Second Belgian Symposium on the Integration of Molecular Biology Advances into Oncology Clinical Practice

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Summary

The second Belgian symposium on the integration of molecular biology advances into the oncology clinical practice was held at the Pullman Brussels airport hotel in Diegem from November 21st till November 22nd. This meeting is the result of a cooperation between the Jules Bordet Institute and the Belgian Society of Medical Oncology (BSMO) and was supported by the European Society of Medical Oncology (ESMO). The aim of this symposium was to describe how recent advances in the understanding of the molecular biology of several cancer types are translated into oncology clinical practice. The following report does not intend to give a complete overview of the symposium but will focus on two sessions clearly illustrating the high scientific level of the meeting.

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Does EGFR status predict the clinical outcome and response to anti-EGFR therapy?

Nowadays, more and more targeted clinical agents are entering the market. However, *Dr. Heike Allgayer* pointed out that many important issues still need to be resolved before these agents can convincingly address the correct patient populations. A first important issue that needs to be addressed is *tumour heterogeneity*. Tumours consist of many different cell types each with their own characteristics. This extreme heterogeneity has been illustrated by microarray studies indicating that different regions of the same tumours display a completely different gene-expression profile. Moreover, it is important to realize that the phenotype of tumour cells changes over time. All these issues need to be addressed much more thoroughly when talking about molecularly targeted therapy.

A second important question concerns *target gene expression*. In a recent study by *Scagliotti et al*, the effect of pemetrexed treatment of non-small cell lung carcinoma (NSCLC) was linked to the expression level of thymidylate synthase (TS), the molecular target of pemetrexed. This study demonstrated that patients with squamous NSCLC benefited significantly less from pemetrexed treatment compared with patients having an adenocarcinoma (squamous NSCLC patients had significantly shorter survival rates compared with adenocarcinoma patients). The most logical explanation for this observation is the fact that squamous NSCLC cells express significantly less TS compared with adenocarcinoma cells. This study raises the challenging question whether it is necessary to measure TS levels or whether it is sufficient to rely on tumour histology.

Two other questions concerning target gene ex-

pression are whether target gene expression reliably predicts treatment response and how target gene expression can reliably be defined.

The *FLEX study* is a phase III randomised study assessing the efficacy of cetuximab in combination with cisplatin/vinorelbine (CV) compared with CV alone in patients with advanced NSCLC. In total, 1,125 patients were randomized and the study demonstrated a significant survival benefit for cetuximab plus CV over CV alone in patients with advanced EGFR-positive NSCLC (11.3 months vs 10.1 months, HR= .871, p= .0441). The FLEX study also indicated that cetuximab response seems independent of EGFR mutation status. Data on the predictive value of gene amplification are still conflicting although a recent study by *Hirsh et al* showed that EGFR gene amplification can predict response to cetuximab. However, these data need prospective validation. In order to evaluate the predictive value of EGFR immunohistochemistry, a stringent definition of EGFR positivity (1% of cells positive, 1 positive tumour cell, etc.) needs to be formulated and an optimal immunohistochemistry methodology needs to be defined. However, until now there is no convincing evidence showing that EGFR expression is a reliable marker for response to cetuximab. In a study by *Allgayer et al*, seven NSCLC cell lines with comparable EGFR levels were treated with cetuximab. The response to cetuximab varied significantly amongst these seven cell lines indicating the lack of predictive value of EGFR expression. In this study, a clear correlation was seen between the levels of E-cadherin and u-PAR (an important metastasis related protein) and the response to cetuximab. Cell lines expressing high levels of E-cadherin had a better response to cetuximab and overexpression of E-cadherin in cetuximab resistant cell lines resensitized these cells to cetuximab. On the other hand, cell lines showing a high expression of u-PAR were somewhat resistant to cetuximab and knockdown of u-PAR with siRNAs in these cell lines resensitized these cells to cetuximab. This study needs further validation but clearly indicates that there may be better markers for cetuximab response than EGFR expression alone.

Another important issue to be taken into account when considering cetuximab treatment is the k-RAS status. The *OPUS study* demonstrated that colorectal cancer patients with wildtype k-RAS show a significantly better response to cetuximab compared with colorectal cancer patients harbouring a mutated k-RAS gene. The FLEX data are currently being investigated to evaluate whether k-RAS mutation status influences cetuximab response in NSCLC patients.

A last issue addressed by *Dr Allgayer* concerning response to therapy was the fact that inherited genetics variants (Single Nucleotide Polymorphisms, SNPs) can modulate the response to certain therapies. This was illustrated by a study from *Taron et al* presented at ASCO 2006. This study demonstrated that the presence of a ERCC1-8092 A/A polymorphism in the nucleotide excision repair gene ERCC-1 was correlated with a significantly lower response rate to cisplatin based chemotherapy. Similar studies demonstrating a correlation between the presence of certain SNPs and the response to certain targeted compounds are to be expected in the coming years.

In his lecture, Prof De Grève focussed on the impact on clinical practice of anti-EGFR treatment for lung cancer. An important starting point is that EGFR expression is not a malignant property and most lung cancers inherited their EGFR expression from their normal progenitor bronchio-epithelial cells which can express very high levels of EGFR. Most lung tumours express wild-type EGFR which is irrelevant for the pathogenesis and as a consequence is an irrelevant target for treatment. Currently, the EGFR pathway can be blocked using small molecules and monoclonal antibodies. Several phase III studies demonstrated that the concomitant use of tyrosine kinase inhibitors (TKIs) and chemotherapy has no effect. Studies investigating the use of gefitinb as second line therapy after failure of chemotherapy were negative. On the other hand, the *BR21 study* investigating the use of erlotinib as second line therapy in lung cancer showed a small but significant survival benefit in the sequential arm compared with the chemotherapy arm. However, these studies indicated that certain subgroups of patients benefit more from this sequential approach. Patients with an adenocarcinoma who never smoked have a response rate of 60% to these agents. This indicates that the clinical phenotype is an important predictive biomarker. Moreover, the BR21 study showed that the presence of EGFR gene amplification and EGFR expression are also biomarkers for response to erlotinib treatment. Other studies also demonstrated that the presence of activating mutations in the tyrosine kinase domain of the EGFR result in an increased sensitivity to TKIs.

Currently, the TKI treatment in Belgium is reimbursed as 2nd line treatment for patients with

Table 1. Treatment algorithm for the treatment of RCC			
Regimen	**Setting**	**Therapy**	**Options**
Treatment naive	Good or intermediate risk	Sunitinib Bevacizumab + IFNα	HD IL-2 Cytokines
	Poor risk	Temsirolimus	Sunitinib Sorafenib
≥ 2nd line therapy	Cytokine refractory	Sorafenib	Sunitinib Sorafenib
	VEGF/VEGFR refractory	Everolimus	Sequential TKIs or VEGF inhibitors

advanced NSCLC with positive EGFR immunohistochemistry. Prof De Grève strongly criticized this indiscriminate reimbursement strategy and illustrated this with several studies. First of all, the *INTEREST study* compared 2nd line gefitinib with 2nd line docetaxel in NSCLC patients. This study showed a comparable outcome for both drugs (docetaxel is known to have little activity in NSCLC) in the general patient population. Moreover, the use of gefitinib resulted in an inferior outcome in FISH and EGFR mutation negative patients. Secondly, a study by *Kelly et al* comparing 2nd line maintenance gefitinib therapy with placebo showed an inferior outcome for gefitinib. The results of a similar study using erlotinib (*Saturn trial*) will probably be reported at ASCO 2009. Prof De Grève predicts that a benefit will be seen in FISH positive and EGFR mutant patients, but no benefit or worse will be seen in other patients. In conclusion, genomic analysis is absolutely critical when considering anti-EGFR therapy. On the other hand, immunohistochemistry is futile and even harmful. Anti-EGFR therapy for FISH positive or EGFR mutation positive patients should be reimbursed completely. FISH negative or EGFR mutation negative patients with wild type k-RAS should be enrolled in randomised or observational trials. Should such a patient respond to anti-EGFR therapy, in depth genomic analysis is warranted. FISH positive patients with mutant k-RAS are not eligible for anti-EGFR therapy and should be included in other studies.

Cytokines vs. multitargeted kinase inhibitors in the treatment of kidney cancer

Currently there are 6 approved drugs for the treatment of kidney cancer. As a consequence the question nowadays is: 'which drug to use for which patient population?'. A treatment algorithm was proposed based on the results of several phase III studies (*Table 1*). However, the choice of treatment should also be based on other factors such as histology and prognostic factors. The importance of histology in treatment decision is illustrated by the fact that the response to high dose Interleukin- 2 (IL-2) is much lower in non clear cell RCC compared with clear cell RCC. Recent data show that tumour histology may also be important when using targeted agents. A trend towards a higher clinical benefit (higher survival rates) was observed after temsirolimus treatment for patients having a tumour with a non-clear cell histology compared with patients having a tumour with a clear cell histology. The best known prognostic scoring system for RCC is the MSKCC system which is based on 5 prognostic factors. However, recently *Negrier et al* proposed a much easier scoring system, which is based on two factors: performance status and the number of metastatic sites. Both systems divide RCC patients into three risk groups: low, intermediate and high risk.
For patients in the poor risk group, treatment with cytokines is of no use. At the moment temsirolimus should be the therapy of choice as this is the only drug showing activity in this group of patients. For many years, cytokines were part of the treatment of patients in the intermediate risk group. However, a recent study by *Negrier et al* demonstrated that the use of cytokine based regimens is of little benefit in this group of patients. In a study by *Motzer et al* presented at ASCO 2007, first line sunitinib was compared with IFNα in 750 patients with metastatic RCC (mRCC). The median progression free survival (PFS) was 11 months in the sunitinib arm (95% CI: 10-11) vs. 4 months in the IFNα arm (95% CI: 4-5) clearly indicating a significant survival benefit for sunitinib. In a second trial by *Escudier et al*, comparing the combination of bevacizumab and IFNα with placebo and IFNα as first line treatment in 649 patients with mRCC. Median duration of progression-free survival was significantly longer

in the bevacizumab plus IFNα group than it was in the control group (10.2 months vs 5.4 months; HR= 0.63, 95% CI:0.52-0.75; p= .0001). In conclusion, both sunitinib and bevacizumab plus IFNα can be used in this setting. The decision for either therapy may depend on the slightly better efficacy seen with sunitinib compared with bevacizumab plus IFNα (slightly higher response rate with sunitinib, 37% vs 31%) or on the better safety profile of bevacizumab compared with sunitinib.

The question now arises whether there are any markers predicting the response to TKI. The only possible marker that is currently known was described in a study by *Patel et al* presented at ASCO 2008. In this study, the expression level of HIF 2α was correlated with the response to sunitinib. However, this needs further validation in larger studies. Concerning response prediction to temsirolimus therapy, the only suggested biomarker is pAKT expression. A study from *Cho et al* presented at ASCO 2005 demonstrated that patients expression low levels of pAKT were very likely not to respond to temsirolimus. Again, these data need further validation.

Prof Schöffski took a closer look at the Belgian situation and learned us that the treatment algorithm presented by *Bernard Escudier* cannot be implemented in Belgium. This manly is the consequence of the fact that most of these drugs are not reimbursed (Bevacizumab-IFNα; everolimus, sequential TKI approaches) in Belgium. Cytokines are currently undergoing a 'pharmacoptotic' process (programmed premature death of drugs) in Belgium and nowadays play a minor role in the treatment of RCC.

Interleukin-2 is currently reimbursed after failure of surgery with a maximum of one prognostic factor (ECOG PS 1-3; interval between nephrectomy and failure more than 24 months, metastases in more than 2 organs). Currently, there are no recruiting trials in Belgium involving IL-2, there is no active compassionate use programme and no new trials are planned. *IFNα* is reimbursed for advanced RCC which extends the renal fascia, relapsing after partial resection or being metastatic. Currently, there are two recruiting clinical trials which involve IFNα in Belgium (bevacizumab/IFNα vs. bevacizumab/temsirolimus and bevacizumab/IFNα vs. bevacizumab/everolimus). However, these trials aim at replacing IFNα in the treatment of RCC. At the moment, *sunitinib* is dominating the market and is reimbursed for advanced and/or metastatic RCC (stage IV) for all lines of treatment irrespective of the histotype of the disease. Currently, there are no recruiting trials in Belgium involving sunitinib, there is no active compassionate use programme and no new trials are planned in the Belgian domain. *Sorafenib* is being reimbursed for the treatment of advanced RCC failing IFNα or IL-2 or for cases considered unsuitable for such treatment. Two clinical trials involving sorafenib are currently recruiting patients: the first comparing sorafenib with placebo in the adjuvant setting (*SOURCE trial*) and the other one comparing sorafenib with AMG386 as 1st line treatment. With regard to *temsirolimus,* there is good news as temsirolimus has been approved very recently and the official launch is expected early 2009. Currently, there is one recruiting clinical trial comparing bevacizumab/IFNα with bevacizumab/temsirolimus. *Bevacizumab/IFNα* and *everolimus* are not reimbursed for the treatment of RCC and no reimbursement files have been submitted. There is one recruiting clinical trial in Belgium comparing bevacizumab/IFNα with bevacizumab/everolimus and a study is planned to investigate the activity of everolimus in papillary RCC. An active compassionate use programme for everolimus is open in several academic institutions in Belgium. AMG102, a hepatocellular growth factor receptor antagonist, and AMG386, an angiopoietin inhibitor, are two additional experimental agents available in Belgium. Moreover, various non-disease specific phase I studies are available for patients with RCC.

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