Third Belgian Symposium on the integration of molecular biology advances into oncology clinical practice

27-28 November 2009, Pullman Brussels Airport, Diegem, Belgium

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Key words	Circulating tumor cells, PARP inhibition, predictive markers, prostate cancer, PCA4, PET-CT, PSA

Summary

The third Belgian symposium on the integration of molecular biology advances into oncology clinical practice was held at the Pullman Brussels airport hotel in Diegem from november 27th till November 28th. This meeting is the result of a collaboration 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 molecular biology in several cancer types are translated into everyday clinical practice. This report does not intend to give a complete overview of the symposium but will focus on a few sessions illustrating the high scientific level of the meeting.

(BJMO 2009;Vol 3;6:282-285)

A particular role for PARP inhibition in the treatment of familial breast and ovarian cancer

The poly(ADP-ribose)polymerase (PARP) family consists of 17 isoforms of which PARP-1 is best characterised. PARP is active in most tissues and is involved in single strand DNA repair. It uses NAD as a substrate to form ADP-ribose polymers on histone proteins and on itself. Furthermore, it is involved in several other functions such as epigenic regulation of chromatin structure and gene expression, interaction with transcription factors and interaction with kinetochore proteins. A such, PARP is a clear example of a housekeeping gene and as such one can doubt whether PARP is a decent target for anticancer drugs. However, the rationale for the development of PARP inhibitors for cancer treatment was found in the fact that PARP-1 inhibition *in vitro* was shown to potentiate monomethylating agents (temozolomide), topoisomerase 1 inhibitors (topotecan, irinotecan) and radiation therapy.

In a Phase 0/1 study evaluating the activity of the PARP inhibitor AGO14699 (Pfizer), substantial PARP inhibition (≥90%) was observed in blood mononuclear cells and tumor biopsies without significant toxicity attributable to PARP as a single agent. Furthermore, some clinical activity was observed.[1] When comparing the results of a phase II trial of AGO14699 combined with temozolomide in the treatment of melanoma with the results in the temozolomide alone arm of a phase III trial comparing DTIC with temozolomide, revealed that the AGO14699-temozolomide combination was associated with a higher partial response rate (PRR, 17.4% vs. 10.9%), progression-free-survival (PFS, 3.5 months vs. 1.9 months) and overal survival (OS, 9.9 months vs. 7.7 months).[2]

Most interest for PARP inhibition in the treatment of cancer was generated by the results of two studies showing that mutations in BRCA1 or BRCA2 lead to an extreme hypersensitivity to PARP inhibition.[3,4] Carriers of BRCA1 and

BRCA2 mutations are predisposed to breast, ovarian and a number of other cancers. BRCA1 and BRCA2 are involved in homologous recombination DNA repair, which is an error-free DNA repair mechanism. In mutation carriers experiencing damage to the second, functional BRCA allele, this error-free DNA repair mechanism is eradicated leaving error-prone DNA repair as the only option, which results in a higher cancer incidence. When inhibiting PARP, single strand DNA breaks persist which ultimately leads to a double strand DNA break. In normal cells, this double strand break is rapidly corrected by homologous recombination, which is probably the explanation for the low toxicity of PARP inhibition seen in normal cells. In BRCA deficient cells however, this homologous recombination process is compromised which ultimately leads to cell death, a process referred to as synthetic lethality.

At the 2009 ASCO meeting, the results of two phase II studies evaluating olaparib in patients with BRCA mutant ovarian or breast cancer were presented. Both studies demonstrated an overal response rate (ORR) of approximately 50% and even more patients showed some clinical benefit of the olaparib treament.[5,6] Interestingly, in the ovarian cancer study, platinum resistant patients had a higher response rate compared with platinum sensitive patients (38% vs. 14%).[6]

In summary, PARP inhibition provides a specific therapy for tumors arising in patients with BRCA1 or BRCA2 mutations. PARP inhibition has also been shown to potentiate chemotherapy agents, particularly in tumors with low homologous recombination repair capabilities.[7] However, resistance to PARP inhibitors due to reactivating BRCA mutations and genotoxicity remain important issues when using PARP inhibitors as single agents. When combining PARP inhibitors with chemotherapy, bone marrow toxicity compromising dosing may also form an obstacle.

An important question now is whether PARP inhibitors should undergo clinical trials for chemoprevention in known BRCA mutation carriers. This could potentially prevent all BRCA related cancers and would avoid invasive surgery. However, PARP inhibition is potentially genotoxic and other long term organ toxicities are yet unknown. Nevertheless, the fact that the high cancer risk seen in mutation carriers could be reduced significantly may justify a small excess risk of other cancers. To be investigated.

Predictive markers of response to therapy in solid tumors: are they ready for clinical use?

Circulating tumors cells

Circulating tumor cells (CTCs) are occult or micrometastatic cells which can be detected in the peripheral blood of cancer patients. Currently, several platforms for CTC detection exist (CellSearch, Maintrac, RT-PCR) and CTCs have been characterised at DNA, RNA and protein level.

The presence of more than 5 CTCs per ml blood of patients with metastatic breast cancer was shown to be associated with a significantly worse OS compared with patients having 5 CTCs or less per ml blood.[8] Standard imaging is able to differentiate metastatic BC into patients with stable disease (SD) or a partial response (PR) and patients having progressive disease (PD). However, using CTCs, these two subgroups can both be subdivided into a group with more than 5 CTCs/ml blood and a group having 5 or less CTCs/ml blood. Patients in these subgroups display a significantly different OS (patients with SD and PR with more than 5 CTCs vs. 5 or less CTCs: 19.9 months vs. 26.9 months; p=0.04 / patients with PD with more than 5 CTCs vs. 5 or less CTCs: 6.4 months vs. 15.3 months; p< 0.01).[9] Furthermore CTCs were shown to be more potent in differentiating good and bad responders (more than 5 CTCs vs. 5 or less CTCs: 10.9 months vs. 26.9 months, p= 0.0041) than CA15.3 determination (14.2 months vs. 19.5 months; p=0.21).[10] A similar superiority of CTC determination in differentiating responders from non-responders was also demonstrated in castration resistant prostate cancer and colorectal cancer.[11,12]

In conclusion, CTCs provide additional information beyond standard imaging in solid tumors and were shown to be more accurate than serum markers in several small studies. Confirmation in larger trials is however warranted. When addressing the question what the current role of CTCs in clinical practice can be, one must first establish whether CTCs have an added value to the wide range of established prognostic markers already available (tumor size, lymph node involvement, tumor differentiation, Ki67 expression, etc.). Concerning metastatic cancer, it is clear that it is more important to develop more efficient treatment options, not to know earlier that a patient has a bad prognosis. Furthermore, the economic impact of CTC evaluation should be taken into account. In conclusion, CTCs are not yet ready for widespread use in everyday clinical practice.

PET-CT

In contrast to the standardised guidelines integrating the use of PET and CT in melanoma, the evidence in solid tumors is far less clear. In contrast to melanoma, solid tumors are rarely completely cured with chemotherapy and as a result, residual FDG uptake remains even in good responders. Therefore, quantification and standardisation of PET data are needed in solid tumors and uptake thresholds need to be determined. Furthermore, therapy is much more complicated in solid tumors (multimodality treatment) making the timing of the PET scan important. Underestimation of the response due to inflammation and the fact that minimal residual disease cannot be detected further complicates PET in solid tumors. As a result, no standardised PET or PET-CT response criteria for solid tumors are available at the moment.

In a study by *Rouseau et al*, 64 breast cancer patients were treated with 6 cycles of chemotherapy after which the pathological response was evaluated. Afterwards, the correlation between PET and pathological response was determined.[13] First of all, it was clear that even non-responders showed a reduction in FDG uptake. However, the main result was that a better pathological response was correlated with a higher decrease in FDG uptake.[13] Another important observation was that the cut-off of uptake depends on the time of the PET scan. If the PET scan is performed early (after 1 or 2 cycles of chemotherapy) the cut off can be put at a 30% decrease in uptake, whereas the cut-off should be put at 50% to 60% when the PET scan is performed later (after 5 or 6 cycles).[13] Furthermore, an EORTC meta-analysis of studies correlating PET with pathological response in the neo-adjuvant setting containg more than 400 patients in total, showed that for all tumor types, a 10% decrease in SUV is correlated with a 17% increase in pathological response. In conclusion, there is a good correlation between FDG uptake and pathological response.

The available data on the correlation of PET and outcome are however conflicting. This is clearly illustrated by two studies on NSCLC. In a *first* study by *Hoekstra et al*, NSCLC patients were treated with three cycles of cisplatin based chemotherapy after which outcome was correlated with FDG uptake after 1 and 3 chemotherapy cycles. Both after 1 and 3 cycles, a clear correlation between FDG uptake and outcome was observed (after 1 cycle, threshold at 30% reduction: p= 0.007; after 3 cycles, threshold at 60% reduction: p= 0.003).[14] Furthermore, this study demonstrated that measuring FDG uptake added information to RECIST evaluation: in bad CT responders, having a dismal outcome, SUV was of little use. However, good responders on CT with an SUV ≤3 had a significantly better outcome than patients with an SUV ≥3. Positive results were also obtained in a study by *Decoster et al*.[15]

A *second* study, combining two retrospective trials of neoadjuvant CT prior to surgery in NSCLC, on the other hand showed conflicting results. In this study, PET and chemotherapy were determined before the start of chemotherapy and before surgery. FDG-PET did not correlate with outcome at all, whereas CT was correlated with outcome in stage IIIb NSCLC patients.[16] The most likely explanation for the fact that, no correlation was shown in this study is the fact that, in contrast to the first study, PET was not standardised.

In conclusion, until now, no standardised guidelines integrating the use of PET and CT in solid tumors existed. However, the EANM has recently developed procedure guidelines for tumor PET imaging.[17] These guidelines can be consulted at the EANM website. Furthermore, the FDG-PET working group is currently collaborating with the RECIST committee in order to expand the RECIST database with FDG data.

Should PCA3 replace PSA in prostate cancer?

PSA screening is very widespread and in the recently published ERSPC study it was shown to be associated with a 20% reduction in prostate cancer mortality.[18] However, looking at the absolute numbers in this study is quite confronting: a total of 1,410 men would need to be offered screening and an additional 48 would need to be treated to prevent 1 prostate cancer death during a 10 year period.[18]

One of the big problems with PSA as a screening tool is that on average 4 biopsies are required to find one prostate cancer patient.[18] Furthermore, a negative initial biopsy will frequently result in one or more repeat biospies as 10% to 35% of negative initial biopsies harbour prostate cancer on repeat biopsy and 11% of men with a negative initial biopsy develop prostate cancer within 7 years. A third problem with systematic PSA screening is that many 'indolent' prostate cancers are diagnosed and as a result overtreated. Therefore, the challenges for new prostate cancer markers are to reduce the proportion of first and repeat biopies and help reduce the overtreatment by improving the identification of in-

dolent prostate cancer.

The prostate cancer gene 3 (PCA3) is only expressed in prostate cells. Furthermore it is very prostate cancer cell specific as it is expressed 66 times more in prostate cancer cells compared with normal prostate cells. The PCA3 score is determined using a double PCR assay quantifying the amount of PCA3 and PSA mRNA and subsequently dividing both values. This PCA3 score yields a much better correlation with the prostate biopsy than PCA3 alone.[19] The higher the PCA3 score, the greater the probability of a positive repeat biopsy. As such, the use of PCA3 can spare 3 biopsies every 4 patients. Furthermore, the PCA3 score is correlated with tumor volume, Gleason score and low volume/low grade cancer versus significant cancer.[20]

The PCA3 test requires the collection of the first 20 to 30ml of voided urine after a digital rectal examination (DRE). Without DRE the test provides valid results in approximately 80% of the cases, but DRE increases this yield to more than 98%. The test takes 4 to 10 days costs 264€. In conclusion, PCA3 has the potential to become an additional specific marker for early prostate cancer.

References

1. Plummer et al. Clin cancer Res 2008;14(23):7917-23.
2. Plummer et al. J Clin Oncol 2006;24:456S.
3. Bryant et al. Nature 2005:434:913-7.
4. Farmer et al. Nature 2005:434:917-21.
5. Tult et al. J Clin Oncol 2009;27:15s.
6. Audeh et al. J Clin Oncol 2009;27:Abstract 5500.
7. O'Shaughnessy et al. J Clin oncol 2009;27:Abstract 3.
8. Cristofanelli et al. New Enj J Med 2004;351(8):781-91.
9. Budd et al. Clin Cancer Res 2006;12(21):6403-9.
10. Stopeck et al. Presented at ASCO 2005.
11. de Bono et al. Clin Cancer Res 2008;14(19):6302-9.
12. Cohen et al. J Clin oncol 2008;26(19):6302-21.
13. Rouseau et al. J Clin Oncol 2006;24(34):5306-72.
14. Hoekstra et al. J Clin Oncol 2005;23:8362-70.
15. Tanvetyanon et al. J Clin Oncol 2008;26:4610-6.
16. Decoster et al. Lung Cancer 2008;62(1):55-61.
17. Boellaard et al. Eur J Nucl Med Mol Imaging 2009; Epub ahead of print.
18. Schröder et al. New Engl J Med 2009;360:1320-8.
19. Groskopf et al. Clin Chem 2006;52:1089-95.
20. Nakanishi et al. J Urol 2008;179:1804-9.

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Conflicts of interest: the author has nothing to disclose and indicates no potential conflicts of interest