Insulin-like growth factor 1 (IGF-1) pathway targeting in the treatment of cancer

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The insulin-like growth factor 1 (IGF-1) pathway has been under therapeutic investigation for many years, both in cancer and in other diseases. This signaling pathway plays an important role in the normal growth and development of vertebrate organisms, but has limited function in adults. At the cellular level it is fundamental in a variety of processes including cell proliferation and survival.[1,2] As such, the pathway plays a major role in tumour cell biology, including proliferation and survival, making it an apparently attractive target for therapeutic intervention. IGF1 is ubiquitously expressed in all organs with extreme high levels (compared to all other organs) found in the normal prostate. This review aims to give a short overview of reported clinical trials with drugs targeting the source of the pathway and in particular efforts targeting the Insulin-like Growth Factor Receptor-1 (IGF-1R).

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Anatomy of the IGF-1 pathway

The initiating elements of the IGF-1 pathway are 3 ligands, IGF-1, IGF-2 and insulin; 3 cell membrane receptors, IGF-1R, Insulin receptor (IR) and IGF-2 receptor; and 6 high-affinity IGF binding proteins (IGFBP). IGF-I and IGF-II are found in the circulation, complexed to IGFBP's, which serve to regulate bioavailability of these ligands in the tissue.

The IGF-1R is a receptor tyrosine kinase functioning as a heterotetramer of 2 extracellular ligand binding α subunits and 2 β subunits comprising the transmembrane and tyrosine kinase domains.[2] It shares 60% homology at the amino acid sequence level with the insulin receptor (IR).[3] The IGF-1R has high affinity for both IGF-1 and IGF-2. Binding of the ligands to the IGF-1R leads to the de-inhibition of the intrinsic tyrosine kinase activity, which results in autophosphorylation of tyrosine residue. This leads to binding of substrates and initiation of phosphorylation cascades that serve to transmit the IGF-1R signal. As a result 2 distinct pathways are activated: the PI3K-Akt-mTOR pathway which predominantly stimulates cell survival and the RAS-RAF-MAPK, which predominantly mediates cell proliferation (*Figure 1*).[2,4,5]

Implication of the IGF-1 pathway in malignancy

The IGF-1R and its 2 ligands play a critical role during embryogenesis and development in humans. In general, serum IGF-1 levels decline progressively after puberty. The implication of the pathway in can-

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cer can be considered in itself or in its relationship with other oncogenic pathways.

The IGF-1 pathway

Increased expression of IGF-1, IGF-2, IGF-1R, or combinations have been documented in various malignancies, including breast cancer, ovarian cancer, malignancies of the gastrointestinal tract such as colorectal cancer, hepatocellular carcinomas, pancreatic carcinomas and haematological malignancies.[6-9] In addition, epidemiological studies have shown that high levels of serum IGF-1 and/or lower levels of IGFBP's are associated with an increased risk for several cancers, including premenopausal breast cancer, prostate cancer, lung cancer and colorectal cancer.[10]

In vivo, overexpression of the IGF-1R accelerated the progression of pancreatic cancer in a mouse model, mainly by promoting the capability for invasion and metastasis.[11]

The functional and clinical prognostic significance of the IGF-1R expression and of its ligand levels has already been demonstrated for some malignancies (such as multiple myeloma) but still needs to be determined for most.

So far, the relative overexpression of the IGF-1R in a tumour compared to normal tissue is shown in a number of studies, e.g. in colon cancer.[12] The constitutive nature and, as a consequence, the importance of such overexpression for the pathogenesis and progression of most human cancers remains to be determined. Only in a few examples evidence of constitutive activation of the pathway is available. In some sarcomas, ligand overexpression seems to be constitutively driven by genomic alterations in the tumour. In Ewing sarcoma the characteristic t (11; 22) chromosomal translocation resulting in the EWS-FLI1 gene fusion has been shown to cause up-regulation of IGF-1 and down-regulation of IGFBP-3 causing autocrine stimulation of the IGF-1R.[13] Synovial sarcomas exhibit characteristic t (X; 18) translocations resulting in enhanced transcription of the IGF-2 gene and hyperactivation of IGF-1R signaling.[14] Amplification of the IGF-1R gene has been found infrequently in breast cancer (<2%) and melanoma.[15,16] In small cell lung cancer, some low level amplification or polysomy was found, but did not affect prognosis.[17] In non-small cell lung cancer,

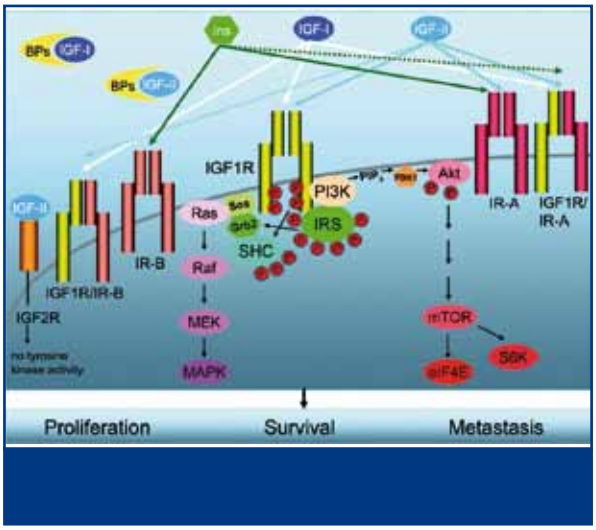

Figure 1. The IGF pathway (adapted from Sachdev D and Yee D. Disrupting insulin-like growth factor signaling as a potential cancer therapy.[5])

gene amplification was found in 2.8%.[18] In addition, IGF-1Rprotein and gene expression were not associated with survival, whereas high IGF-1Rgene copy number had a *positive* prognostic value.[14] Mutations of the receptor have been described only in a few human cancer cases (brain, lung, renal) in genome wide sequencing efforts.[19] In Multiple Myeloma (MM), IGF-1R expression seems to be linked to t (4; 14) translocations and to the expression of certain cell markers.[9] CD45 phosphatase inhibits IGF-1 signaling while CD56 positive myeloma cells reacted to IGF-1, whereas CD56 negative cells did not.[20,21] The functional consequences of direct or indirect constitutive activation of the pathway and value for therapeutic targeting remain to be defined further.

In relationship to other oncogenic pathways

The IGF-1 pathway has also been shown to cross-talk with a number of other signaling pathways and is involved in feedback loops that are activated when other, activated, pathways are therapeutically inhibited. For example, functional up-regulation of IGF-1R signaling has recently been implicated in the development of resistance to anti-cancer therapy such as human epidermal growth factor receptor 2 (HER2) targeting and EGFR targeting.[22,23] This mechanism could be a rationale for combined targeting of the

EGFR or HER2 on the one hand and IGF-1R on the other hand. In MM, a cross-talk exists between the IL-6 and the IGF-1 pathway, with IGF-1 enhancing IL-6 effects.[24] In addition, IGF-1R signaling has also been implicated in resistance to endocrine therapies in breast cancer, radiotherapy and a variety of chemotherapy agents, providing additional rationale for the investigation of combinatorial strategies.

Therapeutic targeting the IGF-1 pathway in cancer

The IGF pathway could thus be considered as a therapeutic target on its own or as an additional target to help other targeted therapies.

The IGF-1R is thought to be of potential therapeutic value because of its importance to cell growth, cell metabolism and cell survival and some hope that combining IGF-1R inhibition might enhance the activity of other targeted therapies, chemotherapy or radiotherapy. In vitro and in vivo inhibition of IGF-1R signaling in unselected cancer cells resulted in apoptosis in malignant cells and inhibition of tumour formation.[25]

However, based on expanding clinical evidence with several other therapeutic molecular targets, it is to be expected that the IGF-1R as a primary therapeutic target on its own would be specifically worthwhile to be investigated only in instances in which the pathway is constitutively activated through mechanisms elaborated above or yet to be discovered.

Strategies to inhibit the IGF-1R pathway include on the one hand the reduction of ligand levels or activity and on the other hand inhibition of receptor function using anti-receptor antibodies or small molecule tyrosine kinase inhibitors.

As primary target

An attempt to reduce IGF-1 levels using a somatostatine analogue did not result in the intended declines in IGF-1 or insulin levels in early stage breast cancer patients.[26] Anti-IGF-1 antibodies have shown interesting preclinical activity and are being investigated further.[27]

Antibodies targeting the IGF-1R that are very selective for IGF-1R are available. Binding of IGF-1R antibodies to the receptor prevents ligand-induced activation and induces receptor internalisation and degradation by endocytosis. Most of the known antibodies are fully human or humanised IgG1 antibodies, except figitumumab which is an IgG2 antibody.[28]

In MM, several IGF-1 antibodies have been preclinically tested with encouraging results: Imclone's IMC-A12, Pfizer's CP-751,871 and Merck's Dalotuzumab all show anti-tumour effects in murine models.[29-31] Tyrosine kinase inhibitors (TKI's) inhibit receptor activation by directly binding to and blocking the catalytic kinase domain. However, TKI's are less selective for the IGF-1R because of the homologies with the IR at the amino acid level, which may result in greater potency but also significantly increased toxicity due to co-targeting of the IR.[32] Despite their limited selectivity, several TKI's have been investigated preclinically in several cancer types including MM: NVP-ADW742 and NVP-AEW541 from Novartis, PPP or BVP-51004 from Biovitrium and GSK1838705A and GSK1904529A from GlaxoSmithKline.[7,33-36] All show promising anti-tumoural effects.

Targeting IGF-1 pathway in combination therapies

Several preclinical studies have been performed, for example in MM to analyse the effects of combining anti-IGF-1R therapy with existing conventional drugs. Rapamycin (an mTOR inhibitor) has been shown to work synergistically with IMC-A12 to inhibit tumour growth in vitro and IMC-A12 has also been shown to synergistically reduce tumour growth in a xenograft model when combined with bortezomib and/or melphalan.[29] NVP-ADW742 combined with melphalan synergistically reduces in vivo tumour growth and NVP-AEW541 enhances the effects of lenalidomide and bortezomib in vitro.[7,32] Recently NVP-AEW541 has also been combined with a novel mTOR inhibitor, namely Rad001 to reduce myeloma growth in vitro.[38]

Clinical trials

Phase I trials

As primary target

Phase I trials with different drugs targeting the IGF-1R have revealed a favourable profile with most adverse events described as mild. The most common

Table 1. Summary of clinical trial results with anti-IGF-1R antibodies

Agent	Dosing schedule	Trial Results
CP-751,871 (figitumumab) fully human IgG2	q3-4 weeks intravenous	Phase I: EWS 1CR STS 12/20 SD adrenal carcinoma 9/13 SD MM +dexamethasone 9/27PR CRPC + docetaxel: 8/20 PR Phase II: NSCLC + carboplatin/paclitaxel: OR 54% Phase III: NSCLC carboplatin/paclitaxel +/- figitumumab: closed prematurely, no benefit and increased toxicity
A12 (cixutumumab) fully human IgG1	q2 weeks intravenous	Phase I: SD>9 months in 2 pts (1 male breast cancer; 1 HCC) Phase II: CRPC: SD>6 mo in 29% CRC +/- cetuximab: insufficient activity
AMG-479 (ganitumab) fully human IgG1	q2 weeks intravenous	Phase I: EWS: 1CR carcinoid tumor: 1PR CRC refractory to cetuximab: +panitumamab 1PR Phase II EWS or desmoplastic small round cell tumors: OR 6%; OR+SD>24weeks 20% pancreas carcinoma + Gemcitabine: trend towards longer PFS, longer 6 months OS; more SD
R1507 (pobatumumab) fully human IgG1	q1-3 weeks intravenous	Phase I: EWS: 2PR Phase II: sarcoma: activity observed in EWS, rhabdomyosarcoma and osteosarcoma EWS: OR 14.4%
MK0646 (dalotuzumab) humanized IgG1	q1-2week intravenous	Phase I: solid tumors: 2 pts with SD>1 year; 3 pts with metabolic response Phase II: NET: insufficient activity

EWS: Ewing sarcoma; CR: complete remission, STS: soft tissue sarcoma; SD: stable disease; PR: partial remission; MM: multiple myeloma; CRPC: castration resistant prostate cancer; pts: patients; HCC: hepatocellular carcinoma; CRC: colorectal cancer; PFS: progression free survival; OS: overall survival; NET: neuroendocrinal tumour

adverse events seem to be due to endocrine changes, including hyperglycaemia. Co-administration of anti-diabetic agents may be necessary to control blood glucose. Up to 20% of severe hyperglycaemia is seen in studies in which anti-IGF-1R antibodies are combined with chemotherapy regimen that require corticosteroids as premedication.[39] Haematological toxicity including grade 3 thrombocytopenia has been observed mainly with IgG1 antibodies.[40,41] Hypersensitivity reactions were rare.[32,42]

In different phase I trials objective responses have been reported in patients with Ewing sarcoma: 1 complete remission (CR) with AMG-479[40], 1 CR with CP-751,871 (figitumumab) and 2 objective responses (OR) and 2 stable disease (SD) with R1507 (robatumumab).[40,43,44] Figitumumab also showed signals of activity in sarcoma (12 patients with disease stabilisation) and in prostate cancer (PSA responses in combination with docetaxel) and in MM 9/27 patients with relapsed disease responded while no dose-limiting toxicities were identified.[41,45,46] Dalotuzumab is currently also in phase I clinical trial for various solid tumours and MM.[31]Two previous phase I trials in advanced solid tumours demonstrated metabolic response in 3 patients and SD lasting for over a year in 2 patients.[47,48]

A phase I trial with OSI-906, a small-molecule dual inhibitor of IGF-1R/IR, demonstrated stable disease lasting for over 12 weeks in 7/20 patients, including 1 thymus carcinoma, 1 adrenal carcinoma and 1 colorectal carcinoma.[49]

Targeting IGF pathway in combination therapies

For example, in MM, a phase I trial has been completed combining IMC-A12 with temsirolimus (a rapamycin analogue) in patients with advanced disease and a phase I trial is ongoing combining the TKI AVE-1642 (Sanofi-Aventis) with bortezomib in MM patients with relapsed disease, results are not available yet (source: NIH).

Phase II trials

As primary therapeutic target

A phase II trial of R1507 in patients with recurrent or refractory sarcoma reported clinical significant activity in Ewing sarcoma, rhabdomyosarcoma and osteosarcoma.[50] The same monoclonal antibody was investigated in patients with recurrent or refractory Ewing sarcoma family of tumours and demonstrated an OR in 14.4% with 12/125 patients responding at least 6 weeks with a median duration of 25 weeks.[51] Another phase II trial with AMG-479 in Ewing sarcoma and desmoplastic small round cell tumours demonstrated an OR in 6% (2 patients with PR) but a clinical benefit (PR+ SD lasting more than 24 weeks) of 20%.[52] In colorectal cancer refractory to cetuximab or panitumumab, cixutumumab with or without cetuximab did not show any activity.[53] A phase II trial of cixutumumab monotherapy in castration refractory prostate cancer suggested modest antitumour activity with disease stabilisation for over 6 months in 29% of patients.[54] In prostate cancer the administration of preoperative figitumumab demonstrated biological activity with PSA decline.[55] The activity in prostate cancer is intriguing, as a specific mechanism of genomic activation of the pathway in prostate cancer has not been documented yet. Perhaps this could be related to the high importance of IGF-1 in the normal prostate or a yet to be defined constitutive driver of the pathway which might very well include the driving of the IGF-1 pathway due to constitutive activation (by gene rearrangement) of Ets and Erg in an important fraction of prostate cancers.[56]

Targeting the IGF pathway to help other targeted therapies

In the virtual absence of the current identification of sensitising mutations in the IGF-1 pathway in human cancer, a major application for IGF-1 pathway targeting might reside in augmenting the therapeutic effect of targeting other activated oncogenic pathways.

A phase II trial with figitumumab in combination with paclitaxel and carboplatinum as first line treatment in patients with locally advanced or metastatic non-small cell lung cancer reported a promising OR of 54% versus an OR of 42% in the chemotherapy alone arm.[57] The response rates were the highest in patients with squamous cell carcinoma. Based on these results, a randomised phase III trial was initiated (see below).

Another phase II trial adding AMG-479 to gemcitabine in metastatic pancreatic cancer, demonstrated a trend toward longer progression free survival, 6 months overall survival and higher rates of stable disease.[58]

Phase III trials

In NSCLC a randomised phase III trial compared the combination of figitumumab to carboplatinum and paclitaxel versus carboplatinum and paclitaxel alone. This trial was suspended after the accrual of 681 of the planned 820 patients because an interim analysis showed no improvement of the efficacy over chemotherapy alone and an increase in toxicity.[59] A similar negative experience has been made in breast cancer reported recently at the San Antonio Breast Cancer Conference.[60]

Both clinical development strategies have suffered from the failure to preselect patients at least for the presence of expression of the targeted protein. It is most unfortunate that such costly efforts (that also demand active participation of patients) due to these design limitations risk throwing out erroneously some possibly valuable treatments for a subset of patients.

Conclusions

Preclinical and early clinical results have suggested potential utility of IGF-1R targeting agents in the management of cancers. Promising preclinical work and even phase II data have however not led to further validation of the therapeutic strategy as yet, except for 2 cancers in which the IGF-1 pathway might be indirectly constitutively activated: Ewing sarcoma and prostate cancer. Patient selection may

be the key to success in developing this therapeutic strategy further. Indeed, in other cancers, the most striking therapeutic effects have been obtained when the target gene itself is genomically activated, by mutation (e.g. EGFR in lung cancer, c-KIT in GIST) or translocation (bcr-abl in CML, Alk fusion gene in lung cancer). Significant but slightly less impact is observed in cases in which the target gene is amplified (HER2 in breast cancer, gastric cancer). In contrast, when the target gene is in its wild type status, minimal or no therapeutic benefit can be observed (e.g. wild type EGFR in lung cancer). When the therapeutic target is indirectly activated by an upstream driver (e.g. VEGF in renal cell cancer), a therapeutic benefit can be obtained, but in the cases at hand, of less magnitude than when the target gene itself is activated.

The minority of breast and lung cancers that have some IGF-1R gene amplification could therefore be explored for the therapeutic efficacy of this anticancer strategy. Similarly, as a secondary target, this strategy could be investigated further in combination with other targeted agents in populations with a genomically activated primary oncogenic pathway (e.g. mutant EGFR in lung cancer or HER2 amplified breast cancer), but at least with proper selection of patients with regard to expression of the IGF-1R.

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