New Possibilties in Cancer Treatment

New Anticancer Drugs in Perspective

Improvements in our understanding of the biology of cancer and the discovery of specific gene alterations have led to the development of a high number of new anti-cancer agents, some of them now representing the standard of care in specific tumour types. Recently, the advent of immunotherapy has opened new possibilities in the treatment of both solid tumors and lymphomas, while adoptive cell therapies may create a new therapeutic scenario in selected hematologic malignancies. Despite the optimism generated by these new therapeutic options, important questions regarding their use remain still unsolved: for most of the new agents no predictive biomarkers of response have been identified, making difficult to select patients most likely to benefit. In addition, even in patients achieving a response to these treatments, resistance often emerges and there is a continuous need to develop better therapeutic strategies.

Verbesserungen im Verständnis der Biologie von Krebs und die Entdeckung spezifischer Genveränderungen haben zur Entwicklung einer grossen Anzahl neuer Krebsmedikamente geführt, von denen einige heute den Standard in der Behandlung bestimmter Tumorarten darstellen. Vor kurzem hat das Aufkommen der Immuntherapie neue Möglichkeiten in der Behandlung von soliden Tumoren und Lymphomen eröffnet, während adoptive Zelltherapien ein neues therapeutisches Szenario bei ausgewählten hämatologischen Malignomen schaffen können. Trotz des Optimismus, den diese neuen Therapieoptionen hervorrufen, bleiben wichtige Fragen bezüglich ihres Einsatzes ungelöst: Für die meisten der neuen Wirkstoffe wurden keine prädiktiven Biomarker identifiziert, so dass es schwierig ist, Patienten auszuwählen, die am ehesten davon profitieren. Darüber hinaus treten auch bei Patienten, die auf diese Behandlungen ansprechen, häufig Resistenzen auf, und es besteht ein kontinuierlicher Bedarf, bessere therapeutische Strategien zu entwickeln

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Oncology remains one of the branches of medicine with the higher failure rate in terms of new drugs approvals and a lot of work has still to be done in order to bring significant improvements to patients (1). In this short review we present some of the current challenges in the development of new anticancer drugs.

Targeting kinases

Over the last years several small molecules have been used to target the product of specific DNA alterations. However, the same drug is not always equally effective across different cancers, despite the presence of the same gene alteration. Our comprehension of the tumoral micro-environment and of the interconnection between different pathways involved in cancer development is still incomplete and the presence of a specific alteration is often not enough to determine the success of a targeted therapy.

An example is represented by B-Raf inhibitors which have shown efficacy in melanoma and hairy cell leukemia (2-4), but results were disappointing in colorectal cancer, suggesting a greater complexity of this signalling pathway (5-9).

A recent strategy based on an histology-agnostic approach which targets different tumors harbouring the same molecular alterations irrespectively of histology, is represented by entrectinib, a selective TKI of the tropomyosin receptor kinases (TRKs), ROS1 and anaplastic lymphoma kinase (ALK). Rearrangements of genes encoding for these proteins result in activation of pathways involved in cancer progression such as PI3K/Akt/mTOR an MAPK (10). Combined results from two phase I clinical trials (119 patients) reported an overall response rates (ORR%) of 100%, 85% and 57% for patients with rearrangements of NTRK, ROS1 and ALK respectively (11-12). Despite the majority of patients (nearly 60%) had lung cancer, entrectinib appears to be effective independently of tumor histology. Similar outcomes have been reported with larotrectinib, a highly selective TRK inhibitor. Drilon and colleagues reported an ORR of 75% in 55 patients with TRK rearranged cancers enrolled in three different studies (13-15) . Responses were observed regardless of tumor type and TRK fusion characteristics (16). Future studies should clarify if the inhibition of this signaling pathway can be a valid therapeutic option among different histotypes (17).

Unfortunately, even when a molecular target is successfully inhibited, cancer cells develop resistances over time, usually through the acquisition of new DNA alterations.

An example is the onset of T790M mutation of EGFR which occurs in 50%-60% of cases of non-small cell lung cancer (NSCLC) resistant to erlotinib and gefitinib (18-19). Several strategies have been developed aiming to overcome this resistance, such as the employment of second generation EGFR inhibitors alone or in combination with cetuximab, but results were disappointing (20-24). Osimertinib, a third generation EGFR tyrosine kinase inhibitor (TKI), resulted in a response rate of nearly 70% in T790M mutated patients (25), however acquired resistance has already been observed limiting the long-term efficacy of this drug (26-28).

Genome alterations conferring drug resistance may be present in some subclonal cancer cells already before the start of a targeted therapy and these cells can subsequently expand due to the selective pressure following the treatment (29-30).

Increasing evidence supports the existence of molecular heterogeneity not only between different cancers but also within a single tumour, resulting in the parallel development of different driver genome alterations (31). DNA sequencing has been used to investigate this heterogeneity and have demonstrated that there is a huge variability, ranging from zero to thousands of coding mutations among different tumours types (32). Intratumoral heterogeneity, a feature not only limited to coding mutations but also to epigenetic mechanisms (33), may be associated with an increased risk of recurrence and death (34-39).

Targeting immune evasion

Checkpoint inhibitors are humanized monoclonal antibodies that inhibit the transmission of immunosuppressive signals delivered from cancer cells through the PD-1 and CTLA-4 pathways (40, 41). Impressive clinical activity has been observed and these drugs became the standard of care in several clinical settings such as melanoma (42-49), relapsed/refractory Hodgkin lymphoma (50, 51), lung (52-56), bladder (57-62) and kidney cancer (63) (Tab. 1). Unfortunately not all patients will respond to these drugs which can be also associated with immune-related side-effects, making essential to identify predictive biomarkers of response, in order to recognize those patients who can potentially benefit without exposing others to risks (64).

Adoptive cell therapies

A new therapeutic strategy which is being developed both for solid and haematologic malignancies is represented by adoptive T cell therapies which are based on the infusion of T lymphocytes, able to recognize specific tumor antigens.

Many different approaches have been attempted, such as the infusion of autologous ex vivo expanded Tumor Infiltrating Lymphocytes (74) or the creation of T cells expressing a high affinity T-cell receptor (TCR) able to recognize specific tumour associated antigens presented by MHC.

Recently, Chimeric Antigen Receptor (CAR) T cells have been developed; these are redirected T cells expressing a hybrid receptor, in which an extracellular domain derived from an antibody is fused with the intracellular domain of a TCR, allowing the recognition of antigens in MHC unrestricted manner (75-77). Further components can be added to the CAR, such as co-stimulatory domains, aiming to enhance CAR-T cells persistence and expansion (78, 79).

CAR-T cells have been particularly effective in the treatment of haematological malignancies recently obtaining FDA approval for relapsed or refractory acute lymphoblastic leukemia and large B-cell lymphoma (80-84). In solid tumors, results have not been encouraging thus far, although some positive results have been registered in neuroblastoma (85), sarcomas(86) and NSCLC (87).

Conclusions

Significant advances have been obtained during the last years in cancer treatment. The advent of genome sequencing techniques has changed the approach to treatment permitting to identify tumour-related genome alterations and consequently target them using small molecules. In addition the advent of immunotherapy (immune-checkpoint inhibitors and more recently adoptive cell therapies) has opened new directions in the treatment of patients with solid and haematologic malignancies. Results in specific clinical settings (e.g. NSCLC, melanoma, Hodgkin and non-Hodgkin lymphoma) have been so impressive to justify the definition that we live in the era of immunotherapy in cancer treatment.

TAB. 1 Clinical indications of checkpoint inhibitors

Drug	Target	Clinical Indications
Nivolumab	PD-1	
		Unresectable/metastatic melanoma, as a single agent (45, 46). Unresectable/metastatic melanoma, in combination with ipilimumab (48). Melanoma Adjuvant Teatment (65) Hepatocellular Carcinoma (66) Metastatic colorectal cancer (67) Urothelial Carcinoma (59) Metastatic NSCLC (52) Advanced renal cell carcinoma (63). Classical Hodgkin lymphoma (51). Recurrent/ metastatic HNSCC (68).
Pembrolizumab	PD-1	Advanced melanoma (42-44)
		Advanced NSCLC (53) Recurrent/metastatic HNSCC (69) Recurrent/advanced/metastatic Microsatellite instability high cancers (70) Classical Hodgkin Lymphoma (50) Advanced/metastatic urothelial carcinoma (60) Recurrent/Advanced/metastatic gastric or gastroesophageal junction cancer (71)
Atezolizumab	PD-L1	Advanced/ metastatic urothelial cancer (58) Metastatic NSCLC (54, 55)
Avelumab	PD-L1	Metastatic Merkel Cell Carcinoma (72) Advanced/metastatic Urothelial carcinoma (61)
Durvalumab	PD-L1	Stage III unresectable NSCLC (56) Advanced/metastatic urothelial carcinoma (62)
Ipilimumab	CTLA-4	Unresectable/ metastatic melanoma alone or in association with nivolumab (47-48) Resected melanoma with involvement of regional lymph nodes (49) Advanced renal carcinoma in association with nivolumab (73)

While it is possible that these new therapeutic strategies may bring significant improvements in the outcome of many patients with cancer, there is still need to make more efforts and identify patients most likely to benefit. In addition significant toxicities that may limit treatment compliance have been observed and particular attention should be made during the development of these compounds in order to identify the most appropriate therapeutic schedule and dose. Finally, the high costs associated with many of the new anticancer drugs should be reconsidered in the future given their possible use in an always increasing number of patients.

Schussfolgerungen

In den letzten Jahren wurden bedeutende Fortschritte in der Krebsbehandlung erzielt. Das Aufkommen von Genomsequenzierungstechniken hat den Behandlungsansatz verändert, der es erlaubt, tumorbedingte Genomveränderungen zu erkennen und diese mit Hilfe kleiner Moleküle zu bekämpfen. Darüber hinaus hat die Einführung der Immuntherapie (Immun-Checkpoint-Inhibitoren und neuerdings auch adoptive Zelltherapien) neue Wege in der Behandlung von Patienten mit soliden und hämatologischen Malignomen eröffnet. Die Ergebnisse in bestimmten klinischen Situationen (z.B. NSCLC, Melanom, Hodgkin und Non-Hodgkin-Lymphom) sind so beeindruckend, dass sie die Definition rechtfertigen, dass wir in der Ära der Immuntherapie in der Krebsbehandlung leben

Obwohl es möglich ist, dass diese neuen Therapiestrategien das Ergebnis vieler Krebspatienten signifikant verbessern können, müssen noch mehr Anstrengungen unternommen und die Patienten identifiziert werden, die am ehesten davon profitieren werden.

Darüber hinaus wurden signifikante Toxizitäten beobachtet, die die Therapietreue einschränken können, und es sollte bei der Entwicklung dieser Verbindungen besondere Aufmerksamkeit geschenkt werden, um den geeignetsten Therapieplan und die geeignetste Dosis zu ermitteln.

Schliesslich sollten die hohen Kosten, die mit vielen der neuen Krebsmedikamenten verbunden sind, in Zukunft überdacht werden, da sie bei immer mehr Patienten eingesetzt werden können.

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