Review

Monoclonal Antibodies in Oncology and their Effect on Arterial Stiffness – A Systematic Review

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ABSTRACT

Introduction: Malignancies are the second leading cause of death worldwide. Treatment Monoclonal Antibody (MAbs)-based treatment of cancer has been established as one of the most successful therapeutic strategies in the last 20 years; however, there is a growing concern about the effects of these agents on patients' cardiovascular profile.

Areas Covered: In this manuscript we summarize current evidence regarding MAb effects on arterial stiffness, which is an recognised biomarker of cardiovascular risk. For this purpose, we explored two bibliographic databases [PubMed, Scopus] and one full-text database (Google-Scholar) for all publications published on MAbs' effects on arterial stiffness until December 2019. Only few of the monoclonal antibody agents used in oncology have been investigated as per their effects on arterial properties and this limited evidence suggests that cancer therapy with monoclonal antibodies demonstrates either a temporary or long-term increase in arterial stiffness.

Discussion: It seems that by targeting 'checkpoints' in cancer genesis, anticancer MAbs also affects vascular properties causing endothelial dysfunction and arterial stiffness. Furthermore, several MAbs cause hypertension and may as a result increase pulse wave velocity. On the other hand, MAbs that target inflammatory cytokines seem to improve cardiovascular survival however, their effect on arterial stiffness is yet to be investigated. Further research is warranted in order to elucidate the biochemical pathways, clinical implications and potential reversibility of monoclonal antibody chemotherapy-induced vascular dysfunction.

1. INTRODUCTION

Malignancies are the second leading cause of death worldwide and are responsible for approximately 9.6 million deaths in 2018 [1]. Monoclonal Antibody (MAbs)-based treatment of cancer has been established as one of the most successful therapeutic strategies for both hematologic malignancies and solid tumors in the last 20 years. The agents that are currently used in oncology and their targets are summarized in Table 1.

Despite the advances that biological agents have brought in pharmacology and the significant improvement in cancer survival rate, there is a growing concern about the effects of these agents on patients' cardiovascular profile. Cardiotoxicity is already an established severe adverse reaction for MAbs, such as trastuzumab, bevacizumab, lapatinib, and sunitinib [2]. Data suggest that trastuzumab-induced cardiotoxicity is a result of HER2 receptors blockage, as these receptors are expressed on cardiac myocytes and play an important role during embryonic cardiac development [3]. However, little is known on what are the short- and long-term effects of Mab-based cancer treatment on patients' cardiovascular risk.

Aortic stiffness is an established vascular biomarker that independently predicts cardiovascular risk [4–6]. The concept behind the use of this biomarker, which has been endorsed by Scientific Societies [7,8], is that early vascular aging rather than chronological aging can offer better risk prediction. Even estimated Carotid Femoral Pulse Wave Velocity (cfPWV) predicts outcomes independent of the Framingham Risk Score and peripheral blood pressure as we recently shown in a secondary analysis of the systolic blood pressure intervention trial (SPRINT) [9].

The aim of this review article was to summarize current evidence regarding the effects of MAb on arterial stiffness.

2. METHODS

For purpose of this review, we explored one full-text database (Google-Scholar) and two bibliographic databases [PubMed, Scopus] using two methods: (1) searching for keywords using variations of "arterial stiffness", "aortic stiffness", "arterial elasticity", "arterial properties", "arteriosclerosis" and "PWV," and "monoclonal antibody therapy", "monoclonal antibody chemotherapy", "chemotherapy"; (2) searching for keywords using variations of specific chemotherapy Mab agents and variations of "arterial stiffness" as above. Our search included all publications published until the writing of this manuscript

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Table 1 | Summary of monoclonal antibody agents used in oncology, targeting antigen and cancer type

Monoclonal antibody agent (Mab agent)	Cancer	Target
Trastuzumab	Breast	HER2
Rituximab	NHL	CD20
Alemtuzumab	CLL	CD52
Cetuximab	Colorectal	EGFR
Panitunumab	Colorectal	EGFR
Pertuzumab	Breast	HER2
Necitumumab	Metastastic squamous NSCLC	EGFR
Dinutuximab	Pediatric higg risk neuroblastoma	GD2
Bevacizumab	Metastatic colorectal	VEGF-A
	HER2 positive breast cancer	
	Metastatic or recurrent NSCLC	
	Metastatic renal cancer	
	Metastatic, recurrent or persistent cervical cancer	
	Gliovlastoma	
	Recurrent epithelial ovarian, fallopian tube or primary peritoneal cancer	
Ramucirumab	Advanced or metastatic gastric or gastroesophageal junction cancer, metastatic colorectal, mestatic NSCLC	VEGFR-2
Olaratumab	Soft tissue sarcoma	PDGFR-a
Ipilimumab	Unresectable or metastatic melanoma, cutaneous melanoma	CTLA-4
Nivolumab	Unresectable or metastatic melanoma	PD-1
	Squamous NSCLC	
	Metastatic NSCLC	
	Advanced renal cell cancer	
	Recurrent or metastatic HNSCC	

NHL, non-hodgkin lymphoma; CLL, chronic lymphocytic leukemia; NSCLC, non-small cell lung carcinoma; HNSCC, head and neck squamous cell carcinoma; PDGFR-a, platelet-derived growth factor receptor A; HER, human epidermal growth factor receptor.

(December 2019) in this subject. As described in detail in this manuscript, only few of the monoclonal antibody agents used in oncology have been investigated as per their effects on arterial properties.

3. EFFECT OF MAbs ON ARTERIAL STIFFNESS

3.1. Trastuzumab

Trastuzumab (Herceptin) is a humanized monoclonal antibody of the IgG1 subclass that blocks the Epidermal Growth Factor Receptor (EGFR), specifically the HER2 receptor. HER are cell membrane-bound glycoproteins that form four receptors, HER1–4 [10,11]. These receptors consist of three regions, the extracellular ligand binding region, an intracellular region with tyrosine kinase activity and a region that spans the cell membrane in order to anchor the receptor to the cell membrane. Ligand binding to the extracellular region of the receptor activates tyrosine kinase and triggers a cascade of complex cell functions such as angiogenesis apoptosis adhesion and motility. Most HER receptors are activated by binding a mitogen to their extracellular region. However, there is no known ligand for HER2 receptors. Overexpressed HER2 receptor (which is found in 20–30% of early stage breast cancers) sends signals without

mitogen binding and this promotes invasion survival and angiogenesis of tumoral cells [12]. Trastuzumab binds to the extracellular region of HER2 receptor and causes cell arrest during the early stages of cell division (G1 phase). It also downregulates HER2 receptor. As mentioned earlier in this manuscript, one of the significant complications of trastuzumab is cardiac dysfunction, which is seen in 2–7% of cases [13], and hypertension; therefore regular clinical evaluation and cardiac screening with echocardiography is mandatory for patients under treatment. Only a few studies have investigated the effects of trastuzumab in arterial stiffness.

The effect of anthracycline and trastuzumab therapy on arterial stiffness was explored in a study published in 2018. In this study the investigators enrolled 45 participants with HER2-positive early breast cancer who received therapy and had follow-up for 6 months without recurrence. Control group 30 adult volunteers, without clinical or documented evidence of cardiovascular or cardiorespiratory diseases who were admitted to internal medicine outpatient clinic. Thirty four patients received anthracycline + taxane + trastuzumab therapy, 10 patients received anthracycline + trastuzumab and one patient received trastuzumab + taxane therapy. Thirty four patients received adjuvant hormonal therapy either with tamoxifen or aromatase inhibitors. Arterial stiffness assessment was assessed with brachial cuff oscillometry, by measuring PWV and augmentation Index (AIx). Mean PWV was considerably higher in patient group (7.3 ± 1.2 vs 5.8 ± 1.4 m/s in the control group) ($p < 0.01$). PWV changes were related to the type of hormonal treatment ($p < 0.01$) but were not affected by the operation type ($p = 0.5$) and existence of radiation treatment ($p = 0.07$). Patients taking different chemotherapy regimens did not demonstrate differences in mean PWV. Patients receiving tamoxifen had considerably lower PWV compared with patients taking aromatase inhibitors ($p < 0.01$). This study demonstrated that breast cancer patients, who received anthracycline- and trastuzumab-based therapy, have an increased aortic stiffness and are at higher risk for future cardiovascular events [14].

In a recent study published in 2019, 43 breast cancer patients who received neoadjuvant therapy with anthracyclines along with transtuzumab, followed by surgery and radiotherapy were enrolled. Control group consisted of 20 healthy women. cfPWV, Shoulder Ankle PWV (saPWV) and Carotid Intima Media Thickness (CIMT) were used as arterial stiffness indices, at baseline and during every anticancer therapy session. Breast cancer patients demonstrated higher saPWV and cfPWV levels at baseline ($p < 0.05$). Furthermore, during chemotherapy, there was a temporary decrease in cfPWV and saPWV levels along with decrease in blood pressure and an increase heart rate. Interestingly, systolic blood pressure and central blood pressure had been restored by the end of the follow-up period. Moreover, the investigators demonstrated that radiation therapy along with age ≥48 years old were both risk factors for CIMT increase and atherosclerosis progression ($p < 0.05$) [15] (Atherosclerosis progression was determined as new stenosis ≥15% or as an increase of pre-existing stenosis ≥5% and CIMT increase ≥0.1 mm).

In a prospective study published in 2015, 27 breast cancer patients and 12 healthy volunteers, underwent cardiac MRI at baseline, 1, 4 and 14 months post-therapy. Patient group received anthracycline and/or trastuzumab containing chemotherapy regimens (14 patients received anthracycline, 12 patients received trastuzumab, one patient received combination therapy). Patients were evaluated with left ventricular (LV) function assessment, measurement

of aortic PWV using velocity encoded imaging and distensibility assessment at Ascending Aorta (AA) and proximal descending aorta (which was measured using the cine image, the aortic lumen was magnified 400–800% and manually traced to determine the maximum and minimum luminal area). The investigators demonstrated that adverse aortic remodelling occurs early (within 4 months) after commencement of chemotherapy. At 4 months CMR-PWV increased acutely, $p = 0.002$ (4 months), then decreased by 14 months ($p < 0.001$), while AA distensibility decreased 1 ($p = 0.001$) and 4 months ($p < 0.001$) of commencing therapy. At the 14 month follow-up, partial decrease was noted in PWV, yet aortic distensibility at the AA failed to demonstrate a significant return to normal. Cancer patients demonstrated statistically significant LV functional changes, from baseline (ejection fraction (EF) 72 ± 5) to 4 months (EF 66 ± 7, $p = 0.001$). These changes persisted at 14 months (EF 67 ± 7, $p = 0.001$). Furthermore, patients showed greater decline in aortic distensiblity in the anthracycline group rather than the trastuzumab group. However it should be noted in this study that trastuzumab group had completed their therapy 1 month prior to 14th month follow up while anthracycline group had completed their therapy 6 months prior to 14th month follow up. Long-term follow up of these patients may elucidate whether trastuzumab on its own causes limited effects, or with time, it causes similar changes in aortic stiffness as seen with anthracylines [16].

Conclusively, although there are only a few small population studies that have investigated trastuzumab's effects on arterial stiffness, the results seem to support that arterial stiffness increases in cancer patients receiving therapy with trastuzumab.

3.2. Panitumumab

Panitumumab is a human monoclonal antibody that binds to the human EGFR. EGFR is a transmembrane glycoprotein of the subfamily of type I receptor tyrosine kinases. When normal ligands bind to EGFR, a series of intracellular proteins are activated. These proteins control the transcription of genes involved with cellular growth and survival, proliferation, and motility. Overexpression of EGFR is identified in many human cancers, including those of the colon and rectum. Panitumumab binds selectively to EGFR on both normal and tumor cells, and inhibits the ligands for EGFR. Nonclinical studies have demonstrated that EGFR binding by panitumumab prevents autophosphorylation and activation of receptor-associated kinases, resulting in initiation of apoptosis and inhibition of cell growth [17].

In 2018, our team published a prospective study that assessed 171 cancer patients before and after completion of chemotherapy. cfPWV and crPWV as well as AIx were used to evaluate arterial stiffness. Among these patients, 93 patients had metastatic colorectal cancer and received therapy with panitumumab–oxaliplatin-based chemotherapy ($n = 44$), panitumumab–irinotecan-based chemotherapy ($n = 28$), and panitumumab–capecitabine-based chemotherapy ($n = 21$) for six to eight cycles. A significant increase was demonstrated in AIx, cfPWV, crPWV (17.2% vs 21.8%, $p < 0.001$; 7.7 vs 8.6 m/s, $p < 0.001$; 7.6 vs 8.4 m/s, $p < 0.001$; respectively) in this subgroup, indicating a deterioration of arterial elastic properties in patients receiving panitumumab adjuvant chemotherapy [18].

3.3. Rituximab

Rituximab is a humanized monoclonal antibody, binds to CD20 antigen, inducing complement- or antibody-mediated cytolysis. CD20 is a membrane-embedded surface molecule, which plays a role in the development and differentiation of B-cells into plasma cells [19]. The biological function and natural ligands of CD20 are currently unknown, while *in vitro* studies suggest that they work as a store operated Ca^{++} channel [20]. Rituximab is most commonly used for the treatment of autoimmune diseases such as rheumatoid arthritis, Wegener granulomatosis, microscopic polyangiitis and pemphigus vulgaris. Only recently it has been approved for the treatment of Non-Hodgkin Lymphoma as part of the Rituximab-cyclophosphamide, Doxorubicin, Vincristine, and Prednisolone (R-CHOP) regimen.

Rituximab mechanism of action includes complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity. There are also indirect actions, which include apoptosis, structural changes, and sensitization of cancer cells to chemotherapy. However, not all patients respond equally to rituximab, and *in vitro* studies have identified a possible mechanism of resistance involving the anti-complement inhibitors CD55 and CD59 [21].

There is only one small study published in 2018, in which rituximab adjuvant chemotherapy was associated with changes in arterial properties. Specifically, 13 patients with B-cell malignant lymphoma who were treated with R-CHOP chemotherapy were assessed for arteriosclerosis. Arteriosclerosis was assessed with Cardio-ankle Vascular Index (CAVI) and carotid artery ultrasonography during each chemotherapy cycle. In nine patients there was demonstrated progression of arteriosclerosis with new plaque formation or progression of intima-media thickness by carotid artery ultrasonography. Plaque score after completing the therapy was elevated significantly from 6.4 ± 4.33 to 6.8 ± 4.65 ($p = 0.0313$). Some patients demonstrated elevation of CAVI index during the progression of treatment. However, there was no substantial rise of the index during the treatment. These data indicate that R-CHOP therapy may progress the arteriosclerosis and further research is warranted to prove this theory [22].

There are also several small studies with controversial findings, showing either an increase or no change in arterial stiffness in patients with rheumatoid arthritis receiving rituximab [23,24]; however, we do not analyse these studies in this manuscript as our main focus in monoclonal antibodies effects in arterial properties when used as anticancer agents.

3.4. Bevazicumab

Bevazicumab is a chimeric, monoclonal antibody that binds to the biologically active form of Vascular Endothelial Growth Factor A (VEGF-A), a potent angiogenic cytokine that induces mitosis and also regulates the permeability of endothelial cells, and prevents interaction with its endothelial cell receptors. Bevazicumab is Food and Drug Administration (FDA) approved for the treatment of many advanced solid tumors, including colorectal cancer, Non-small-cell Lung Cancer (NSCLC), breast cancer, glioblastoma, renal cell cancer, ovarian cancer, and cervical cancer [25–27].

In a study designed to assess capillary density changes before and after treatment with bevacizumab, PWV and Flow – Mediated Dilation (FMD) were also assessed as part of the additional measurements. Fourteen patients receiving bevacizumab monotherapy or combination therapy for breast or colorectal cancer were eligible for participation. BP measurements and vascular assessments were carried out at baseline (<7 days before first bevacizumab administration), after 6 weeks (before third 3-weekly bevacizumab administration) and >3 months after last bevacizumab administration. Only seven patients carried out follow up for all three measurements. The results showed that mean PWV increased after 6 weeks of treatment ($p = 0.027$) and decreased after bevacizumab discontinuation. FMD and BP remained unchained while capillary density significantly decreased after 6 weeks of bevacizumab treatment and was reversible after discontinuation of bevacizumab ($p = 0.00001$ using a general linear model repeated measures test) [28].

The key studies that investigated the association between monoclonal antibody anticancer agents and arterial stiffness are summarized in Table 2.

4. DISCUSSION

We summarize the current knowledge regarding the effect of monoclonal antibody agents on arterial properties when used in oncology. Limited evidence at this stage reveals that patients with malignancies receiving therapy with monoclonal antibodies demonstrate either a temporary or long-term increase in arterial stiffness. While intense research is needed to clarify the mechanisms and the reversibility of vascular toxicity induced by chemotherapeutic agents, integration of this biomarker in the evaluation of cancer patients is promising.

4.1. Clinical Implications

Cardioprotection along with vascular protection are emerging challenges in patients with malignancies who receive chemotherapy. The last 20 years, treatment based on Monoclonal antibodies has been emerged as a revolutionary therapeutic strategy, regarding solid tumors and hematologic malignancies, while there is already extensive literature demonstrating the possible pathways through the cardiotoxic effects of certain monoclonal antibodies effects on the ejection fraction of the left ventricular. However, little is known about possible vascular toxicity and its effects on cardiovascular morbidity and mortality. Furthermore, while there is a direct effect of MAbs on the myocardium, a contribution of arterial stiffening on left ventricular dysfunction is plausible. Given its predictive role [4,8], arterial stiffness could prove a useful clinical tool to identify early signs of toxicity and to serve as to be a prognostic marker for cancer patients that receive chemotherapy.

4.2. Possible Mechanisms

The catastrophic characteristics of cancer cells are the increased mitosis, the decreased apoptosis and the ability to evade the immune system. Accordingly, monoclonal antibodies that are used in oncology are designed to target 'checkpoints' in the various cell function pathways that seem to induce these mechanisms. Such 'checkpoints' are (1) the cytotoxic T lymphocyte associated antigen-4, (2) the Programmed cell Death protein (PD-1) and the PD-1 Ligand (PD-L1), (3) the endothelial growth factor (VEGF) and platelet-derived growth factor, (4) the epidermal growth factor receptor (HER), (5) the CD20 B-cell surface molecule and (6) the CD52 mature B-cell surface molecule. Anti-cancer monoclonal antibodies target either malfunctioning

Table 2 | Key studies that investigated the association between arterial stiffness and treatment with monoclonal antibody anticancer agents

Therapy associated with arterial stiffness	Number of patients	Effects on arterial stiffness	References
Trastuzumab + anthracycline + taxane Trastuzumab + taxane Trastuzumab + anthracycline (34 patients received adjuvant therapy with taxane or aromatase inhibitors)	45	↑Baseline mean PWV in patient group ↑Mean PWV after treatment (especially patients that received aromatase inhibitors)	[15]
Anthracycline + trastuzumab	43	↑Baseline mean PWV in patient group Temporary ↓ cfPWV along with SBP during chemotherapy	[16]
Anthracycline + trastuzumab Trastuzumab	27	↑CMR-PWV at 4 months ↓Aortic distensibility especially in anthracycline group	[17]
Panitunumab + oxaliplatin Panitunumab + irinotecan Panitumumab + capecitabine	99	↑AIx, ↑cfPWV ↑crPWV	[19]
Rituximab (R-CHOP therapy)	13	↑CAVI ↑Carotid intima-media thickness	[23]
Bevacizumab	14	↑Mean PWV during treatment (which was restored after discontinuation of treatment) SBP and FMD unchanged ↓Arterial density (reversible after discontinuation of treatment)	[29]

PWV, pulse wave velocity; CfPWV, carotid femoral pulse wave velocity; SBP, systolic blood pressure; FMD, flow mediated dilation; CAVI, cardio-ankle vascular index; AIx, augmentation index; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisolone.

mechanisms during cancer formation, or normal cell function mechanisms in order to reduce blood supply and cell mitosis and induce cell apoptosis. Whether by targeting these 'checkpoints' in cancer genesis, anticancer MAbs could also affect the vascular properties is a matter of investigation and at this stage mechanisms can only be speculated.

Arterial stiffness may be affected through pressure-dependent mechanisms or through deterioration of intrinsic vascular properties and different agents may affect arterial stiffness through different pathways. Bevazicumab, ramucirumab and rituximab are known to cause hypertension [29]. The incidence of hypertension reported in different trials for bevazicumab range from 4% to 35% [26,30].

In the case of bevazicumab, inhibition of the VEGF signaling pathway seems to play a role. Specifically it allows Vascular Smooth Muscle Cell (VSMC) proliferation and affects expression of endothelial nitric oxide synthase. Furthermore, trastuzumab interferes with HER4 and HER2 survival pathways leading to over-production of reactive oxygen species and reduction of NO, which eventually causes endothelial dysfunction [31]. In addition, apoptotic VSMC may act as nucleation sites of calcification [32,33].

The role of inflammation is intriguing. Inflammation increases arterial stiffness [34,35]. However, there is robust evidence that monoclonal antibodies that target inflammation pathways reduce cardiovascular events. Specifically, the canakinumab anti-inflammatory thrombosis outcomes study (CANTOS) trial showed that canakinumab, an IL-β inhibitor, reduces the risk for cardiovascular events and cardiovascular death when lowering high sensitivity CRP levels [36]. Interestingly canakinumab may also act as an anticancer agent. Accordingly, whether targeting inflammatory pathways with MAbs may improve rather than deteriorate arterial elastic properties warrants further investigation.

For the proper interpretation of available evidence, it should be noted that in most cases monoclonal antibodies were used as adjuvant treatment and not as monotherapy, therefore additional studies are required in order to elucidate the effects of monoclonal antibodies on arterial stiffness independently of concurrent treatment that patients might be receiving. Furthermore, cancer is a condition that causes endothelial dysfunction and possibly plays by itself a role in arterial stiffness deterioration [18,37].

5. CONCLUSION

Little current evidence suggests that cancer therapy with MAbs demonstrates either a temporary or long-term increase in arterial stiffness. Given its prognostic role, arterial stiffness is an appealing biomarker to identify and follow the progression of arteriosclerosis in cancer patients receiving such therapy. Additional research is needed to shed light on the mechanisms and the reversibility of vascular toxicity induced by monoclonal antibodies chemotherapy in order to modify the progressive development of long-term vascular complications in cancer survivors. Whether MAbs that target inflammatory cytokines and improve cardiovascular survival may also improve arterial function should be investigated.

CONFLICTS OF INTEREST

The authors declare they have no conflicts of interest.

AUTHORS' CONTRIBUTION

All authors contributed to the design and implementation of the research, to the analysis of the findings and to the writing of the manuscript.

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