Perspectives of Anti-Cancer Targeted Therapies

Rome, May 18, 2012

Director
Giampaolo Tortora M. D.
Oncologia Medica
Azienda Ospedaliera Universitaria
Integrata di Verona
Verona

Program

Friday, May 18

8.30 Registration

9.00 - 11.00
Introduction
Giampaolo Tortora, Verona

Moderator: G. Tortora

EGFR targeting/ Lung cancer
Floriana Morgillo, Naples

HER-2 Targeting/ Breast
Sabino De Placido, Naples

K-ras/ Colon
Alberto Bardelli, Turin

11.00-11.30
Coffee Break

11.30-13.00

MAPK targeting and MEK inhibitors/ Pancreas
Michele Milella, Rome

New and existing targets of treatment in advanced prostate and renal neoplasia / Kidney and prostate
Sergio Bracarda, Arezzo

B-raf ecc/ Melanoma
Paolo Ascierto, Naples

13.00 - 14.00
Lunch

14.00-16.00
Moderator: S. Iacobelli

Genome sequencing and new strategies for future targeted therapies
Aldo Scarpa, Verona

New rules for early phase studies
Silvia Marsoni, Candiolo (Turin) – (Sostituto: Davide Melisi, Verona)

New strategies for trial design and biomarker discovery
Emilio Bria, Verona

16.00- 16.30
Discussion & Conclusions

Descrizione

The rapidly changing scenario of diagnosis and therapy of cancer, due to the implementation of highly refined molecular diagnostics and new generation sequencing techniques and to the coming of a new wave of targeted agents, requires a timely, precise and expert update.

Aim of the course "Perspectives of Anti-Cancer Targeted Therapies" to be held in Rome, May 18, 2012 is to provide state of the art knowledge on all these topics. They will include: the most relevant signalling pathways and their role in cancer pathogenesis and in the onset of resistance to therapy, current and novel molecular diagnostic techniques, preclinical reliable mouse-human models to study significant molecular alterations and relative treatments, new therapeutic options in relevant types of cancer, challenges and new regulatory issues in early phase studies with new targeted agents.

The invited lecturers of the course are internationally acknowledged experts in all the above fields.

Abstract significativi

Alberto Bardelli

I pazienti affetti da carcinoma del colon-retto metastatico (mCRC) hanno un tasso di sopravvivenza a 5 anni inferiore al 5%. Nuovi farmaci diretti contro il recettore per il fattore di crescita epidermico (EGFR) sono di recente stati approvati per uso clinico, come gli anticorpi monoclonali (mAb) cettiximab e panitumumab. Tali agenti, spesso in combinazione con farmaci chemioterapici di ultima generazione, sono in grado di indurre la regressione del tumore e prolungare la sopravvivenza di pazienti affetti da neoplasie maligne, dimostrando l'importante ruolo delle vie di trasduzione dipendenti dall'EGFR nella crescita tumorale. Da recenti studi è emerso che solo il 10-20% di questi pazienti ha tratto un beneficio clinico dal trattamento con anticorpi anti-EGFR. Un grande interesse si è quindi sviluppato attorno a studi volti a comprendere i meccanismi molecolari responsabili della sensibilità e resistenza a questi farmaci. Il nostro gruppo di ricerca ha contribuito alla scoperta che mutazioni somatiche in KRAS, presenti nel 35-45% dei pazienti mCRC, costituiscono un importante predittore negativo per i pazienti trattati con cetuximab o panitumumab (Benvenuti S 2007). Inoltre, tra i tumori con KRAS wild type, mutazioni in BRAF o PIK3CA o perdita di espressione di PTEN, possono anche predire resistenza al trattamento con anticorpi anti-EGFR (Di Nicolantonio F 2008; Sartore-Bianchi A 2009; Bardelli 2010; De Roock W 2011). Molto recentemente abbiamo inoltre dimostrato come la presenza della amplificazione del gene HER2 sia correlata alla mancata risposta alle terapie anti EGFR nei carcinomi colorettali. In conclusione lo sviluppo clinico degli anticorpi monoclonali anti-EGFR cetuximab e panitumumab costituisce il primo esempio di trattamento individualizzato del cancro colonrettale metastatico.

Referenze

- Andrea Bertotti, G.M., Francesco Galimi, Francesco Sassi, Davide Torti, et al. A molecularly annotated platform of patient-derived xenografts (‘xenopatients') identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. Cancer Discovery (2011).
- Bardelli and Siena Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. J Clin Oncol 2011
- Benvenuti, S. et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. Cancer Res (2007).
- De Roock, W. et al. Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. JAMA (2010).

- Di Nicolantonio, F. et al. Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol (2008).
- Sartore-Bianchi, A. et al. PIK3CA mutations in colorectal cancer are associated with clinical resistance to EGFR-targeted monoclonal antibodies. Cancer Res 69, 1851-7 (2009).

Ascierto

B-RAF and melanoma.

Paolo A. Ascierto – Vice-Director of Medical Oncology and innovative Therapy Unit

The development of targeted therapies has provided new options for the management of patients with advanced solid tumors. In patients with metastatic melanoma several new strategies have been evaluating that was considered the main promising treatment, has shown limited success. Actually there are different approaches to improve the efficacy of melanoma therapies. There has been particular interest in agents that target different pathways involved in tumor growth, survival and angiogenesis.

Alpha

In melanoma, the constitutive activation of protein kinase signal stimulated by mitogens (ERK/MAPK: mitogen activated protein kinases) is involved in proliferation, invasion and resistance to apoptosis. In 50% of melanomas, the activating mutation affects the kinase BRAF, in 20% of cases are present NRAS mutations, which are mutually exclusive with those of BRAF. The most frequent mutation of BRAF, detectable in 90% of cases mutated in V600, is the V600E, which involves the substitution of valine with glutamic acid at codon 600.

The V600K mutation has a frequency of about 6-8%, while other mutations, such as V600R and V600D, are less frequent.

Mutations of genes NRAS and BRAF have been identified with high frequency both in snow and in cutaneous melanomas. Therefore they represent early events in the development of melanocytic tumors.

Inhibition of mutated BRAF, using the specific inhibitor vemurafenib, has shown antitumor effects in melanoma cell lines that have the BRAF V600E mutation and no effect on cell lines not mutated.

Then the activity of the inhibitor has been confirmed in clinical development both in phase I, in which a MTD corresponding to 960 mg orally twice / day is established, both in the phase II, with an overall response rate of 53% and a duration median response of 6.7 months.

Alpha

Phase III trial BRIM-3, conducted on 675 patients carrying the BRAF V600E mutation, showed a relative reduction in risk of death of 38% and a reduced in risk of progression disease of 68% in patients treated with vemurafenib compared to patients treated with only dacarbazine.
The median increase in PFS was 4 months (5.3 with vemurafenib vs 1.6 with dacarbazine) and 3 months in OS (13.2 with vemurafenib 9.9 vs with dacarbazine).
The most frequent adverse events were largely related to the skin, characterized by photosensitivity (12%), rash (18%), keratoacanthoma (8%), and minimally invasive squamous cell carcinomas (12%); arthralgias and asthenia were reported in 21% and in 13% of cases respectively.
The analysis by sequencing revealed that some patients enrolled in the study had mutations other than V600E or V600K and V600D.
Based on these results , in August 2011 the Vemurafenib has been approved by FDA for the treatment of metastatic melanoma with a mutation B-V600 BRAF; In February 2012 the drug was also approved by the EMEA.
The future of melanoma treatment is going toward the combination of immunotherapy, biological therapy and chemotherapy.

S. Bracarda

Prostate cancer is one of the leading causes of death for cancer in the male. Treatment of choice for advanced or inoperable disease is represented by androgen ablation (achieved through surgical or medical castration, respectively orchidectomy or luteinizing-hormone releasing-hormone analogues), active in about 80-85% of the patients.
Unfortunately, despite this initial high tumour response, eventually all patients progress to an androgen-independent status within 12-18 months. A possible survival advantage could be achieved, in some cases, by adding a peripheral non-steroidal anti-androgen to medical or surgical castration (maximum androgen blockade or MAB), from the beginning, as partially showed in published meta-analysis (Prostate Cancer Trialist Group, The Lancet, 2000, and others). Other cases could be evaluated for second-line hormone-therapy options, by adding antiandrogens, in pts submitted to LH-RH analogues alone, or removing the same drug in patients submitted to MAB (with anti-androgen withdrawal syndrome evaluation).
The overall response rate with secondary hormonal therapy ranged between 20% and 80%, nevertheless the response is usually short-lived, ranging between 2 and 6 months, and not related with an improved survival.
As a conclusion all eligible Castration-Resistant Prostate Cancer (CRPC) cases should be subsequently evaluated for possible docetaxel-based chemotherapy options, according to the two

recently published randomized studies demonstrating, for the first time an increased overall survival (TAX-327, SWOG 99-16). Unfortunately, however, these improvement in survival do not yet indicate an increased possibility of cure for advanced disease and prognosis of patients with CRPC remain extremely poor, suggesting an increased need of testing novel approaches and novel agents in this setting, alone or combined with classical chemotherapy drugs to increase the possibility of control of what is recognized as an heterogeneous disease.
Principal targets of interest include, novel classical chemotherapy agents, the Androgen Receptor Pathway, neo-angiogenic and apoptosis (programmed cell death) pathways, all frequently involved in CRPC.

M. Milella

Cancer is increasingly recognized as a signaling disease; indeed, selective interference with signaling pathways to which cancer cells become addicted has proven clinically successful in tumors characterized by specific driver genetic lesions. However, in PDAC many molecularly targeted agents hitting EGFR, matrix metallo-proteases, farnesyl transferase, or vascular endothelial growth factor have failed to improve outcomes. Recent developments in the molecular epidemiology of pancreatic cancer and an ever evolving understanding of the molecular mechanisms underlying pancreatic cancer initiation and progression raise renewed hope to find novel, relevant therapeutic targets that could be pursued in the clinical setting. In particular, inhibition of the MEK/ERK module downstream of RAS (which is mutated in up to 90% of PDAC cases) appears of particularly appealing, given the current availability of many, highly potent MEK inhibitors in clinical development. The RAS/RAF/MEK/ERK (MAPK) is a major signaling pathway involved in transcription, protein synthesis, regulation of cell proliferation and survival and angiogenesis and is frequently altered in tumors, where it promotes resistance to apoptosis and fosters tumor progression. However, MEK blockade may induce compensatory signaling through both upstream pathway elements (RAF) and parallel pathways (PI3K), thereby potentially inducing its own resistance factors and explaining the highly variable functional (and clinical) responses to MEK inhibition in different cellular contexts. This may stem from the disruption of ERK-activated intra-pathway negative feedback loops, involving upstream acting receptor tyrosine kinases, adaptor proteins, and MAPK-specific phosphatases, and from the activation of compensatory signaling through the PI3K pathway. Paradoxical and/or compensatory activation of the MEK/ERK module may also be elicited by either upstream inhibition of the MAPK pathway (e.g., by selective BRAF kinase inhibition) or by interference with PI3K pathway activity (e.g., by mTOR inhibition), making response to specific interference with a single signaling component somewhat unpredictable and sometimes

‘undesired’ from a therapeutic perspective. Based on this rationale, combined inhibition of either multiple steps along the MAPK cascade or both the MAPK and PI3K pathways appears particularly appealing from a clinical perspective; however, mounting evidence indicates that the functional outcome of such combination strategies is crucially dependent on the specific set of feedback/crosstalk signaling mechanisms that operate in individual genetic and cellular contexts and that combinations of targeted agents may exert frankly antagonistic effects if applied inappropriately, making the in depth preclinical study of the molecular mechanisms of action of MEK/MAPK pathway inhibitors particularly relevant in PDAC where therapeutic failure has so far been the rule.

Aldo Scarpa
Dept of Pathology and Diagnostics and ARC-NET Research Centre at University of Verona, Europe

The genetic basis of cancer, discovered using a candidate gene approach, was based on the common occurrence of alterations in few “initiator genes” sometimes specific for the organ of origin such as KRAS2 in pancreas, APC in colorectal, VHL in Kidney. The involvement of “progressor” genes such as TP53 and others being common to diverse malignancies. We knoe now that we find a variety of genes inactivated in diverse cancer types in less than 5% of cases including TGFBR1, TGFBR2 and many others. The development of high throughput sequencing methods have paved the way for identification of most coding genetic alterations in cancer. This permits the several types of distinct somatic mutations (insertions, deletions, translocations, gain/amplifications) that occur in the DNA sequence of the cancer genome cell to be identified. Large-scale genome analysis showed that cancer evolves by accumulating driver mutations in as many as 20-100 cancer genes. Difficulties in developing cancer biomarkers is also due to a failure in addressing issues of cancer heterogeneity. In this respect, a recent reappraisal of pooled expression profiling data has shown the existence of at least two distinct molecular subtypes of pancreatic cancer: classical amd quasimesenchymal. This implies that markers useful in subgroups of patients with a specific molecular cancer subtype may not show efficacy in larger disparate molecular phenotype groups. Preliminary data on cancer genome from the International Cancer Genome Corsortium (ICGC) suggest that distinct molecular phenotypes are numerous and in most cancer types each phenotype accounts for 10% or less. However, the specific genomic alterations found at deep sequencing of a great number of cases may permit a molecular subclassification of the disease that opens the way to personalized therapy and follow-up as well as to the discovery of a classifiers permitting the development of early diagnostic markers and novel specific targets.