Journal of Cell Science & Therapy

Eda, et al., J Cell Sci Ther 2015, 6:1
http://dx.doi.org/10.4172/2157-7013.1000193

Review Article Open Access

Pharmacological and Clinical Importance of Integrin Antagonists in Treatment of Cancer

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Rec date: Dec 05, 2014; **Acc date:** Jan 28, 2015; **Pub date:** Feb 03, 2015

Abstract

Integrins are heterodimeric molecules that are composed of 18 α-subunits and 8 β-subunits. They exist in 24 distinctive shapes based on combination of these sub-units and are mainly responsible for the adhesion of extracellular matrix (ECM) and immunoglobulin family molecules. Integrins mediate adhesion of epithelial cells to the basement membrane and also help in the migration, proliferation and survival of tumor cells. Studies also reveal that certain integrins act as markers for tumor cells and they also assist in both tumor progression and apoptosis. Studies reveal that unligated integrins in association with caspase 8 result in inhibition of ECM adhesion might result and integrin mediated death (IMD) on the other hand integrins in association with oncogenes or receptor tyrosine kinases can result in enhanced tumorigenesis. Among several types of integrins, αvβ3 and $\alpha_5\beta_1$ have gained importance in anti-angiogenesis studies.

Hence the role of antiangiogenesis antagonists has come into light. These include a variety of monoclonal antibodies and peptides. Each one of them has their own mechanism of action and antiangiogenesis activity. Current review aims at studying the phase 1 and 2 trails of these antagonists for anti-angiogenic function.

Keywords: Integrins; Integrin mediated death; Extra cellular matrix; Anti-angiogenesis

Introduction

Integrins

Integrins are a heterodimeric cell surface receptors that assist in the adhesion of extracellular matrix (ECM) and immunoglobulin family molecules. They play a vital role in the cell motility and invasion as they can directly adhere to the various components of the ECM. Integrins also control the ECM remodeling and proliferation processes [1]. Integrins are a family of heterodimeric molecules that are composed of 18 α-subunits and 8 β-subunits. They exist in 24 distinctive structures by the combination of these subunits, each one with multiple activation sites and distinctive expression and glycosylation activity based on their composition. The extent to which a cell can adhere or migrate on different matrices can be determined by the composition of the integrin it possesses. The presence of RGD (Arg-Gly-Asp) sequence in the respective ligands can be identified by the presence of the αv and $\alpha_5\beta_1$ integrins [2]. Furthermore the presence of various adhesive sequences in the ECM proteins such as EILDV (Glu-Ile-Leu-Asp-Val) and REDV (Arg-Glu-AspVal) can be identified by the presence of the α4β1 integrin. On ligating to the ECM, integrins cluster and recruit various signaling and adaptor proteins at a particular site called as focal adhesion point to initiate important cellular functions. The composition of such sites are truly depend on the 2 or 3 dimensional contact conditions. At the enriched site, integrins inherit kinase functionality by recruiting active kinases such as Focal adhesion kinases (FAK's) and SRC family kinases (SFK's), assist in the association of ECM to actin- cytoskeleton by recruiting proteins such as talin, paxilin, α-actinin, tensin and vinculin and further associated with cellular migration and survival the help of PINCH (a territory complex consisting of an integrin linked kinase) and Parvin. A group of membrane proteins called Tetraspanins are responsible for regulating the integrin function in the tumor cells by recruiting integrins to the membrane microdomains. The extent of cell adhesion and migration on ECM is controlled by the recruitment specific integrins and other Focal adhesion proteins, which in turn became potential candidates for cancer therapy [3-6].

Cell survival is maintained by various integrin mediated mechanisms involving increase in expression of BCL-2, activation of PI3K-AKT, p53, vascular endothelial growth factor 2 (VEGFR2) pathways and by preventing the intrinsic and extrinsic apoptosis pathways [7]. Unligated integrins together with caspase 8 can induce integrin –mediated death (IMD), which is different from anoikis.

Under normal conditions integrins assist in regulating the integrity of the various organs and tissues of the body. The previous studies reveal that $\alpha_5\beta_1$ integrin, could assist in tumor progression by activating the oncogene-induced transformation. The solid tumors formed from epithelial cells are found to be with higher level of $\alpha_6\beta_4$, $\alpha_6\beta_1$, $\alpha_v\beta_5$, $\alpha_2\beta_1$ and $\alpha_3\beta_1$ integrins and retained with different expression levels during tumor cell survival, proliferation, progression and migration. The higher expression levels of integrins $\alpha_v\beta_3$, α5β1 and $\alpha_v\beta_6$ in some tumors acts as the marker proteins, while they are under expressed in normal epithelial cells [6]. Integrins in association with oncogenes or receptor tyrosine kinases can result in enhanced tumorigenesis. Integrin $\alpha_6\beta_4$ along with ERBB2 in breast cancer and α1 activated KRAS-G12D- induce tumors in the lung [3,4,8,9]. Beyond to the advantages and disadvantages of various integrins, the therapeutic effects of integrin antagonists still remained unexplored as it is believed that inhibition of ECM adhesion might result in IMD. In the current review, we have selected the important of two αvβ3 and $\alpha_5\beta_1$ integrins to enumerate the importance in the generation of antagonists in the treatment of cancer.

Integrin $\alpha_v\beta_3$: The $\alpha_v\beta_3$ integrins are a part of a family of αv integrins, a group of five members: $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ and $\alpha_v\beta_8$ whose prime function is regulation of cell adhesion to ECM, proliferation and migration. It adheres to the extracellular matrix proteins using an amino acid sequence of arginine-glycine-aspartic acid [6,10,11]. The $\alpha_v\beta_3$ integrin, vitronectin receptor is a member in the family of αv integrins, a group of 5 members: $\alpha_v\beta_1$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$ and $\alpha_v\beta_8$ whose prime function is regulation of cell adhesion to ECM, proliferation and migration. It adheres to vitronectin, an extracellular matrix protein with the help of RGD sequence [6,10,11]. These are the prime type of integrins that are present in the endothelial cells and helps in angiogenesis via the basic fibroblast growth factor (bFGF) and tumor necrosis factor-α and also contribute to the malignant spread of various tumor cells such as breast carcinoma, prostrate carcinoma and melanoma [12-14]. Up regulation of $\alpha_v\beta_3$ integrin is observed profoundly upon neo-vessel formation to vascularize the most of the human cancer cells during angiogenesis and invasion [6,15,16]. Hence the inhibition $\alpha_v\beta_3$ integrin by cyclic RHD peptides, peptidomimetics and monoclonal antibodies induce endothelial cell apoptosis there by resulting in angiogenesis inhibition and are considered as potential targets to attain antiangiogenic properties.

Integrin $\alpha_5\beta_1$: $\alpha_5\beta_1$ integrin interacts with fibronectin (ECM glycoprotein) at the RGD sequence and plays a crucial role in neovascularization by generating survival signals for active endothelial cells and mediates angiogenesis by regulating endothelial cell growth, proliferation and migration in cancerous cells by suppressing the protein kinase A (PKA) [3,4,17]. Stimulation of angiogenesis growth factors such as bFGF, TNFa and IL8 result in the upregulation of integrin $\alpha_5\beta_1$ and its expression is controlled by the home box family transcription factor 3 (Hox 3) [18-21]. The inhibition $\alpha_5\beta_1$ integrin via certain antagonists such as antibodies or small molecules results in the inhibition of endothelial cell survival and proliferation both *in vivo* and *in vitro* to block angiogenesis and there by resulting in apoptosis.

Integrin antagonists in tumor and angiogenesis inhibition

Integrin antagonists in clinical development include both antibodies and small molecules (Table 1) These antagonists include: (a) chimeric or humanized antibody inhibitors. (b) peptide inhibitors of individual integrins as well as peptides that inhibit integrins, and (c) non-peptide, organic inhibitors. In the current review, an attempt is made to target *av* and *a5* integrin with different integrin-targeted agents, which are in clinical development and clinical trials in cancer therapy.

Integrin	Antagonists	Function	Disadvantage/ Advantage
avb3	Monoclonal ab Vitaxin (LM 609 mAb)	Inhibits cell adhesion, blocks Vitronectin receptors & Bax apoptotic pathway, upregulates matrix degradation inhibitors	Short half life and inefficient interaction No tumor regression
	First generation of MEDI – 523 & Second generation of MEDI-522	Inhibits MAPKinase pathway, inhibits MMP- activation, lowers TGF- β1 accumulation	No clinical significance due to less affinity and stability
	Intetumumab (CNTO 95)	Inhibits the contact between ECM and tumor cells, inhibits angiogenesis	Safe for long term administration
	EMD 525797 (DI17E6) mAb Non-peptide inhibitors MK0429	Inhibits the ligand binding to αv heterodimers	Efficacy, dose dependent tolerability and under phase II trails
	PSK1404	Inhibits osteoclast formation in bone metastasis	Oral compound is not developed even though safe and tolerable
	IH1062	Inhibits osteoclast bone resorption and inhibits ovarian and breast cancer	Preclinical study is limited
	S 137 and S247 17E6	Inhibit the cell growth and enhance apoptosis by inhibiting the interaction with ligand Inhibits vitronectin binding, Inhibits pulmonary metastasis	Provides promising results in tumor metastasis
	GIPG0187,RGD antagonists	Decreases BCl-2/Bax ratio and survivin protein	Reduces the development of liver metastasis
	DisBa-01, novel monomeric P-II SVMP-derived RGD disintegrin ATN-161, acetylated, amidated PHSCN peptide	Promotes endocytosis of αvβ3 integrin, Anti tumor, anti adhesive and anti metastatic activities Decreases Aldehyde dehydrogenase and increases zE-cadherin/vimentin ratio Inhibits angiogenesis Impairs TGF-β signalling Inhibits VEGF expression and angiogenesis	Under clinical trial Under Phase I trails in cancer therapy Novel in anti-metastatic therapy Under Phase II trails

		Inhibits MMP-2 activity Inhibits angiogenesis and metastasis by reducing VEGF expression Anti tumorigenic and anti metastatic Prevents recurrence of cancer	
α5β1	Volociximab	Inhibits the function of α5β1integrin Induces apoptosis in cancer cells Inhibits angiogenesis	Inhibits tumor growth significantly
	GIPG0187, non peptide RGD antagonists	Decreases Aldehyde dehydrogenase and increases E-cadherin/vimentin ratio Inhibits angiogenesis Impairs TGF-β signalling	Under Phase I trails in cancer therapy
	Resveratol, natural polyphenolic antioxidant	Down regulates α5β1 integrins Induces apoptosis	Further study is required

Table 1: Monoclonal antibodies and other non peptide mediated antagonists of αvβ3 and α5β1 integrins and the details are given in the text.

Vitaxin: Vitaxin is a function blocking humanized monoclonal antibody that specifically interacts with the integrin $\alpha_v\beta_5$ [22]. The humanized version is derived from the LM 609 antibody [11,23]. The LM 609 antibody is the most specific anti-integrin $\alpha_v\beta_5$mAb which blocks the interaction of $\alpha_v\beta_5$ complex with its matrix ligands and inhibits the cell adhesion [14]. The LM 609 mAb blocks the VN receptor in the presence of growth factor stimulation and results in activation of p53. It also leads to increase the BAX apoptosis pathway by enhancing the $p^{21waf-1/CID-2}$ levels. This molecular mechanism triggers the apoptosis of endothelial cells and regression of angiogenic blood vessels. It also blocks the induction of TGF-β1 and stimulate SMC migration by inducing the expression of various ECM proteins and at the same time up regulate the expression of matrix degradation inhibitors and tissue inhibitors of MMPs [24,25]. Despite of numerous clinical studies the therapeutic approach of LM 609 is limited in humans due to its short serum life and inefficient interactions with human immune effector cells [14].

To overcome these issues LM 609 is humanized to interact specifically with integrin αvβ5 and Vitaxin is the first generation (MEDI-523) of humanized version that is developed. The humanized version comprise the human IgG1, kappa and grafted murine CDRs onto human framework and their by retaining the parent monoclonal LM 609 antibody properties [14,26]. Vitaxin binds to conformational epitope that is formed by α_v and β_5 subunit with equal affinity [24]. By preventing Erk $_{½}$ phosphorylation, it suppress the tumor growth and also angiogenesis. Blockade of integrin $\alpha_v\beta_5$ by vitaxin is able to block the conversion of pro MMP-2 to active MMP-2 thereby preventing the localization and activation of MMP-2 [11].

The *in vivo* studies performed in the ballon injured hypercholesterolemic rabbit demonstrated that vitaxin dose dependently inhibited Rb-1 SMC migration at 20 μg/mL concentration. Vitaxin significantly reduces neointima formation in both LDV and HDV groups even in presence of hypercholesterolemia, a stimulus to integrin $\alpha_v\beta_5$ accumulation. It also reduced the artery size, enhanced cellular apoptosis in injured arteries and lowered the amount of TGF-β1 accumulation. These results encouraged to study the efficacy of with integrin αvβ5blockade [11]. Later the safety and pharmacokinetics of the vitaxin where evaluated in Phase-I clinical studies. In this Phase-I, open label, single centre, dose escalating study patients with late stage breast, lung, colon cancer were administered intravenously with increasing doses of vitaxin (0.1 mg/kg-4.0 mg/kg) for six weeks. The drug therapy was well tolerated with no significant toxicity at any dose level. The pharmacokinetics of the vitaxin demonstrated a dose dependent elimination because the half-life of the vitaxin is 4-9 fold lower when compared to higher dose and tend towards non linearity. Even though this study did not determine the optimum dose it suggested that vitaxin could administered safely without any toxicity over prolonged periods and evidenced that humanized vitaxin does not appear to be immunogenic [22]. The optimum dose of the vitaxin was characterized in a pilot trail conducted in patients with metastatic cancer. This clinical trial suggested that the doses level of vitaxin equivalent to or in excess 50 mg can be administered and to maintain circulating levels with good plasma recovery a dose of 200 mg is recommended. Because the half-life plasma recovery for 10 mg dose level was very low, for 50 mg it was 76% and for 200 mg it was 95%. The treatment was well tolerated with no tumor regression [25]. But due to the absence of significant clinical responses, affinity and stability *in vivo* issues of MEDI-523 encouraged to develop second generation humanized anti integrin $\alpha_v\beta_5$ monoclonal antibody MEDI-522 (Abegrin).

The second generation MEDI-522 derived from MEDI-523 have greater affinity and stability towards integrin $\alpha_v\beta_5$. It also retained the tumor targeting and antibody retention properties from predecessor mAb [23,27]. The preclinical *in vitro* and *in vivo* inhibitory studies suggested that the continuous serum concentration at a minimum of 10 μg/mL to 30 μg/mL is sufficient for MEDI-522 activity. The safety and tolerability of MEDI-522 was evaluated in Phase-I, open label, dose escalation trail. The patients with solid tumors were treated with MEDI-522 with dose levels ranging from 2 to10 mg/kg. No significant toxicity and maximum tolerated dose was identified but few adverse events noted were low-grade constitutional symptoms, gastro intestinal symptoms, infusion reactions and asymptomatic hypophosphatemia. Only three patients with metastatic renal cell cancer experienced prolonged stable disease on treatment suggesting that MEDI-522 could be further investigated as an anti-integrin $\alpha_v\beta_5$ [13].

The clinical studies that used immunotherapy with radionuclides showed efficacy of the MEDI-522 and the level of radiotherapy and molecular inhibition was also established. In the *in vitro* and *in vivo* micro PET studies, MEDI-522 (AbegrinTM) was conjugated with DOTA and labelled with ^{64}Cu. The ^{64}Cu-DOTA-AbegrinTMconjugate exhibited high integrin $\alpha_v\beta_5$ specificity with shorter half-life in mouse than in humans [28]. In the tumor imaging studies by using ^{111}In-DOTA-AbegrinTM conjugate the uptake of the conjugate is high in integrin $\alpha_v\beta_5$ positive tumors when compared to the $\alpha_v\beta_5$ negative tumors and there by exhibiting the high binding affinity to human integrin $\alpha_v\beta_5$ [29]. The efficacy and maximum tolerate dose of Abegrin was evaluated in a murine xenograft glioblastoma model in which DOTA-Abegrin was conjugated with ^{90}Y. Animals treated with 300 µCi had higher mortality rate and reduction in all hematologic counts. The distribution of the antibody was found high in liver and spleen and serum $t_{1/2}$ of ^{90}Y-DOTA-Abegrin was found to be 12-24 hours. The maximum dose tolerated was 200 µCi with maximum antitumor efficacy and no toxicity was observed with good hepatic clearance [30]. The success of radio labelled imaging *in vitro* and *in vivo* studies of Abegrin using radionuclides provides the success in to clinic to evaluate the tumor targeting efficacy, dose optimization, dose interval and pharmacokinetics of MEDI-522.

The Phase-I study of the MEDI-522 evaluated the safety, immunogenicity and pharmacokinetics in sixteen patients with solid tumors in dose escalating manner (1, 2, 4 and 6 mg/kg). The treatment was well tolerated at doses upto 6 mg/kg and no evidence of immunogenicity was observed. The only biological effects observed were leucopenia, anaemia, hypocalcemia, hypokalemia, hyponatremia and hypophosphatemia. The pharmacokinentic analysis observed a nonlinear increase in half-life [31]. The antitumor efficacy and safety data of MEDI-522 were assessed in randomized, open-label, two arm Phase-II study. The stage-IV melanoma patients were randomized to receive MEDI-522 and MEDI-522 + dacarbazine. The therapy with MEDI-522 + dacarbazine did not appear to be more effective in metastatic melanoma and the most adverse events observed were gastro intestinal, metabolic and infusion related [32]. These studies specified the binding efficacy of the MEDI-522 for human integrin $\alpha_v\beta_5$ Phase I/II clinical studies and will enter Phase III for further evaluation.

Volociximab: Volociximab, clinically represents as a first function blocking, high affinity human/mouse chimeric IgG4 monoclonal antibody that specifically interacts with integrin $\alpha_5\beta_1$ [33]. The constant region of volociximab comprises human IgG4 heavy and kappa light chain combined with murine antibody variable regions, including the integrin $\alpha_5\beta_1$ directed complementarity determining regions [34,35].

In vitro models of angiogenesis, a preclinical evaluation study of volociximab suggest that volociximab is potent inhibitor of angiogenesis. It inhibits the $\alpha_5\beta_1$ integrin function by inducing apoptosis in proliferating endothelial cells but not resting cells. The *in vivo* studies conducted in cynomolgus model of revascularization also suggest that voloxicimab inhibit integrin $\alpha_5\beta_1$ function with a greater inhibitory potential. These data demonstrated that volociximab has therapeutic potential in diseases such as cancer and age- related macular degeneration [36]. The antitumor activity assessment of volociximab in syngeneic rabbit VX2 carcinoma model reported that systemic administration of volociximab whether prophylactically or after the tumor establishment as a potent anti-cancer agent. These studies supported the use of volociximab as potent inhibitor in malignant disease because when maintained relatively high levels of antibody for at least two weeks in the model there was significant decrease in tumor volume growing subcutaneously or intramuscularly [37].

The safety profile, feasibility, anticancer activity, pharmacokinetic and pharmacodynamic behavior of volociximab were evaluated in the phase I study based on the supporting rationale provided by the preclinical studies. In this multicentre, open label, dose-escalation study of 21 patients with tumors, showed unresponsive to standard therapies were administered with volociximab. Over 60 min at dose levels ranging from 0.5 to 15 mg/kg with a total of 223 infusions. But, observed no DLT and neither required dose reductions. The common adverse events observed in high dose groups were fatigue and myalgias, however, there was neither hematologic toxicity nor infectious complications. But few non-hematologic adverse events which included gastrointestinal symptoms, head ache, edema, hypertension and low grade constitutional symptoms were observed. The binding and saturation of integrin $\alpha_5\beta_1$ sites by volociximab was determined as a dose-dependent because estimates of volociximab declined with increasing doses which was achieved at the highest dose of 15 mg/kg. These findings suggested that volociximab can be safely administered to target multistep angiogenesis process in a feasible and safe approach [38].

The non-randomized Phase II disease specific clinical trials for volociximab were carried in patients with malignant melanoma, pancreatic, renal cell carcinoma, ovarian and non-small cell lung cancers. These clinical trials established the safety and efficacy of volociximab as single-agent or in combination [39]. All these preliminary data demonstrate the efficacy of volociximab but randomized trials and future studies are required to validate the efficacy.

Intetumumab: Intetumumab (CNTO 95) is a fully human IgG1 mAb which do not cross react with mouse integrins but have limited cross reactivity with rat integrins [40]. It is generated by immunizing mice transgenic for part of the human immunoglobulin receptors. It recognizes multiple αv integrins with broad specificity with a dissociation constant of Kd 1-24 nmol [41]. Studies conducted showed that CNTO 95 bound to purified human $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins with high specificity and as a promising agent to inhibit integrin mediated tumor growth and angiogenesis [42]. It inhibits angiogenesis in tumors by ligating with the integrin receptors on the tumor cells and thereby blocking or reducing the signalling between the tumor cells and ECM [43]. The *in vivo* preclinical studies in nude mice and nude rats demonstrated that CNTO 95 has potent anti-tumor and anti-angiogenic properties where intetumumab dose dependently inhibited the adhesion of HUVECs and human melanoma cells to all $\alpha_v\beta_3$ and $\alpha_v\beta_5$ ligands, indicating the function blockade of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins. The *in vitro* sprouting and inhibitory studies demonstrated CNTO 95 as an inhibitor of angiogenesis because the proliferation of bFGF simulated endothelial cells was inhibited by intetumumab in dose dependent manner compared to unstimulated cells [40]. Another preclinical study in cynomolgusmacque evaluated the safety of CNTO 95. The results postulated that terminal elimination half-life was increased with dose and reduced clearance of mAb at 10 mg/kg and 50 mg/kg doses. The serum concentration time profile exhibited a short, rapid distribution phase. The *in vitro* and *in vivo* immunolocalization studies showed that CNTO 95 bound strongly to human and mouse tissues. This preclinical data suggested that intetumumab is safe for long term administration [44].

The supportive data in preclinical evaluations of intetumumab exhibited the anti tumor and anti angiogenic inhibitory effects of the antibody. In the Phase I study of CNTO 95 the biological activities like cell motility, cell signalling, tumor growth, tumor metastasis and angiogenesis were determined by using breast carcinoma cells. In four human breast cancer cells (MCF-7, MDA-MB-231, MDA-MB-468, and MX-1) with estrogen positive and negative receptor showed the reduction in cell viability by CNTO 95 in a dose dependent manner. It also specifically inhibits the integrin αv-vitronectin receptor suggesting potential effects of the mAb on cell motility and adhesion. It inhibits this interaction by promoting tyrosine dephosphorylation of FAK and paxillin. The MDA-MB-231 cells in SCID mice treated with CNTO 95 resulted in significant inhibition of metastasis by providing additional anti-cancer benefit [41]. An open label, single centre, first-in-human, multiple administration, dose escalating (0.1, 0.3, 1.0, 3.0, 10.0 mg/kg) study in 24 patients evaluated the safety and pharmacokinetics of CNTO 95. Over all the therapy was well tolerated with only observation of dose related increase adverse events. The low doses (≤3.0 mg/kg) cleared more rapidly from serum where as higher dose (10 mg/kg) cleared more slowly indicating saturation of tissue binding at 10.0 mg/kg. This pharmacokinetics studies indicate the increase of drug exposure in greater than proportional manner over the range evaluated. When pre-treated and post-treated tumor cells with CNTO 95 were observed, the levels of Bcl-2, a proto-oncogene which inhibits apoptosis was distinctly present in pre-treated tumor cells. The immune-histochemical analysis indicate that CNTO 95 was able to penetrate in to the tumor and bind to the target integrin αv [45]. But this study did not provide any information regarding the maximum tolerated dose (MTD) in pharmacodynamics studies. Another multicentre, open-label Phase-I study conducted with higher dose (20 mg/kg) of CNTO 95 than previous Phase-I (10 mg/kg) in 19 patients observed no dose limiting toxicity, no complete or partial responses and adverse effects like head ache, vomiting, nausea, fatigue were similar to that of previous study. Four patients experienced disease progression, changes in mental status and two metastatic melanoma patients had a stable disease response. The pharmacodynamics assessments suggested down regulation of integrin. AUC and Cmax increased proportionally every 3 weeks and terminal $t_{½}$ was slightly longer for the 20 mg/kg dose than that of 10 mg/kg dose. These safety evaluation studies suggested the CNTO 95 maximum tolerated dose MTD of 10 mg/kg dose levels for future studies [42]. The safety and efficacy of intetumumab as a single agent or in combination with other agents by using radiation therapy was established. The pharmacokinetics results in a multicentre, randomized, Phase-II in stage-IV melanoma patients in combination with dacarbazine were nonlinear with greater than dose- proportional at 10 mg/kg serum concentrations. The therapy with intetumumab and dacarbizine was well tolerated with association of very low grade adverse effects in patients receiving intetumumab and patients treated with dacarbazine experienced hematologic toxicity [46]. The *in vitro* inhibitory studies in colon cancer cell lines (HCT 116 which express $α_vβ_5$ and RKO cells which express $α_6β_1$, $α_2β_1$, $α_6β_4$) conferred that combination regimen of CNTO 95 and dasctinib were greater than drug alone. This dual inhibition reduced paxillin activation and inhibit cell migration in HCT 116 cells but not in RKO cells in low concentrations [47].

The intetumumab and radiation combination therapy in human tumor xenografts and rats established, intetumumab as a potent and effective agent for cancer therapy along with radiation. The human xenograft model in nude rats established with human head, neck and non-small cell lung cancer cell lines established the effectiveness of intetumumab in combination with radiation therapy. A limited antitumor activity was observed with a significant reduction of VEGFR and integrin αv expression along with the density reduction of micro vessels [48]. It also inhibited spontaneous lung metastasis of A 549 tumors. When radiation therapy is combined with intetumumab the perfusion rate and blood volume in tumours were enhanced significantly which were totally different as a single agents of treatment [49]. These results encouraged the potent efficacy of intetumumab along with fractionated radiation therapy and were consistent with the Phase-I.

Studies from uterine serous papillary carcinoma (USPC), colorectal adeno carcinoma, breast cancer demonstrated the anti-metastatic and prognostic effect of intetumumab. The cell adhesion of uterine serous papillary carcinoma (USPC) cell lines that express αv integrins to ECM proteins were significantly inhibited at low doses of intetumumab. The *in vitro* and *in vivo* studies employing 8.0 µm pore poly carbonate membrane demonstrated the ability of intetumumab to inhibit the migration of uterine serous papillary carcinoma cells [43]. In a hematogenous metastasis study the rats treated with intetumumab did not develop any brain lesions compared to contrast result of control rats. Intetumumab significantly improved the survival and incidence of multiple brain metastases in MRI was also reduced. It also reduced the human 231 BR-HER2 cells adhesion to the cultured plates with 97-100% viability [50]. These results emphasized the prophylactic effect and the anti-metastatic effect of intetumumab in nude rats. A recent study in non-small cell lung cancer (NSCLC) assessed the potential growth inhibition mechanism by using intetumumab. In the cells deleted with SMARCA 4 gene, ZEB 1 gene expression was up regulated whereas E-cadherin expression was down regulated. These results to gain the information regarding the inhibition mechanism and suggest ZEB I acquires SMARC 4 independent mechanism to repress E-cadherin expression. The results also showed strong enrichment in several chromosomal locations in which the down regulated genes were highly enriched on chromosome 19p while the up regulated genes were enriched on chromosome 4q in resistant cells [51]. This information is necessary to support further clinical evaluation of intetumumab to evaluate the antitumor and anti angiogenic effects.

EMD 525797 (DI17E6): EMD 525797 (DI17E6) is a novel de-immunized monoclonal immunoglobulin G2 antibody that is developed specifically to direct against the human αv integrins. It prevent the cell adhesion and motility of the tumor cells by binding to the human αv integrins and inhibits the ligand binding to all αv heterodimers thereby antagonizing their interactions. The Phase-I studies evaluated the safety, efficacy, tolerability, anti-tumor activity and pharmacokinetics of the DI17E6. In a multicentre, open-label, dose escalating (250 mg, 500 mg, 1000 mg, 1500 mg) study enrolled with 26 patients of metastatic CRPC showed a dose-dependent and non-linearity pharmacokinetics profile of EMD 525797. The terminal elimination half-life of low dose (250 mg) observed approximately four fold divergence when compared to high dose level (1500 mg). No DLTs and dose dependent relationship in TEAEs were observed. But there was significant decrease in primary tumor only in one patient and over all the treatment with EMD 525797 was well tolerated and it appeared to be safe in metastatic CRPC patients [52]. In another Phase-I, first-in-human study with 54 subjects studied observed the EMD 525797 elimination from serum with $t_{½}$ of 13 fold difference to 1500 mg dose group. The results demonstrated that the pharmacokinetics of EMD 525797 was dose-dependent with dose proportion increase of Cmax values and treatment was well tolerated with ascending doses of EMD 525797 (35 mg to 1500 mg) [53]. A

Phase-II randomized, double-blind placebo controlled in mCRPC patients was ongoing with 750 mg and 1500 mg of EMD 525797 [52]. Over all these results suggest EMD 525797 as a potent single agent inhibitor but further evaluation of predictive markers and controlled randomized trials are necessary to evaluate the efficacy of the EMD 52579.

GIPG0187: GIPG0187 is a non-peptide RGD antagonist for all six integrin receptors. It displays a unique anti-integrin, anti-tumor, anti angiogenic, anti-osteoporotic and anti-resorptive profile [54]. In human prostate cancer PC-3M-Pro4/luc+ cells treated with GIPG0187, reduced tumor growth and bone metastases were observed. It diminished the aldehyde dehydrogenase and increased the E-Cadherin/vimentin ratio in the *in vivo* study performed in the prostate cancer cells. In the *in vitro* study it significantly prevented the ORX-induced bone loss and reduced the number of osteoclasts. These *in vitro* and *in vivo* results suggest it as a potent inhibitor of angiogenesis [15]. The exposure of the GIPG0187 to GL-261 and SMA-560 mouse glioma cells resulted in reduced viability and cell death at very low concentrations (1 nM). Also the impaired TGF-β signalling was observed when pSmad2 levels were reduced in GL-261 and SMA-560 mouse glioma cells cultured on the collagen-1 coated cell plates [55]. This agent progressed to clinical trials in advanced cancers with the supportive results from Phase-I and further evaluation is much more important for cancer therapy.

MK0429: MK0429 is a small, active, potent, non-peptide αvβ3 integrin inhibitor [23,56]. It functions to have potent inhibition activity for osteoclast formation and osteoclastic bone resorption. In multicentre, randomized Phase-I double-blind trail enrolled with 21 HRPC and bone metastatic patients, rapid absorption of mk-0429 at lower dose was evident. The treatment was well tolerated with no DLTs and adverse effects and assumed to be safe [57]. Even though the positive results for safety and tolerability were observed for this orally bioavailable compound it is not being developed.

PSK1404: PSK1404 is a non-peptide antagonist for $\alpha_v\beta_3$ integrin [58]. It inhibits osteoclast bone resorption and exhibits antitumor effect in ovarian and breast cancer cells. In *in vitro* and *in vivo* studies it significantly blocked the tumor cell invasion and inhibited bone marrow colonization in $\alpha_v\beta_3$ integrin expressing cancer cells. It also exhibits multiple inhibitory effects on endothelial cells, cancer cells and osteoclasts [16]. But very limited pre-clinical study is done further evaluation of PSK 1404 is very vital to understand the αvβ3 integrin inhibitory mechanism in bone metastases therapy.

IH1062: IH1062 (3,5-dichlorophennylbiguanide) is an effective $\alpha_v\beta_3$ integrin inhibitor derived form 3, 4-dichlorophenylbiguanide. It specifically inhibits the binding of $\alpha_v\beta_3$ integrin to its vitronectin (ligand to $\alpha_v\beta_3$ integrin) and leads to cellular apoptosis. In M21 (human melanoma cell line) it induced anoikis, lead to decrease of Bcl-2/Bax ratio and survivin proteins, dephosphorylate Tyr925 in the carboxyl region of FAK. It also inhibited the pulmonary metastases in established melanoma pulmonary metastasis mouse model in dose dependent manner [59]. These *in vitro* and *in vivo* results established for IH1062 in human melanoma cells is promising development to treat and prevent tumor metastasis.

DisBa-01: DisBa-01 is a novel monomeric P-II SVMP-derived RGD disintegrin. It is derived from venom gland RNAs of Bothropsalternatus by recombinant DNA techniques. It interacts in a stable and specific manner with purified αvβ3 integrin, induced by bFGF in endothelial cells [60]. DisBa-01 inhibits angiogenesis in a dose dependent manner and by reducing the expression of VEGF and its receptors significantly. In HMEC cells at 10 nM and 100 nM concentrations of DisBa-01 showed the down regulated VEGFR1 and VEGFR2. In fibroblasts it contributed to reduce migration ability by inhibiting the MMP-2 activity. It also impaired the proliferation by αvβ3 and inhibits the adhesion of B16F10 and HMEC-1 to vitronectin. These *in vitro* reports demonstrate the anti-adhesive properties of DisBa-01. The ex vivo and *in vivo* studies demonstrate the anti-metastatic and protective effect of disintegrin [61]. All these results describe the essentiality to understand the molecular mechanism underlying that target integrin-mediated processes using novel anti-metastatic therapies.

S137 and S247: These are non-peptidic and β-amino acid compounds. The potency of the S137 is slightly lower than S247. Both these compounds inhibit the cell growth, motility, adhesion and enhance the apoptosis of tumor cells in dose dependent manner. *In vitro* results suggest that they actively inhibit ligand binding to αv integrin and induce apoptosis in HUVEC cells [62,63]. The continuous regime of S247 in an animal model significantly reduced the development of liver metastases with better survival.

17E6: 17E6 is a function blocking, non-RGD, allosteric inhibitor which contacts exclusively the propeller domain of αv integrin. 17E6 antibody behaves as an extracellular ligand and promotes the endocytosis of αvβ3 integrin by preferring integrin dependent-receptor mediated pathway. It alters the distribution of αv integrins on the cell surface and induces the relocalization of focal adhesion proteins [64]. It possesses anti-tumor, anti-adhesive, anti-metastasis activities and interacts specifically against the human and primate $\alpha_v\beta_3$ αvβ1 and $\alpha_v\beta_5$ integrins [65,66]. 17E6 significantly inhibited the adhesion of vitronectin and fibrinogen, ligands of αv integrins to cutaneous melanoma DX3 line [67]. A strong morphological change was induced in adhered M21 melanoma cells and blockade of tumor growth was observed in nude mice suggesting the anti-tumor activity of the compound [68]. In signalling cascade events 17E6 plays a vital role by promoting FAK phosphorylation, partially interrupting apoptotic signalling pathway that is activated by β-amyloid, activating FAK/paxillin/p130 CAS signalling pathway, inhibiting the tumor suppresser p53 protein expression, activating cell survival via PI3K/Akt signaling [69]. In the performed in vivo study significantly hindered the tumor growth in the positive $\alpha_v\beta_3$ xenografts that express the melanoma cells [70]. Study performed using infected macrophages reported a reduced HIV-1 Bal proviral DNA and also inhibited the HIV infection at an early stage of the viral cycle suggesting the interference of 17E6 for HIV replication in macrophages [71]. Currently this monoclonal antibody was in clinical trials for treating cancer.

ATN-161: ATN-161 is a five amino acid acetylated, amidated PHSCN peptide derived from the synergy region of human fibronectin PHSRN sequence [72]. The Arginine amino acid in the original sequence is replaced with cysteine residue. ATN-161 induces neovascularization in matrigel plug assays performed in nude mice and observed a dose dependent regulation of $\alpha_5\beta_1$ integrin in human microvascular endothelial cells [73]. These down regulation of $\alpha_5\beta_1$ integrin resulted in apoptosis through the suppression of the Akt activity [74]. PHSCN peptide sequence reduced the tumor growth in rats to much more extent than rats treated with HSPNC which was inactive (because tumor growth in rats treated with HSPNC increased rapidly in both treated and untreated) suggesting the anti-tumorigenic activity of the peptide [75]. In the murine colon cancer model it decreases the formation of liver metastases with enhanced survival, proposing the anti-metastatic activity [18]. It is also the first PHSRN synergy potent inhibitor sequence with anti-tumorigenic and anti-metastatic to be evaluated in clinical trials where it prevented progression of metastatic disease and recurrence for prolonged periods [76]. In preclinical and Phase-I trials using lewis lung carcinoma and HT 29 colon carcinoma model a U-shaped dose response was observed for ATN-161 peptide with rapid clearance from serum [77]. The therapy with ATN-161 administration in combination with tetrathiomolybdate and also with 5-flurouracil also suggested the ATN-161 as more anti-tumorigenic agent [18,78]. Few other analogues of ATN-161 like ATN-453, PHSCN-polylysine dendrimer (Ac-PHSCNGGK-MAP), PhScN (where Histidine and Cysteine were replaced with D-isomers), PHSC(S-OAc)N, PHSC(S-Me)N, PHSC(S-acm)N reported to be more potent in metastatic human prostate cancer cells [20]. The Phase-II clinical trials of this agent are proceeding to be extremely changeling because no maximum tolerated dose was achieved in former trials.

Resveratol: Resveratol (3, 4’, 5-trihydroxy-trans-stilbene) is natural polyphenolic antioxidant found in plants and fruits (mostly grapes) in Cis and trans stereoisomer forms, the trans isomer being significantly more potent than Cis isoform. It regulates the expression of various genes encoding to integrins that are involved in cellular process like apoptosis, metastasis, adhesion and angiogenesis [79,80]. The *in vitro* and *in vivo* studies showed the inhibitory ability of the Resveratol in chick embryo and murine melanoma B16 by inhibiting the adhesion by down regulation of cellular $\alpha_5\beta_1$ integrins [81]. A recent study reported that in the treatment with Res inhibited the adhesion of ovarian cancer cell to HPMCs, dose dependently [82]. The receptor sites on $\alpha_5\beta_1$ integrin for Res induces apoptosis that is p53-dependent via ERK $_{1/2}$ mediated pSer15 and also requires pool of inducible cyclogenase-2 [83]. However more clinical studies regarding the mechanism of action and how resveratol induces apoptosis are yet to be examined.

Conclusion

In recent years, great progress has been made towards integrin antagonists that target cancer. Their effectiveness in blocking tumour progression has been demonstrated in preclinical as well as clinical studies. At present there are multiple ongoing clinical trials on integrin antagonists agents and few other novel compounds like JSM6427 [84], β-lactam derivatives [6] and a Tenascin (TN)-C derived TNIIIA2 peptide [85] showed promising biological activity to target integrins but in depth investigations are necessary for these compounds in the malignancies that express high levels of integrins.

Acknowledgement

The authors acknowledges to Acharya Nagarjuna University, Guntur, Andhra Pradesh and Indian Institute of Technology Hyderabad, Telangana for the continuous support and encouragement.

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