Molecular Pathways: Clinical Applications and Future Direction of Insulin-like Growth Factor-1 Receptor Pathway Blockade

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Abstract

The IGF1R signaling pathway is a complex and tightly regulated network that is critical for cell proliferation, growth, and survival. IGF1R is a potential therapeutic target for patients with many different malignancies. This brief review summarizes the results of clinical trials targeting the IGF1R pathway in patients with breast cancer, sarcoma, and non–small cell lung cancer (NSCLC). Therapeutic agents discussed include both monoclonal antibodies to IGF1R (dalotuzumab, figitumumab, cixutumumab, ganitumab, R1507, AVE1642) and newer IGF1R pathway targeting strategies, including monoclonal antibodies to IGF1 and IGF2 (MEDI-573 and BI 836845) and a small-molecule tyrosine kinase inhibitor of IGF1R (linsitinib). The pullback of trials in patients with breast cancer and NSCLC based on several large negative trials is noted and contrasted with the sustained success of IGF1R inhibitor monotherapy in a subset of patients with sarcoma. Several different biomarkers have been examined in these trials with varying levels of success, including tumor expression of IGF1R and its pathway components, serum IGF ligand levels, alternate pathway activation, and specific molecular signatures of IGF1R pathway dependence. However, there remains a critical need to define predictive biomarkers in order to identify patients who may benefit from IGF1R-directed therapies. Ongoing research focuses on uncovering such biomarkers and elucidating mechanisms of resistance, as this therapeutic target is currently being analyzed from the bedside to bench.

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Learning Objectives

Upon completion of this activity, the participant should be able to explain the unique outcomes of the clinical application of IGF1R inhibition in patients with sarcoma, breast cancer, and non–small cell lung cancer, and the participant should also understand the pathophysiologic basis of current strategies that can identify patients who are more likely to benefit from IGF1R inhibition.

Background

The insulin-like growth factor (IGF) signaling pathway is a complex and tightly regulated network that is critical for cell proliferation and survival (1). This pathway (Fig. 1) is composed of three receptor tyrosine kinases—insulin-like growth factor-1 receptor (IGF1R), insulin-like growth factor-2 receptor (IGF2R), and insulin receptor (INSR)—three ligands (insulin, IGF1, and IGF2; refs. 2, 3), and six serum insulin-like growth factor binding proteins (IGFBP), which serve as regulators of the pathway by...
The IGF1R signaling pathway is composed of three receptor tyrosine kinases (IGF1R, IGF2R, and INSR), three ligands (insulin, IGF1, and IGF2; formerly known as somatomedins; refs. 1, 2), and six serum insulin-like growth factor binding proteins (IGFBP). The IGFBPs, of which IGFBP3 is the most common, serve as regulators of the pathway by determining the bioavailability of IGF1 and IGF2 ligands (4). Both IGF1 and IGF2 exert their effects through autocrine, paracrine, and endocrine mechanisms, and both can activate the IGF1R pathway.

For simplification, IGF1 ligand only is shown binding to IGF1R. IGF1 binding to IGF1R promotes receptor homodimerization or heterodimerization with INSR. Ligand-activated IGF1R first binds to intracellular adaptor proteins, such as IRS1 and SHC. These adaptor proteins transmit signals through the PI3K–AKT1–mTOR pathway and through the MAPK pathway. Activated IGF1R promotes cellular motility through activation of IRS2, which alters integrin expression through poorly understood mechanisms involving the small G protein RHOA, FAK, ROCK, PI3K, and other signaling molecules. Of note, IGF2R is a repository for IGF2, and it has no intracellular signaling activity. IGF2R acts as a tumor suppressor gene, as when IGF2R function is lost, IGF2 is able to bind IGF1R and promote tumorigenesis (17). Targets for potential monotherapy and combinatorial therapeutic strategies are noted in the figure. TKI, tyrosine kinase inhibitor.

determining ligand bioavailability (4). The most prevalent of the IGFBPs is IGFBP3 (5). Both IGF1 and IGF2 exert their effects through autocrine, paracrine, and endocrine mechanisms, and both can activate IGF1R signaling.

IGF1R is a type 2 tyrosine kinase transmembrane receptor that is normally found as a heterotrimer with two alpha and two beta subunits (6, 7). IGF1R binding to IGF1 or IGF2 can occur with IGF1R as a homodimer or as a heterodimer with insulin receptor isoforms A or B (INSR-A, INSR-B; refs. 2, 8). While the heterodimer IGF1R/INSR can bind insulin, it has been shown to preferentially favor IGF1-mediated signaling (9, 10).

Once activated, IGF1R activates numerous downstream pathways within the cell. In order to propagate these signals, ligand-activated IGF1R first binds to intracellular adaptor proteins, predominantly insulin receptor substrate1 (IRS1; ref. 11), although other intracellular proteins, such as SHC1 (12), GAB (13), and CRK (14), can interact with activated IGF1R. These adaptor proteins are necessary for IGF1R to transmit signals...
downstream in the cell through the PI3K-AKT1–mTOR pathway and through the MAPK pathway. Ligand-activated IGF1R binds to IRS1, which then binds to the p85 regulatory subunit of PI3K, which then transmits signals to AKT1 and mTOR. Activation of the PI3K-AKT1–mTOR pathway results in pleiotropic effects, including inactivation of the proapoptotic protein BAD (15–19). Concurrently, IGF1R binds to SHC, which interacts with growth factor receptor-bound-2 (GRB2)-son-of-sevenless (SOS) to activate the MAPK pathway (14). Finally, activated IGF1R is thought to promote cellular motility through activation of IRS2, which acts to alter integrin expression through poorly understood mechanisms involving the small G protein RHOA, focal adhesion kinase (FAK), and Rho-kinase (ROCK; refs. 15, 16). Of note, IGF2R is a repository for IGF2, and it has no intracellular signaling activity. In this capacity, IGF2R acts as a tumor suppressor gene, as when IGF2R function is lost, IGF2 is able to bind IGF1R and promote tumorigenesis (17).

Serum IGF1 and IGFBP3 levels are normally regulated by the pituitary gland (18, 19). Elevated serum levels of IGF1 and IGF2 and overactivation of the mitogenic, antiapoptotic, and motility signaling cascades induced by IGF1R have been implicated in many tumor types, including epithelial malignancies (breast, lung, colorectal, prostate, ovarian), mesenchymal tumors (osteosarcoma, rhabdomyosarcoma), and hematologic malignancies (1, 2, 17, 20, 21). Furthermore, IGF1R pathway dysregulation acts as an oncogenic signal in the context of both initial tumorigenesis and resistance to cytoxic and targeted anticancer therapies (2, 3, 22, 23).

Herein, we focus on the role of the IGF1R pathway in breast cancer, sarcoma, and non–small cell lung cancer (NSCLC), as it is in these three malignancies that IGF1R pathway blockade has been most extensively studied. In patients with breast cancer, it has been noted that the IGF1R pathway has extensive cross-talk with the estrogen receptor (ER) and epidermal growth factor receptor 2 (ERBB2) signaling pathways, and IGF1R has been implicated in resistance to hormonal therapy (24, 25). Furthermore, IGF1R is directly upstream of the PI3K–AKT1–mTOR pathway, which is aberrantly activated in more than half of human breast cancers (26). Preclinical data in sarcoma tumor models have shown that the IGF1R pathway is particularly important in tumor growth, metastasis, and angiogenesis in patients with Ewing sarcoma and rhabdomyosarcoma, leading to the initial application of IGF1R inhibitors in patients with these tumor types (27). Finally, IGF1R protein levels have been shown to be high in NSCLC cell lines and patient samples, both in adenocarcinoma and squamous histologies (28, 29). Also, IGF1R expression is associated with poor prognosis in patients with NSCLC (28). It is worth mentioning that IGF1R expression levels have been evaluated in small cell lung cancer (SCLC); however, we only discuss NSCLC.

Numerous therapeutic agents targeting the IGF1R pathway have been developed. These agents include IGF1R monoclonal antibodies (mAbs), IGF1R/INSR tyrosine kinase inhibitors (TKI), and, more recently, IGF1- and IGF2-specific mAbs (Fig. 1). Furthermore, several rational combination therapeutic strategies have been used to attempt to more potently inhibit IGF1R signaling. To date, the most widely tested combination strategy involves the use of IGF1R antibodies with mTOR allosteric inhibitors, such as temsirolimus (30) or ridaforolimus (3). There is an established preclinical rationale for this approach, as numerous studies have now shown that mTOR inhibition paradoxically results in activation of the IGF1R pathway (31).

In the following sections, we describe the current state and future directions of the application of IGF1R targeting agents in patients with breast cancer, sarcoma, and NSCLC, with a summary of the high-impact trials provided in Table 1.

Clinical–Translational Advances

IGF1R pathway inhibition in patients with breast cancer

Four different anti-IGF1R mAbs have been tested in early clinical trials involving small numbers of patients with advanced, treatment-refractory breast cancer with largely unimpressive results (5, 32–35). Consequently, three phase 1 clinical trials assessing the combination of IGF1R mAbs with mTOR inhibitors in patients with advanced, treatment-refractory breast cancer have been completed (19, 36, 37). In a phase 1 clinical trial with dalotuzumab and the mTOR inhibitor ridaforolimus, a subset of patients with ER-positive (ER+) highly proliferative disease was shown to have exceptional responses, experiencing a disease control rate (stable disease [SD] plus partial response [PR]) of 55% (6/11 patients). These promising results created momentum for a recently completed phase II clinical trial involving patients with advanced luminal B breast cancer treated with dalotuzumab, ridaforolimus, and hormonal therapy (NCT01234857; ref. 36). In a phase I clinical trial with cixutumumab and the mTOR inhibitor temsirolimus, among 26 patients with breast cancer (86% with ER+ disease), 4 patients (15%) had SD, and no PRs or complete responses (CR) were observed. The results of this trial, in which the median number of prior chemotherapeutic regimens was three, stimulated interest in testing the combination of cixutumumab and temsirolimus in patients with metastatic breast cancer and no more than two prior lines of chemotherapy, but initial trial results have shown no tumor responses (NCT00699491; ref. 37). Finally, unlike combination with mTOR inhibition, the combination of IGF1R inhibition with exemestane or fulvestrant in patients with advanced breast cancer was unsuccessful in a phase II trial (38), halting the application of combination hormonal therapy and IGF1R inhibition in patients with breast cancer.

IGF1R pathway inhibition in patients with sarcoma

Because of successful initial clinical trials in patients with advanced, treatment-refractory sarcoma treated with IGF1R mAbs (5, 32, 34, 35, 39), larger trials with a combined total of 362 patients have been completed (27, 40–42). In summation of these clinical trials, disease stabilization rates have been 16% to 40%, PRs have ranged from 2% to 12% of patients, and 2 of 362 patients have achieved a CR. Overall, the exceptional response of some patients to IGF1R inhibitor monotherapy has led to speculation that a subset of patients with sarcoma, especially Ewing sarcoma, are uniquely dependent on IGF1R signaling (19).

The combination of mTOR inhibition with IGF1R inhibition in patients with advanced sarcoma has yielded results similar to those from IGF1R monotherapy (19, 30, 36, 43, 44), and the combination of IGF1R inhibition with cytotoxic chemotherapy has yielded provocative results in patients with leiomyosarcoma (18, 45). Overall, the clinical trials of anti-IGF1R mAbs in patients with sarcoma have shown occasionally profound responses and disease stabilization rates ranging from 16% to up to 70% when IGF1R mAbs have been combined with mTOR inhibitors (43).
However, larger trials are needed to determine the optimal therapeu tic strategy (monotherapy vs. combination therapy with mTOR inhibitors) and also to parse out which subsets of patients are most likely to benefit.

**IGF1R pathway inhibition in patients with NSCLC**

The combination of IGF1R inhibition with cytotoxic chemotherapy has been tested in several large clinical trials in patients with NSCLC (46-48). The most well-studied IGF1R mAb in lung cancer is figitumumab. When the combination of figitumumab, carboplatin, and paclitaxel was used as first-line therapy in 98 patients with advanced NSCLC, the objective response rate (ORR) was initially reported to be 57%, with an additional 10% to 20% of patients experiencing stable disease. These encouraging results prompted the completion of a phase III trial comparing figitumumab plus carboplatin/paclitaxel to carboplatin/paclitaxel alone in patients with treatment-naive advanced NSCLC. This clinical trial was closed early due to increased rates of serious adverse events and treatment-related deaths in patients treated with figitumumab (46). The phase III

| Table 1. Published clinical trials involving IGF1R pathway inhibition in patients with breast cancer, sarcoma, or lung cancer |
|---|---|---|---|
| References | Phase | n | Tumor types | Therapy | Disease control rates |
| Atzori et al., 2011 (32) | I | 80 | Colorectal (24%), breast (21%), sarcoma (11%), other (43%) | Dalotuzumab (MK-0646) | SD 8%, PR 4%, CR 0% |
| Di Cosimo et al., 2015 (36) | I | 87 | Breast (26%), colorectal (22%), NSCLC (18%), sarcoma (16%), other (18%) | Dalotuzumab (MK-0646) + ridaforolimus | SD 46%, PR 7%, CR 0% |
| Higano et al., 2015 (33) | I | 40 | Lung (20%), colon (15%), breast (7.5%), other (57.5%) | Cuxotumab (IMC-A12) | SD 25%, PR 0%, CR 0% |
| Ma et al., 2013 (37) | I | 26 | Breast (100%); ER positive (86%) | Cuxotumab (IMC-A12) + temsirolimus | SD 15%, PR 0%, CR 0% |
| Naing et al., 2011 (19) | I | 42 | Adrenocortical (24%), breast (21%), sarcoma (21%), other (41%) | Cuxotumab (IMC-A12) + temsirolimus | SD 43%, PR 0%, CR 0% |
| Tolcher et al., 2009 (34) | I | 53 | Sarcoma (42%), other (58%) | Ganitumab (AMG-479) | SD NA, PR 4%, CR 2% |
| Gojo et al., 2012 (47) | I | 19 | NSCLC (100%) | Figitumumab (CP-751,871) + carboplatin and paclitaxel | SD 42%, PR 37%, CR 0% |
| Molife et al., 2010 (45) | I | 46 | Prostate (48%), esophageal (20%), sarcoma (6.5%), NSCLC (4.3%), other (21.2%) | Figitumumab (CP-751,871) + docetaxel | SD 26%, PR 9%, CR 0% |
| Murakami et al., 2012 (5) | I | 19 | Breast (21%), gastric (16%), NSCLC (10%), sarcoma (10%), other (43%) | Ganitumab (AMG-479) | SD 37%, PR 0%, CR 0% |
| Kurzrock et al., 2010 (33) | I | 35 | Sarcoma (51%), lung (5.5%), breast (5.5%), other (38%) | R1507 | SD 35%, PR 5%, CR 0% |
| Macaulay et al., 2013 (18) | I | 58 | Ovarian (21%), sarcoma (9%), breast (7%), NSCLC (5%), other (58%) | Ave1642 + docetaxel OR gancitinib OR doxorubicin | SD 40%-70%, PR 2.5%-20%, CR 0% |
| Puzanov et al., 2014 (8) | I | 86 | Colorectal (49%), NSCLC (4%), sarcoma (4%), other (43%) | Linsitinib (OSI-906) | SD 36%, PR 1%, CR 0% |
| Haluska et al., 2014 (50) | I | 43 | Urothelial (46.5%), sarcoma (9%), colorectal (5%), breast (25%), NSCLC (25.9%), other (34.3%) | MED-573 | SD 30%, PR 0%, CR 0% |
| Haluska et al., 2007 (39) | I | 24 | Colorectal (25%), lung (17%), sarcoma (17%), other (41%) | Figitumumab (CP-751,871) | SD 41%, PR 0%, CR 0% |
| Olmos et al., 2010 (27) | I | 29 | Sarcoma (100%); Ewing sarcoma (55%) | Figitumumab (CP-751,871) | SD 28.5%, PR 3.5%, CR 3.5% |
| Naing et al., 2012 (30) | I | 21 | Ewing sarcoma (85%), desmoplastic small round cell tumor (15%) | Cuxotumab (IMC-A12) + temsirolimus | SD 25%, PR 0%, CR 10% |
| Quek et al., 2011 (43) | I | 21 | Sarcoma (90%), adrenal cortical (5%), colorectal (5%) | Figitumumab (CP-751,871) + everolimus | SD 71%, PR 5%, CR 0% |
| Juergens et al., 2011 (40) | I/I | 31 (1) | Sarcoma (100%); Ewing sarcoma (89%) | Figitumumab (CP-751,871) | SD 24%, PR 14%, CR 0% |
| Schoffski et al., 2013 (42) | I/I | 107 (1) | Sarcoma (100%); Ewing sarcoma (18%) | Figitumumab (IMC-A12) | SD 40%, PR 2%, CR 0% |
| Schwartz et al., 2015 (44) | II | 174 | Sarcoma (100%); Ewing sarcoma (15.5%) | Cuxotumab (IMC-A12) + temsirolimus | SD 38%, PR 5%, CR 0% |
| Piaggio et al., 2011 (41) | II | 115 | Ewing sarcoma (100%) | RI507 | SD 16%, PR 9%, CR 1% |
| Karp et al., 2009 (48) | II | 98 | NSCLC (100%) | Figitumumab (CP-751,871) + carboplatin and paclitaxel | SD 10%-20%, PR + CR 54% -> 57% corrected |
| Robertson et al., 2013 (38) | II | 63 | Breast (100%); ER positive (94%) | Ganitumab (AMG-479) + fulvestrant OR exemestane | SD 27%, PR 8%, CR 0% |
| Ramalingam et al., 2011 (49) | II | 172 | Breast (100%) | Erlotinib = RI507 | 12-week PFS: OS 81% mo/10 mo |
| Langer et al., 2014 (46) | III | 338 | NSCLC (nonadenocarcinoma 100%) | Figitumumab (CP-751,871) + carboplatin and paclitaxel | OS: 81 mo/10 mo |

Abbreviations: mo, months; NA, not available; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

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The combination of EGFR plus IGF1R inhibition has been tested in a cohort of unselected patients with lung adenocarcinoma or squamous cell carcinoma, but there was no improvement in PFS or OS compared to treatment with EGFR inhibition alone. Importantly, in this study, less than 5% of patients had an EGFR mutation, as it was proposed that based on preclinical models IGF1R and EGFR cross-talk was a key mechanism of tumorigenesis and resistance to isolated EGFR inhibition in patients with NSCLC, independent of EGFR mutation status (49).

Other therapeutic agents that target the IGF1R pathway

The growing appreciation of INSR-mediated signaling in the IGF pathway has led to two novel strategies to target the IGF1R pathway in patients with advanced breast cancer, sarcoma, and NSCLC. A combined IGF1R and insulin receptor inhibition (8) and therapeutic antibodies directed against the IGF1 and IGFI2 ligands (50, 51).

On the basis of antitumor activity demonstrated in preclinical models in several tumor types, linsitinib, an oral small-molecule TKI of IGF1R and INSR, has been evaluated in 86 patients with advanced, treatment-refractory solid tumors. When patients were treated with linsitinib monotherapy, the overall disease stabilization rate was 36%, and 1 patient with melanoma achieved a PR (8). Recently completed phase II trials have evaluated linsitinib combination therapies with paclitaxel in patients with recurrent ovarian cancer (NCT00889382) and with erlotinib in patients with EGF-mutant NSCLC (NCT01221077). Results from these trials are pending.

MEDI-573, a mAb to both IGFI and IGFI2, has demonstrated the ability to suppress IGF signaling through both IGFI and INSR-A without affecting normal INSR-B-mediated signaling in cancer cell lines, leading to its use in an early clinical trial in patients with advanced, heavily pretreated solid tumors (50). In this trial, the disease stabilization rate was 30% with no PRs or CRs observed. On the basis of preclinical studies showing increased INSR-A:INSR-B mRNA ratios in tumor tissue from patients with hormone receptor–positive, ERBB2-negative tumors, a phase I/II clinical trial is now under way assessing the impact of MEDI-573 combined with hormonal therapy in this subset of breast cancer patients (NCT01446159; ref. 50).

A second mAb to both IGFI and IGFI2, BI 836845, has been tested in phase I clinical trials involving 81 patients with advanced solid tumors (52, 53). The results have demonstrated tolerability, and 2 patients have experienced a PR, resulting in additional ongoing clinical trials involving the combination of BI 836845 with afatinib in patients with EGF-mutant NSCLC in East Asia (NCT02191891) and in combination with everolimus and exemestane in patients with ER– breast cancer (NCT02123823).

Challenges to clinical applications

The most pressing and as yet undefined challenge to the appropriate clinical application of IGF1R pathway blockade is the identification of predictive markers that are able to identify patients likely to respond to this therapeutic strategy. As the clinical trial data show, some treatment combinations have shown disease stabilization rates of one-quarter to one-half of patients, and there has been some intriguing antitumor activity, especially in patients with sarcoma. However, what is now critically needed is development of predictive biomarkers that can guide future clinical trials in applying this therapeutic strategy to the patient populations most likely to benefit.

The identification of predictive biomarkers can be divided into four main categories that have seen varying levels of success: tumor expression of IGF1R and its pathway components, serum IGF ligand levels, assessment of alternate pathway activation, and attempts at identifying specific molecular signatures of IGF1R pathway dependence.

Pretreatment IGF1R expression as assessed by immunohistochemistry has not consistently been correlated with disease control in heterogeneous groups of patients treated with anti-IGF1R mAbs (32, 35, 44). It is important to note that when tumor expression of a target of a therapeutic agent does not correlate with response, there are many possible etiologies of false-negative signals, including sampling bias, variability in sample handling, limited assay sensitivity and specificity, and tumor mutations between the time a sample is obtained and the time when treatment is administered (32).

In the case of IGF ligand assessments, serum ligand levels have consistently demonstrated predictive value in patients with sarcoma and NSCLC, although it must be noted that the degree of correlation between IGF ligand levels in the serum versus in the tumor microenvironment is unknown. In two clinical trials involving patients with sarcoma treated with IGF1R inhibitor monotherapy, elevated pretreatment and on-treatment serum IGF1 levels were associated with improved OS (40, 41). In patients with NSCLC, both a phase I (47) and a phase III clinical trial (46) have demonstrated improved disease control and overall survival in patients with elevated pretreatment serum total IGF1 (46) and greater elevations in serum IGF1 when treated with figitumumab plus carboplatin/paclitaxel (46, 47). In contrast to serum IGF1 levels, pretreatment levels and on-treatment changes in serum IGFBP3 have not been associated with disease control in isolated IGF1R inhibition (5), combination IGF1R and mTOR inhibition (19, 37), or IGF1R inhibition in combination with cytotoxic chemotherapy (18, 47).

The assessment of alternative pathway activation mediating resistance to IGF1R-targeted therapies was the impetus for the combination trials described above. However, the interpretation of the heterogeneous responses to combination therapy necessitates a better understanding of the cross-talk between the IGF1R pathway and other important signaling molecules such as EGFR, SRC, and ER (54–56) and downstream molecules such as mTOR, PI3K, and AKT1, which have been shown to mediate IGF1R resistance in preclinical models (57).

Finally, specific gene expression profiles associated with IGF1R sensitivity or resistance have been identified in models of...
breast cancer and Ewing sarcoma (58–60). This characteristic IGF1-dependent gene expression profile includes upregulation of transcriptional targets of ER, MAPK3, MAPK1, and components of the PI3K–AKT1–mTOR pathway (58). The assessment of these molecular signatures and alternative pathways mediating IGF1R resistance within the context of the significant clinical trial data described above is an important next step in improving the patient-specific application of IGF1R-targeting therapies (61).

Conclusions

In conclusion, the IGF1R pathway is important in the development and maintenance of many different types of malignancies. Drug development targeting this pathway has taken unique routes by different tumor types, from preferential combination therapy in the case of patients with breast cancer to impressive efficacy in patients with sarcoma treated with anti-IGF1R monotherapy to a negative phase III trial in combination with cytotoxic chemotherapy in patients with NSCLC. The most pressing needs for the future development of this therapeutic strategy are identifying biomarkers of response by applying a bedside-to-bench approach with the existing clinical trials data, including an in-depth analysis of tumor samples from patients who have responded to IGF1R-directed therapies. These critical analyses will serve as the foundation to guide the most appropriate application of IGF1R blockade in the clinic.

Disclaimer

The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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