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Genetic aberrations as determinants of response to chemotherapy

R. Rosell[1], B. Massuti[2], D. Isla[3], C. Camps[4], T. Moran[5], E. Carcereny[5], S. Viteri[6], M.A. Molina[6], M. Taron[5], A.F. Cardona[5]. *[1]Catalan Institute of Oncology, Hospital Germans Trias i Pujol Medical Oncology Service, Badalona (Barcelona), Spain; [2]Hospital General de Alicante, Medical Oncology Service, Alicante, Spain; [3]Hospital Lozano Blesa, Medical Oncology Service, Zaragoza, Spain; [4]Hospital General de Valencia, Medical Oncology Service, Valencia, Spain; [5]Hospital Germans Trias i Pujol, Medical Oncology Service, Badalona, Spain; [6]Dexeus University Insitute, Pangaea Biotech, Barcelona, Spain*

Background: The vast majority of clinical trials combining chemotherapy plus targeted agents are based on empirical criteria and in general yield short-lived responses and no substantial benefit in prolonging survival in a meaningful way for the patient. Moreover, some chemotherapy drugs may well be antagonistic when combined with others and even with targeted drugs. Therefore, the first endeavor should focus on the correct choice of chemotherapy drugs and combinations. Experimental evidence suggests that BRCA1 overexpression enhances sensitivity to docetaxel and resistance to cisplatin. RAP80 and Abraxas are interacting proteins that form complexes with BRCA1 and could modulate the effect of BRCA1. In order to further examine the effect of EGFR mutations and BRCA1 mRNA levels on outcome in advanced NSCLC, we performed a prospective non-randomized phase II clinical trial, testing the hypothesis that customized therapy would confer improved outcome over non-customized therapy.
Material and Methods: We treated 123 metastatic non-squamous cell lung carcinoma patients using a customized approach. Patients with EGFR mutations received erlotinib, and those without EGFR mutations received chemotherapy with or without cisplatin based on their BRCA1 mRNA levels: low, cisplatin plus gemcitabine; intermediate, cisplatin plus docetaxel; high, docetaxel alone. An exploratory analysis examined RAP80 and Abraxas expression.
Results: Median survival exceeded 28 months for 12 patients with EGFR mutations, and was 11 months for 38 patients with low BRCA1, 9 months for 40 patients with intermediate BRCA1, and 11 months for 33 patients with high BRCA1. Two-year survival was 73.3%, 41.2%, 15.6% and 0%, respectively. Median survival was influenced by RAP80 expression in the three BRCA1 groups. For example, for patients with both low BRCA1 and low RAP80, median survival exceeded 26 months. RAP80 was a significant factor for survival in patients treated according to BRCA1 levels (hazard ratio, 1.3 [95% CI, 1−1.7]; P = 0.05).
Conclusions: Chemotherapy customized according to BRCA1 expression levels can optimize survival, and RAP80 could play a crucial modulating effect on this model of customized chemotherapy.

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Prostate cancer

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Advances in molecular understanding of prostate cancer

J.A. Schalken[1]. *[1]Radboud University Nijmegen Medical Center, Urology Research Laboratory, Nijmegen, The Netherlands*

Our understanding of the molecular basis of prostate cancer increased significantly over the past decade. As early as 1990 the first papers on specific genetic changes in prostate cancer appeared. Subsequent molecular genetic studies confirmed the frequent involvement of genetic changes on chromosome 13q, 8p, 16 q and others. Subsequently several specific genes were identified that were mutated, deleted or amplified, and genes with a know etiological role in carcinogenesis gained particular interest, such as oncogenes and tumor suppressor genes. The p53 gene was mutated in a relatively small fraction of prostate tumors. Another tumor suppressor gene, however, appeared to be more commonly deleted and/or mutated in prostate cancer, PTEN. More recently, it was shown that in the majority of prostate cancers the erg gene is activated by fusion an androgen regulated gene, TMPRSS2. The biological relevance of both changes was supported by germ line activation (erg) or inactivation (PTEN), suggesting that these genes are critically associated with prostate cancer development. The most common genetic change in patients that aren't responsive to the currently registered endocrine therapies (CRPC) is amplification of the androgen receptor, suggesting an important role of the AR in progression to CRPC. In fact, these insights provide targets for improved diagnosis, prognosis and therapy of prostate cancer. The molecular adaptation that leads to the intracrine production of androgens provided the rationale basis for next generation endocrine therapies.
Through the emergence of high throughput 'omics' platforms the discovery rate of molecular targets/pathways went up significantly and apart from the 'classical' genes, recurrent epigenomic changes and changes in non coding – and microRNAs are identified. Collectively, these findings should be the basis of identifying the specific molecular fingerprint of individual cancers for which molecular profile specific, rather than disease specific, therapies should be indicated.

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Prostate cancer: the bone paradigm . . .

B. Tombal[1]. *[1]Cliniques Universitaires St Luc/UCL, Department of Urology, Brussels, Belgium*

Prostate cancer (PCa) is the most common cancer and the third leading cause of cancer death among men in developed countries. Prostate cancer cells spreading out of the prostate are characterized by an exquisite tropism to bone. In men progressing under hormonal therapy, bone is indeed the primary metastatic site in 80% of the patients. Later on, in end-stage disease, 90% of the patients or more will have bone metastases. Bone metastases can alter the physiological bone remodeling processes and invade the surrounding structures. This results in a morbid cortege of complications such as pathological fractures, pain, spinal chord compression and anemia, best known as skeletal-related event (SRE). In addition, bone metastases and SRE occurs nowadays mostly in an osteopenic environment resulting from the chronic used of androgen deprivation therapy (ADT) as a mainstay treatment of advanced and metastatic disease. Testosterone, indeed, is critical for the normal bone physiology, and ADT causes rapid and profound bone loss, a process named CTIBL, or Cancer Treatment Induced Bone-Loss.
This unique interaction between a selective osteotropism of prostate cancer and a profound alteration of the bone composition creates an interesting "bone paradigm" that we will need to tackle.
Several issues will be addressed:

- There is a crucial need for developing imaging technologies to correctly address drug efficacy at the level of bone metastases. TC-99m bone scan is not imaging the cancer itself but the bone remodeling that goes with it and therefore is not adequate to measure tumor response in bone. New technologies based on MRI and/or PET technologies are currently developed.
- The intense basic research activity on the pathophysiology of bone disease has increased our level of understanding on the "vicious circle" of bone metastases and help indentifying the key molecules that are driving the development of bone metastases such as PTHrP, RANK/RANK-L/OPG, and ET-1/ET-A pathways.
- New drugs are on their way through Phase III trials, giving us the ability to specifically interfere with the progression and maybe the development of bone metastases.

55 INVITED

Drug resistance in metastatic prostate cancer

I. Tannock[1]. *[1]Princess Margaret Hospital, Daniel E. Bergsagel Professor of Medical Oncology, Toronto ON, Canada*

Most men who develop metastatic prostate cancer respond initially to androgen deprivation therapy (ADT) and the preferred initial treatment is with a long-acting GnRH agonist, with a peripheral anti-androgen given transiently to prevent flare. The duration of response is variable with a median of ~2 years. About one third of patients then respond to addition of a peripheral anti-androgen such as bicalutamide, and of those who respond a smaller proportion may respond subsequently to its withdrawal. Previously most men were then regarded as hormone-resistant, although some would respond successively to further hormonal manoeuvres such as estrogens, dexamethasone or ketoconazole plus hydrocortisone. The term castration-resistant prostate cancer (CRPC) is more appropriately used to describe the disease at this stage. Studies have shown that androgen-dependent pathways remain active within CRPC, despite very low levels of circulating androgens, and are often associated with intra-tumour androgens and/or increased androgen receptor expression. This has led to new approaches to overcome or delay resistance to ADT that include use of intermittent treatment, and new drugs such as abiraterone acetate, a potent and specific inhibitor of CYP17, an enzyme that catalyses two steps in androgen synthesis, and MDV 3100, a more potent and structurally different inhibitor of the androgen receptor than bicalutamide. The status of these strategies will be reviewed. However, there is also evidence for a population of tumour-initiating (stem) cells within prostate cancer that do not express the androgen receptor, perhaps setting limits on efficacy of all forms of ADT.
For men who are no longer responding to ADT, chemotherapy with docetaxel has been shown to provide a modest improvement in survival