective treatment and to signal to physicians the importance of changing the treatment. Dr. Hendlisz indicated that structural (radiological) response is the fastest and easiest parameter to assess response. However, radiological response assessment also has some inherent technical (e.g. assumption of spherical tumour, tumour heterogeneity, invalid with non-cytotoxic and locoregional treatments) and methodological (e.g. impact of central review and sample size) downsides. Furthermore, the response assessment poorly correlates with response and the response is assessed too late (6-8 weeks between assessments). Therefore, alternative markers for early response assessment, including molecular markers, circulating tumour cells and metabolic response assessment with FDG-PET have been studied. Of these new methods, FDG-PET seems to be the most promising. This was illustrated by a 100% sensitivity and 100% negative predictive value for FDG-PET demonstrated in a study from the Jules Bordet Institute. Further evaluation of metabolic response assessment in colorectal cancer is currently underway in the PePITA and SoMore study.

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Histology beyond cancer diagnosis

Ki67 is a very popular proliferation marker that is frequently used in the treatment of breast cancer. In a presentation from Dr. Dowsett (*Royal Marsden, United Kingdom*) the potential of Ki67 as a marker in presurgical breast cancer studies was discussed. In the ATAC study, anastrozole was shown to be superior to tamoxifen and the combination of tamoxifen and anastrozole in ER+ postmenopausal women. In the neoadjuvant variant of this study (IMPACT), investigators showed that the reduction in Ki67 was more pronounced in anastrozole-treated patients compared to patients treated with tamoxifen or a combination of both agents. As such, the change in Ki67 expression could predict the treatment benefit. These data suggest that, if IMPACT was set up before ATAC was designed, the combination arm in the ATAC study could have been left out, reducing the cost and shortening the recruitment period of the study. Secondly, Dr. Dowsett illustrated that changes in Ki67 expression were linked to acquired and *de novo* resistance in the IMPACT study. Furthermore, combining the expression levels of Ki67 with the expression of ER, HER2 and PR (the IHC4 score) can be used to predict the residual risk in ER+ breast cancer patients treated with endocrine therapy. This IHC4 score was shown to be at least as good in predicting residual risk as the 21-gene RS score.

Treatment decisions in breast cancer often rely on expression of certain markers in the primary tumour. However, little evidence exists for the stability of the expression of these markers during proliferation. In his presentation, Dr. Bergh (*Karolinska, Sweden*) illustrated the clear differences in gene expression between primary breast cancers and metastases (e.g. discordance ranging from 20-40% for ER and from 0-40% for HER2 expression). One possible explanation for this discordance could be technical in nature. This is certainly the case for immunohistochemistry, but seems less relevant for FISH, which is more robust. As such, therapy predictive factors such as ER and HER2 expression may alter during tumour progression. This may explain some dimensions of resistance to endocrine and anti-HER2 agents. If a certain marker is gained, therapy targeting this marker should be initiated. However, if a marker is lost, it seems reasonable to continue therapy targeting the initial marker.

Molecular-targeted agents as unique therapeutic approach in solid tumours

In the following 2 presentations Prof. Piccart (*Jules Bordet Institute, Belgium*) and Prof De Grève (*VUB Brussels, Belgium*) explored whether molecular-targeted agents as unique therapeutic approach are an option in the treatment of breast cancer and NSCLC respectively.

The addiction of HER2 positive breast tumours to HER2 signaling combined with the high immunogenicity of HER2 makes HER2 positive patients the ideal candidates for chemotherapy de-escalation. Dual blockage of HER2 in HER2+ breast cancer patients was assessed in NeoSPHERE and NeoALTTO. Interestingly, one of the 4 study arms in the NeoSPHERE study was chemotherapy free (patients in this arm only received pertuzumab and trastuzumab. In this arm, 17% of the patients demonstrated pCR (mostly ER negative patients). In the NeoALTTO study, a biological window of 6 weeks was used in which patients received no chemotherapy (only anti-HER2 therapy). In a PET substudy of NeoALTTO, FDG-PET was used to assess response after 2 or 6 weeks. Patients demonstrating a PET response after 2 or 6 weeks, had a 40% chance of reaching a pCR compared to only 20% if no PET response was seen. These studies indicate that a certain population of HER2 positive breast cancer patients demonstrate a good response to anti-HER2 therapy without chemotherapy. These patients could potentially be treated with a 'chemotherapy light' regimen but more research is required to identify this subpopulation.

Secondly, recent data have led to a new hypothesis on the method of action of trastuzumab and pertuzumab, 2 antibodies directed against HER. After binding to HER2, the downstream HER2 signaling is inhibited (ADCC) resulting in cell death and the release of death signals such as HMGB-1 triggering the activation of antigen presenting cells. As a result, CD8-dependent adaptive anti-tumour immunity is generated.

In conclusion, a better understanding of the role of the host immune system combined with the stringent selection of patients that would benefit most from dual HER2 blockage could result in the selection of HER2+ patients that can be cured without aggressive chemotherapy.

In his presentation, Prof. De Grève described how NSCLC patients benefit from drugs targeting driver mutations as a unique treatment. Specifically, NSCLC patients expressing wild-type EGFR do not benefit from treatment with gefitinib or erlotinib. However, EGFR mutant NSCLC patients treated with these tyrosine kinase inhibitors have a significantly better progression free survival (PFS) and quality of life (QoL) compared to EGFR mutant NSCLC patients treated with chemotherapy. Similarly, NSCLC patients harbouring mutations in the ALK gene (3-5%) show a dramatic response to crizotinib with excellent median survival. In addition to this, several other mutations have been identified in NSCLC and are currently being targeted in several clinical studies.

However, these unique targeted treatments are not curative, leaving room for major improvements. Several methods to improve the clinical outcome for patients are currently being explored. A first option is to use dual targeting. One example of this is combining afatinib and cetuximab which was associated with dramatic responses in NSCLC patients with acquired resistance to erlotinib or gefitinib. A second option is to use more potent EGFR inhibitors. However, increasing affinity for EGFR is unfortunately associated with increasing toxicity. Preclinical studies are currently underway evaluating the use of siRNA to block EGFR signaling. Thirdly, TKIs can be combined with chemotherapy. The combination of erlotinib with pemetrexed for example shows synergestic effects in preclinical studies. Lastly, TKIs can be combined with other targeted agents, Many studies are currently underway. The combination of TKIs with MET inhibition showed promising results in preclinical studies which have been validated in a phase II study with erlotinib and MetMAB.

Bypassing TKI resistance in GIST

In a presentation by Dr. Fletcher (*Harvard Cancer Center Boston, United States*), GIST was described as an attractive, predictable model to study mutations resulting in imatinib or sunitinib resistance. Some 85% of all GISTs harbour gain of function mutations in KIT or PDGFRA. The standard first-line treatment for GIST consists of imatinib, but approximately 80% of all advanced GISTs eventually progress on imatinib following secondary KIT mutations. The second-line therapy for GIST consists of sunitinib allthough some KIT mutations also result in sunitinib resistance. Secondary mutations in GISTs are very heterogeneous, including intralaesional heterogeneity. As such, several tumoural subclones can be resistant to several different targeted agents. This makes it difficult to identify a TKI that is capable of targeting all the different subclones. Therefore, broader spectrum and more potent KIT kinase inhibitors are needed (e.g. D3636, soon to be tested in clinical trials). Alternatively, KIT kinase inhibitors can be combined with other targeted agents, but this comes at the cost of increased toxicity.

As such, new approaches to disturb KIT signaling are currently under evaluation. In this light Fletcher described an assay using 54,000 shRNAs directed against 11,000 genes to identify the most crucial gene for survival of GIST tumour cell lines. This assay identified CDC37 as the most interesting target. CDC37 plays a role in KIT-Hsp90 signaling but is also essential for the proteasomic function in normal cells making it difficult to target directly. However, this can be bypassed by targeting PP5, an enzyme involved in the interaction between CDC37 and Hsp90. This hypothesis is currently being tested in preclinical studies.

In conclusion, TKI molecular drug-resistance mechanisms are heterogeneous, making it hard to find a TKI able to target all the different tumoural subclones. Therefore, alternative Hsp90 targeting approaches (e.g. CDC37) may enhance specificity for kinase targets.

The future of PARP inhibitors

PARP inhibitors were initially developed as DNA damage sensitizers, potentiating specific cytotoxic agents. In addition to this, PARP inhibitors can have a synthetic lethal role as single agents in tumours deficient for homologous recombinant repair (HR) (e.g. loss of BRCA1, BRCA2 or PTEN). In his presentation, Dr. Tutt (*Guy's & St Thomas hospital, United Kingdom*) described this as the IKEA-principle. In normal tissue cells, with functioning HR repair, PARP inhibition resulting in impairment of base excision DNA repair, few normal tissue effects are seen. However, in BRCA1/BRCA2 mutated tumour cells, HR repair is deficient and as a result

inhibition of base excision DNA repair with PARP inhibitors leads to specific tumour cell killing. This IKEA-principle was demonstrated in BRCA mutated ovarian and breast cancer. The question now remains whether PARP inhibitors can also be effective in a broader range of cancer.

A first study evaluated whether BRCA-ness can be sufficient for synthetic lethality in sporadic cancers. The study evaluated the use of single agent PARP inhibition in triple negative breast cancer and high-grade ovarian cancer. This study illustrated that BRCA-ness was not sufficient for synthetic lethality in advanced TNBC. However, in ovarian cancer, single agent olaparib was associated with a better response rate and better PFS compared to placebo. Interestingly, this effect was not driven by the BRCA mutant population, but was also seen in ovarian cancer patients with normal BRCA status.

Secondly, other mechanisms by which HR defects might occur in sporadic cancers (apart from BRCA1 or BRCA2 deficiency). This could also induce sensitivity to PARP inhibiton. PTEN pathway loss for example, which is common in breast, colorectal, prostate and endometrial cancer may also impair HR in several tumour types. Alternatively, colorectal cancer patients often display mismatch repair deficiency potentially sensitizing tumour cells for PARP inhibition.

Thirdly, PARP inhibitors were also combined with DNA damaging agents in breast cancer. In this light, veliparib was combined with temozolomide in metastatic breast cancer patients. This study demonstrated a 7% overall response rate. However, this effect was driven by the BRCA deficient patients alone, and no substantial clinical effect was seen in normal BRCA tumours.

To conclude, Dr. Tutt drew some attention to the recent phase III results published for iniparib. After the publication of promising phase II data with iniparib, a phase III study was set up in 519 patients with metastatic TNBC comparing gemcitabine- carboplatin with or without iniparib. However, this phase III study was unable to show an overall survival effect and demonstrated only a weak effect on PFS. However, these data should not be surprising, given the fact that iniparib is not a potent PARP inhibitor. As such, this phase III study does not exclude a potential role of PARP inhibition in this setting.

Conclusion

The 5th Belgian symposium on the integration of molecular biology advances into oncology clinical practice again succeeded in bringing different Belgian and international oncology experts together to discuss the most recent advances in molecular markers and cancer therapeutics and their relevance to daily clinical practice. Given the high quality of the different lectures, it was not surprising to see that the meeting again obtained the ESMO label.