



Report

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Introduction

The 7th International Symposium on Targeted Anticancer Therapies was attended by 429 participants from all over the world. This 3-day symposium offered a broad overview of cancer cell molecular biology and its translation into targeted therapy. The symposium was organized by the NDDO Education Foundation in partnership with the European Society of Medical Oncology (ESMO) and the United States National Cancer Institute (NCI).

Invited speakers and poster presenters opened an immense Pandora's box of potential targets, some of which are discussed here in detail.



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Targeting receptor tyrosine kinases and intracellular tyrosine kinase inhibitors

Insulin-like growth factors

In a great number of epidemiologic and preclinical studies hyperinsulinism (due to obesity and/or a high carbohydrate diet) has been linked to a higher cancer risk and a worse cancer-related prognosis. In the late 1980s, insulin-like growth factor-1 receptor (IGF-1R) expression was found in breast and large bowel tumors. IGF-1R is a receptor tyrosine kinase, which occurs as a dimer in the presence of ligand. Ligand binding leads to activation of the PI-3K/AKT/mTOR and Grb2/Sos/Ras/MAPK signaling pathways, which are important for cell proliferation and cell survival.

Two treatment modes have been developed: IGF-1R can be blocked specifically by a monoclonal antibody or it can be inhibited by small molecules, which affect its kinase activity.

- The first approach results in down-regulation/internalization of IGF-1R. At present, eight IGF-1R monoclonal antibodies have entered clinical trials, either as monotherapy or in combination with other cytotoxic agents. The most frequently encountered adverse effect is hyperglycemia, which is probably due to blockade of IGF-1 action and increased growth hormone production. The safety of prolonged therapy needs to be established.
- Due to the high similarity between IGF-1R and the insulin receptor (IR), it is difficult to develop small inhibiting molecules with clinical benefit, but without serious toxicity. OSI-906 appears to be 4-20-fold more specific for IGF-1R over IR. The preclinical data have been convincing enough to initiate phase 1 clinical studies with OSI-906 monotherapy or its combination with erlotinib.

FLT3 tyrosine kinase

Mutations within the receptor tyrosine kinase FLT3 are found in up to 35% of patients with acute myeloblastic leukemia (AML). Most of the mutations involve insertions of variable lengths of sequence in frame in the juxtamembrane domain of the receptor. Murine studies have shown that such mutations play a key role in the development of myeloproliferative disease. Several FLT3 inhibitors have been tested (phase 1 and 2) in patients with AML. In most patients a fast and almost complete response is seen in the peripheral blood, whereas the myeloblasts in organs and bone marrow remain almost unaffected. For this reason the clinical benefit is usually short. This differential response may be explained by bypass mutations, stromal interaction and primary resistance of cancer stem cells (CSC's).

Combined treatment with tyrosine kinase inhibitors and other targeted agents

The PACCE study and the CAIRO-2 study have shown that adding panitumumab or cetuximab to oxaliplatin or irinotecan-based treatment with bevacizumab for advanced colorectal cancer leads to worse survival. This finding could not be explained by a difference in the number or severity of adverse events. A negative interaction between the two targeted agents is being considered, but an explanatory mechanism has not been elucidated.

Combined treatment with tyrosine kinase inhibitors and immunotherapy

Combined treatment with a tyrosine kinase inhibitor and immunotherapy could be especially relevant for patients with advanced renal cancer. Interferon- α as first-line monotherapy has been replaced by sentinel (clear cell renal cancer, Motzer stage 0–3) and mTOR (mammalian target of rapamycin) inhibitors (other cancer histology, Motzer stage 4–5).

Several studies have been performed to evaluate the additive value of immunotherapy. In two phase 3 trials the combination of bevacizumab and interferon- α led to better survival in comparison with interferon- α alone, but the possibility exists that the difference is entirely attributable to bevacizumab. In another phase 3 trial the additive value of interferon- α in patients treated with temsirolimus was evaluated. Addition of interferon- α did not lead to better survival. Two randomized phase 2 trials have been performed with sorafenib and interferon- α , but the sample size was too small to allow conclusions regarding a possible treatment benefit of the combination.

A second candidate for combination treatment is interleukin-2 (IL-2). The highest response rate (including very long-lived complete responses) can be achieved by high dose intravenous treatment. Two combination studies (sorafenib/subcutaneous IL-2 and sorafenib/high dose IL-2) are ongoing.

Combined treatment with tyrosine kinase inhibitors and chemotherapy

Tyrosine kinase inhibitors are usually multitargeted, for instance vascular endothelial growth factor receptor-2 (VEGFR2), platelet-derived growth factor receptor (PDGFR), kit and FLT3 are places of action of sentinel. A disadvantage is the occurrence of off-target adverse effects. The results of studies on combination chemotherapy with a tyrosine kinase inhibitor in lung cancer patients were discussed. Tyrosine kinase inhibitors appear to enhance the efficacy of chemotherapy, but increase toxicity as well. Patients with a poor performance status, weight loss and/or squamous cell histology are more prone to serious and sometimes fatal adverse effects (pulmonary hemorrhage). The study results discussed highlighted the importance of patient selection, optimal dosing and safety monitoring in the treatment of lung cancer patients with chemotherapy and multi-kinase inhibitors.

Targeting cancer stem cells

Cancer stem cells are the rare population of undifferentiated tumorigenic cells that are thought to be responsible for tumor initiation, maintenance and metastasis. Binary division can result in another stem cell (self renewal) and a tumor cell with rapid proliferation potential. The CSC's anti-apoptotic properties explain their resistance to chemotherapy and radiotherapy. CSCs from glioblastoma, melanoma and cancer of the breast, lung, colon, thyroid and ovary have been isolated and expanded in vitro. Analysis of the critical aberrant signaling network in CSCs may lead to the identification of potential targets for anticancer therapy. Some of the potential targets are the Wnt pathway, NOTCH signaling and the hedgehog pathway.

- Wnt are secreted proteins that bind to receptors called Frizzleds, which cause β -catenin to accumulate and translate into the nucleus, where it binds to the LEF/TC transcription factors and activates the transcription of genes promoting proliferation. This pathway is primarily active during embryonic development and dormant during life. Recently, it was shown that the Wnt pathway plays a central role in lung cancer survival. The development of Wnt inhibitors is still in the preclinical phase.
- NOTCH encompasses a local cell signaling mechanism, which plays a role in differentiation, proliferation, apoptosis, adhesion, migration and angiogenesis. This process can be inhibited either by ligand binding (delta like ligand 4 trapping), or by γ -secretase inhibitors. Both strategies are being tested in phase 1 studies.
- The Hedgehog (HH) pathway is crucial during embryonic development and essential for pattern formation in many tissues including the neural tube, skin and gut. HH proteins act as a ligand to trigger a specific signal pathway facilitated by the transmembrane proteins Patched and Smoothed. Patched is a tumor suppression gene, which relieves the inhibition of Smoothed after binding to HH. Patients with Gorlin's syndrome have a germline mutation in one copy of Patched, which leads to several malignancies, including basal cell cancers. HH appears to be upregulated in other solid tumors, such as pancreatic, breast and colon cancer. In a phase 1 study among patients with advanced breast cancer, the HH-pathway inhibitor GDC-0449 yielded anti-tumor activity in the majority of cases.

Targeting cancer cell death

Restoration of immunogenic signals

Apoptosis due to chemotherapy can be accompanied by an immunological/inflammatory response depending on the agents given. For instance, anthracyclins and oxaliplatin induce immunogenic cell death, whereas etoposide and mitomycin C do not. It has been shown that failure of cancer cells to exhibit immunogenic signals relates to chemoresistance. Dendritic cells need an "eat me"-signal to activate cytotoxic T-lymphocytes. Such a signal could be conferred by targeted agents. Indeed, concomitant radiotherapy or PPD1/GADD34 inhibitors can lead to immunogenic cell death in case of treatment with etoposide or mitomycin.

Restoration of the apoptotic pathway

Evasion from apoptosis due to abnormal intrinsic apoptosis signaling is one of the hallmarks of cancer. Targeting the apoptotic pathway is a novel approach for cancer treatment. In case of intrinsic mitochondrial or extrinsic activation (by binding of ligands to the cell death receptor) the apoptotic pathway leads to cell shrinkage, membrane blebbing, DNA-fragmentation and finally cell death. This pathway can be inhibited by cytosolic proteins, such as inhibitory apoptosis proteins (IAPs). Smac/DIABLO is a mitochondrial protein which antagonizes IAPs. Treatment with Smac-mimetics could restore or enhance apoptosis. Other agents in preclinical testing are Caspase-3-de-repressors, IAP degradation promoters and small molecule Survivin inhibitors. YM155 is a Survivin inhibitor, which has shown a strong inhibition of Survivin expression and tumor growth arrest in preclinical studies. In several phase 1/2 studies and different malignancies monotherapy YM155 has shown antitumor activity in at least 20% of patients. Side effects are mild. Several other Survivin inhibitors have entered the stage of early clinical research.

Stimulation of the death receptors DR4 and DR5 by TRAIL pathway antibodies or recombinant human Apo2L/TRAIL agonists is another way to enhance apoptosis. Several TRAIL pathway antibodies, such as lexatumumab and mapatumumab, have been tested in phase 1/2 trials. The best reported response is stable disease. The Apo2L/TRAIL agonist AMG951 has been tested in a phase 1 study; 56% of patients had stable disease. Common adverse effects were fatigue, nausea, vomiting, anemia and fever. A phase 2 study evaluating the combination of AMG951 and chemotherapy with or without bevacizumab as first line therapy in NSCLC patients is currently being performed.

Bcl-2 was initially cloned from the breakpoint of t(14:18) chromosomal translocation found in follicular lymphoma and acts as an inhibitor of mitochondrion-dependent apoptosis. A whole family of apoptosis modulating proteins (25 to date) with variable degrees of similarity to Bcl-2 has been identified. Either induced by the intrinsic pathway or by the extrinsic pathway, BH3-proteins engage Bcl-2 family members to relieve Bax/Bak inhibition. This eventually

leads to caspase 9 inhibition. Bcl-2-mediated inhibition of apoptosis could be interrupted by treatment with Bcl-2 inhibitors or BH3-mimetics. The first developed Bcl-2 inhibitor, oblimersen, has been tested in combination with chemotherapy in a great variety of malignancies. The phase 3 results published so far have been rather disappointing. The BH3-mimetic ABT263 is a potent inhibitor of Bcl-2 family proteins. In xenograft models of small cell lung cancer (SCLC), leukemia, multiple myeloma and malignant lymphoma it has been shown to improve the cytotoxic effect of chemotherapy. In a phase 1/2 trial among patients with a solid tumor monotherapy resulted in 20% stable disease.

RNA-based transcriptional control

RNA interference is a cellular mechanism for regulating gene expression. Short RNA duplexes called small interfering RNAs (siRNAs) mediate the expression of genes by causing the degradation of homologous single-stranded RNAs. MicroRNAs (miRNAs) are naturally occurring non-protein encoding small RNAs, which function by binding to messenger RNAs and blocking protein translation. miRNAs can be exploited for the silencing of any gene. The concept has been proved by several cancer cell line experiments. For instance, siRNAs targeting sequences in the c-myc gene promoter inhibit c-myc-transcription resulting in tumor growth arrest. There is much to be expected from this treatment concept, which is about to enter early clinical trials.

Targeting DNA repair (in response to chemotherapy or radiotherapy)

Upregulation of DNA repair mechanisms in tumor cells can lead to chemotherapy resistance. Selective targeting of DNA-repair enzymes may increase effectiveness of DNA-damaging therapy. DNA repair mechanisms can be classified into six categories, including base-excision repair and homologous DNA repair. Currently, the usefulness of targeting either of these categories is being tested in advanced preclinical and early clinical studies.

Base excision repair is rarely lost in cancers. It can be disrupted by the inhibition of Poly-ADP-ribose polymerases 1 and 2 (PARPs 1&2). In preclinical models PARP inhibitors have been shown to enhance the efficacy of alkylating agents, topoisomerase 1 inhibitors and radiation. For instance, temozolomide resistance can be overcome by the addition of a PARP 1 inhibitor. In case of disrupted homologous DNA repair, which occurs in BRCA1/2 deficiency, PARP inhibitors are even more potent.

Targeting cytokine signaling

Chemokine receptors and their ligands direct the trafficking of leucocytes and endothelial progenitors into and out of malignant tissues influencing cell motility and survival. In many human cancers and experimental cancer models malignant cells express cytokine receptors. Metastatic cancer cells gain characteristics of chemokine receptor-expressing leucocytes, using chemokine ligands to aid their migration

to, and/or survival at, sites distant to the tumor. Therapies that target chemokines and the ligands involved may render the tumor environment less cancer-friendly.

Myelodysplastic syndrome (MDS) is a disease of defective hematopoiesis resulting from overproduction of myelosuppressive cytokines that cause apoptosis of hematopoietic progenitor cells. P38 MAP kinase (MAPK) is implicated in both the dysregulation in cytokine production and apoptosis signalling. ARRY-614 is one of the compounds which inhibits cytokine synthesis by inhibition of p38 MAPK. Healthy volunteers tolerated ARRY-614 well. In preclinical xenograft models ARRY-614 treatment in doses comparable to the healthy volunteer-study resulted in cancer growth inhibition. Initiation of clinical studies with ARRY-614 in MDS is planned for 2009.

Targeting JAK2/STAT3 signaling

The constitutive activation of signal transducer and activator of transcription 3 (STAT3) is frequently detected in most types of cancer, where it plays an important role in cell growth and survival, drug-resistance and angiogenesis. The majority of normal cell types lack constitutive STAT3 signalling. STAT3 is activated by JAK2 phosphorylation. Agents, such as FLLL32, WP1066 and AG490 bind to JAK2 and STAT3, resulting in inhibition of the STAT3 pathway. FLLL32 has been tested extensively in different preclinical models and shows growth suppression in breast cancer, pancreatic cancer, rhabdomyosarcoma and glioblastoma cells. In breast cancer cells synergy with doxorubicin has been observed. This agent has not yet entered the early clinical stage.

Targeting angiogenesis in tumors resistant to VEGF inhibition

Inhibition of the VEGF pathway has been shown to result in clinically significant inhibition of tumor angiogenesis. Tumors may however be inherently resistant or may become resistant to VEGF inhibitors. Delta-like ligand 4 (DLL4) is a transmembrane ligand for the NOTCH family of receptors, which is predominantly expressed in smaller arteries and microvessels. Expression studies using human or murine tumor samples have shown that DLL4 is dramatically and specifically upregulated within the tumor vasculature. In preclinical models blockade of DLL4 resulted in growth arrest in tumor cells resistant to VEGF inhibition. High-affinity fully human antibodies against DLL4 are in preclinical development.

AVE8062 is a vascular disrupting agent (VDA), which affects tubulin polymerization. It destructs established tumor vasculature, causing central tumor necrosis. AVE8062 has shown synergistic activity with platinum compounds and taxanes in animal models. In a phase 1 study among patients with solid tumors the medication was usually well tolerated. 30% of patients had stable disease and there were no objective responses. At an escalated dose chest pain, abdominal pain, acute coronary syndrome and grade 3 hypertension were observed.

Targeted therapy and trial methodology

Positron Emission Tomography (PET)

Efficacy markers derived from serum, tissue or imaging may accelerate the pace of targeted drug development. PET scanning could be helpful in patient selection and early efficacy evaluation. Radioactively labeled biomarkers can be used during PET imaging to measure tumor angiogenesis (for instance ¹¹¹In-bevacizumab) and tumor proliferation (¹¹¹In-trastuzumab). Tumor accumulation and tissue distribution of new drugs can be monitored by radiolabeling these drugs for PET-scanning.

Common Terminology Criteria for adverse events

The first version of the Common Toxicity Criteria was developed by a task force of the NCI in 1983. The last revision took place in 2003. A new version, including toxicities induced by targeted therapy, is presently under construction. Hypohidrosis and paronychia have been added. Hair loss has been replaced by hypertrichosis and alopecia. Nail changes have been replaced by nail discoloration, nail loss and nail ridging. Rash/desquamation has been replaced by bullous dermatitis, erythroderma, macular rash, maculopapular rash and pustular rash. Objective grading scales have been created to better reflect the current management of these adverse events. Until 10 April 2009 the new version is posted for public comment at <http://ctep.cancer.gov>. Implementation will take place from 27 May 2009.

Should patients with brain metastases be included in phase 1 trials?

A representative of the Institut Gustave Roussy (Paris, France) presented the treatment results of 13 patients with stable brain metastases (the majority originating from lung cancer) and 2 patients with a primary central nervous system (CNS) tumor, who had been included in four recent phase 1 trials. All 15 patients had no CNS symptoms and a World Health Organization (WHO) performance status 0–1. Three out of 13 patients with brain metastases had undergone radiotherapy. Treatment with mTOR inhibitors, anti-VEGFR tyrosine kinase inhibitors (TKIs) and anti-epidermal growth factor receptor (EGFR) TKIs was well tolerated without cerebral hemorrhage and CNS toxicities. Six of 13 patients developed a partial response of brain metastases. This single center experience suggests that patients with asymptomatic brain metastases could be entered in phase 1 trials with targeted agents after careful consideration of possible risks.

Conclusion

This 7th TAT conference gave a nice overview of the novel targets that are investigated in order to develop new targeted agents. In addition, new trial designs with new endpoints and patient populations were addressed. The 8th Symposium on Targeted Anticancer Therapies (TAT 2010) will be held in Bethesda, United States, and will be the next premier 'new drug development' meeting on agents with a cancer-specific molecular target, in particular the most promising ones in advanced preclinical and early phase clinical development.

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