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Immunotherapy and malignant pleural mesothelioma

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Abstract

Malignant pleural mesothelioma is an aggressive type of cancer in which cancerous cells are found in the lining of the abdomen or chest that occurs due to asbestos exposure in the mesothelium. According to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER), there are around 2,500-3,000 new cases per year of malignant mesothelioma observed in the United States, mainly in elderly men. It occurs mainly in males as compared to females and the chances of risk increases with the age, but this cancer can emerge in both males and females at any age. It forms due to the neoplastic transformation of mesothelial cells and it is associated with the genetic changes and other phenotypic changes, which change cell-matrix and cell-cell interaction and regulation of cell death and cell proliferation. The targeted treatment is focused at a precise molecular target, which is very close to a hallmark of cancer. These targets should be assessable with a specific biomarkers and the measurement of these targets should be associated with different clinical outcome when these targeted treatment is administered. Malignant pleural mesothelioma is characterized via a composite genomic modification, through the defeat of chromosomal loci encoding for different tumor suppressor genes such as TP53, NF2, p14, and p16. These types of genomic changes are very ordinary but, unluckily, these are not appropriate to be targeted through the available drugs. Over the last decade, various targeted agents have been explored in malignant pleural mesothelioma, and in some of them; the preclinical rationale was very weak for exploring clinical activity. There are some drugs which consistently revealed their activity in malignant pleural mesothelioma, but these drugs are under clinical trials.

Abbreviations: ADCC: Antibody Dependent Cellular Cytotoxicity; ADC: Antibody-Drug Conjugate; CML: Chronic Myeloid Leukemia; CTA: Cancer Testis Antigens; CTL: Cytotoxic T-Lymphocyte; CTLA4: Cytotoxic T-Lymphocyte-Associated Protein-4; FAK: Focal Adhesion Kinase; G-CSF: Granulocyte Colony Stimulating Factor; GM-CSF: Granulocyte-Macrophage Colony Stimulating Factor; HCF: Hepatocyte Growth Factor; SF: Scatter Factor; IL: Interleukin; M-CSF: Macrophage Colony Stimulating Factor; MAPK: Mitogen-Activated Protein Kinase Kinase; MVA: Modified Vaccinia Ankara; NF: Nuclear Factor; PDGF: Platelet Derived Growth Factor; TAA: Tumor Associated Antigens; TGF-B: Transforming Growth Factor Beta; TSG Tumor Suppressor Gene; VEGF: Vascular Epidermal Growth Factor; WT-1: Wilms Tumor 1.

Introduction

Malignant pleural mesothelioma is a rare and aggressive type of cancer in which cancerous cells are found in the lining of the abdomen or chest. The contact to airborne asbestos particles enhances one's risk of rising malignant mesothelioma. The incidence of malignant pleural mesothelioma has risen since the mid-20th century worldwide [1]. Malignant pleural mesothelioma is one of the rarest causes of death worldwide [2]. According to the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER), there are around 2,500-3,000 new cases per year of malignant mesothelioma observed in the United States, mainly in elderly men. WHO recorded 4.9 per million age-adjusted mortality rates between 1994 and 2008, a mean age of 70 years at death and there is a ratio of 3.6:1 between male and female [3]. It includes different types of histo pathologic and genetic characteristic [2]. In the year 2004, 15 per 1,000,000 incidences may have pointed in the United States.

Malignant pleural mesothelioma occurs mainly in males as compared to females and the chances of risk increases with the age, but this cancer can emerge in both males and females at any age. About one fifth to one third of all malignant pleural mesothelioma are peritoneal [4] and its incidence rate is 0.2–2.0 per million per year in female and 0.5-3.0 per million per year in males [3,4]. Median survival has been reported as 16 months for patients with malignant pleural disease and 5 months for patients with extensive disease. Etiological factors that contribute to the progression of the disease are exposure to asbestos and smoking [5,6].

Etiology/predisposing factors

Malignant pleural mesothelioma is a cancer which occurs due to asbestos exposure in the mesothelium. There are some other risk factors of malignant pleural mesothelioma, which includes smoking, exposure to dusts, radiation and chemicals such as carbon nanotubes, zeolite, radiation, erionite exposure, and simian virus 40 [6]. Age, histology, performance status, and stage are found to be as the most important prognostic factors [1].

Pathophysiology/molecular basis

Malignant pleural mesothelioma forms due to the neoplastic transformation of mesothelial cells and it is associated with the genetic

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Key words: *malignant pleural mesothelioma, mesothelial cells, sarcomatoid, epithelioid, and biphasic ,tumor suppressor gene (tsg), β-catenin protein , platelet derived growth factor (pdgf) , vascular epidermal growth factor (vegf) and hepatocyte growth factor/scatter factor (hgf/sf), granulocyte colony stimulating factor (g-csf), granulocyte-macrophage colony stimulating factor (gm-csf), interleukin (il)-6 or 8, macrophage colony stimulating factor (m-csf), focal adhesion kinase (fak), platelet-derived growth factor receptor (pdgf) and cytokine tumor necrosis factor alpha (tnf-alpha)*

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changes and other phenotypic changes, which change cell-matrix and cell-cell interaction and regulation of cell death and cell proliferation. Usually, malignant pleural mesothelioma is categorized into three histological subtypes and that is sarcomatoid, epithelioid, and biphasic [7]. Currently, such data published on β-catenin protein have shown that this β-catenin protein may translocate to the nucleus and act as a co-activator of different transcription factors, such as LEF/TCF. Different molecular changes in tumor suppressor gene (TSG) are mentioned in Table-1 that is involve in the occurrence of the malignant pleural mesothelioma (Table 1) [8].

The platelet derived growth factor (PDGF) acts as a regulatory factor in malignant pleural mesothelioma cell proliferation, which performed either directly or through the hyaluronan/CD44 pathway. Even all normal pleural mesothelial cells express lower levels of PDGF-A mRNA transcripts and other mesothelial cell show equally higher levels of both PDGF-A and PDGF-B chains. Both PDGF-A and PDGF-B receptors are differentially expressed, correspondingly. Insulin-like growth factor-1 (IGF-1) is also involved in the regulation of mesothelioma cell development. Malignant pleural mesothelioma cell produces mRNA transcripts for IGF-1, IGF-binding protein 1 or 3, and the IGF-1 receptor. In some cases of mesothelioma, there are two growth factors: vascular epidermal growth factor (VEGF) and hepatocyte growth factor/scatter factor (HGF/SF), which may be engaged in an autocrine loop of proliferation, because mesothelioma cells indicated both these factors and their relevant receptors. There are different cytokines such as granulocyte colony stimulating factor (G-CSF), granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin (IL)-6 or 8, macrophage colony stimulating factor (M-CSF), and transforming growth factor beta (TGF-b) which are also expressed through human mesothelioma cells but their appropriate roles are yet to be determined in the pathogenesis of tumors. The transforming growth factor beta (TGF-b) may potentiate the development of mesothelioma cells, and antisense oligodeoxy nucleotides to other isoforms of TGF-b emerge to inhibit the development of tumors [12,13].

Note: [a]Different methods are used in each and every study which is based on specificity/sensitivity rates, and mutations like homozygous deletion in FISH are different. Though, each study used different analytical techniques like single-strand conformation polymorphism analysis, sanger sequencing, PCR, and reverse transcriptase-PCR, western blot analysis, comparative genomic hybridization analysis, and next-generation sequencing.

[b]HD, homozygous deletion.

[c]Data are presented as % (number of positive/total cases).

[d]COSMIC Mutant Export version 64

[e]Cell line data.

Hallmarks of cancer comprise modulating factors and biological capabilities

The targeted treatment is focused at a precise molecular target, which is very close to a hallmark of cancer. These targets should be assessable with a specific biomarkers and the measurement of these targets should be associated with different clinical outcome when these targeted treatment is administered. Recently, clinical guidelines don't suggest any biological or targeted therapy in malignant pleural mesothelioma. The development of cancer in humans is a very complex process with different steps. There are different factors which are involved in the growth of cancer and have been suggested as an important part to raise options for new treatment modalities. Hallmarks of cancer comprises of modulating factors and biological capabilities to produce an environment in which cancer cells can flourish (Figure 1) (Table 2) (Table 3) [15].

Immunotherapy

Kinase Inhibitors

Non-FDA Approved Kinase Inhibitors (Table 4)

Monoclonal Antibody Drugs (MABs)

Non-FDA Approved MAB Drugs (Table 5)

Proteasome Inhibitors

Non-FDA Approved Proteasome Inhibitors (Table 6)

Vaccines

Non-FDA Approved Vaccines (Table 7)

Cytokine treatment

NGR-hTNF: A cytokine-peptide conjugate composed of the cytokine tumor necrosis factor alpha (TNF-alpha) chemically linked to the peptide CNGRC. The peptide moiety CNGRC, a ligand for the membrane-bound metalloprotease CD13, binds to endothelial cells of the angiogenic vasculature that express CD13 (also known as aminopeptidase N); subsequently, the TNF-alpha moiety induces apoptosis in endothelial cells expressing CD13, thereby inhibiting tumor-associated angiogenesis (Table 8).

Gene therapy

TargomiRs: A nanoparticle-based formulation composed of a microRNA 16 (miR-16) mimic, a double-stranded, 23 base pair, synthetic RNA molecule, encapsulated in nonliving bacterial minicells and coated with anti-epidermal growth factor receptor (EGFR) antibodies, with potential antineoplastic activity. Upon intravenous administration and subsequent transfection, nanocell-encapsulated miR-16-based microRNA mimic targets EGFR-expressing tumor cells and facilitates

Table 1. Molecular changes in tumor suppressor gene (TSG) [9-11]

Molecular changes	Cellular perturbation	Potential etiological factor
TP53: Inactivation. a) Low rate of point mutation. b) Binding to viral proteins	Cell cycle control: inactivation of checkpoints controlling apoptosis and cell cycle progression after DNA damage.	a) Asbestos: low rate of point mutations in the murine homologue Trp53 is establishing in mesothelioma cells from asbestos-exposed mice. Loss of heterozygosity in mesothelioma cells from mice, homozygous at the Trp53 locus, exposed to asbestos fibers. b) SV40: binding to large T antigen in human mesothelioma.
NF2: frequent inactivation.	Destabilization of adherens junctions. Loss of negative control of cell proliferation.	Asbestos: recurrent loss of heterozygosity of N*f*2 in mesothelioma cells from mice, homozygous for N*f*2, exposed to asbestos fibers.
P16/CDKN2A and P15/CDKN2B: frequent inactivation, mainly by deletion.	Cell cycle: loss of control of cell proliferation at the G1-S transition.	Asbestos: recurrent inactivation of the murine homologue p16/Cdkn2a is detected in mesothelioma cells from asbestos-exposed mice. P19/Arf is also inactivated.

Table 2. Alteration in TSG in malignant mesothelioma [14]

Gene	Epithelioid	Sarcomatoid	Biphasic	Type of mutation	Not specified	Method	Reference
NF2	50% (13/26)	—	22% (4/18)	Truncation form	—	Seq	Thurneysen et al.
	33% (10/30)	40% (2/5)	43% (3/7)	HD	—	FISH	Takeda et al.
	—	—	—	Mutation including Hde	56% (14/25)	Seq	Cheng et al.
	—	—	—	Mutation including Hde	50% (10/20)	Seq	Murakami et al.
	—	—	0% (0/1)	Mutation	31% (8/26)	Seq	COSMIC
	—	—	—	Mutation (or heterozygous D)	21% (53%) [11(28)/53]	Seq	Bott et al.
CDKN2A (p16INK4a/p14ARF)	67% (20/30)c	100% (3/3)	100% (6/6)	HDb	—	Seq	Bott et al
	69% (49/71)	100% (5/5)	84% (16/19)	HD	—	FISH	Illei et al.
	56% (10/18)	100% (22/22)	88% (7/8)	HD	—	FISH	Wu et al.
	77% (23/30)	100% (5/5)	100% (7/7)	HD	—	FISH	Takeda et al.
	—	—	—	HD	67% (35/52)	FISH	Chiosea et al.
	—	—	—	HD (or heterozygous D)	49% (42%) [16(14)/33]	FISH	Onofre et al
	—	—	—	HD (or heterozygous D)	80% (20%) [12(3)/15]	FISH	Matsumoto et al.
	42% (35/83)	81% (22/27)	44% (17/39)	Mutation	57% (59/104)	Seq	COSMICd
BAP1	21% (8/38)	0% (0/5)	40% (4/10)	Mutation	18% (12/68)	Seq	Bott et al.
	—	—	—	Mutatione	24% (6/25)	Seq	Bott et al.
	81% (13/16)	0% (0/2)	20% (1/5)	Mutation	—	Seq	Yoshikawa et al.
	38% (26/68)	0% (0/7)	29% (6/21)	Mutation	20% (19/93)	Seq	COSMIC

Table 3. Hallmarks of cancer comprises modulating factors and biological capabilities [15]

Characteristic of cancer	Drug	Target	MOA	Clinical trial
Activating invasion & metastasis	Tivantinib	Mesothelin	TKI c-MET	Phase I-II + cisplatin / pemetrexed
	Amatuximab, SS1P	Mesothelin	Inhibitors of HGF/c-MET	Single arm phase II first line + cisplatin / pemetrexed
Avoiding immune destruction	Tremelimumab	CTL4	Immune activating anti-CTL4 mAb	Single arm phase II
	Lambrolizumab	PDL1	Anti-PDL1	-----
	Nivolumab	PD1	Anti-PD1	-----
Evading growth suppressors	-----	RB1, TP53	Cyclin-dependent kinase inhibitors	-----
Enabling replicative immortality	-----	-----	Telomerase inhibitors	-----
Inducing angiogenesis	Cediranib	VEGFR	Inhibitors of VEGF signaling	Single arm phase II first line + cisplatin / pemetrexed
Sustained proliferative signaling	Gefitinib, Erlotinib	EGFR	EGFR inhibitors	Single arm phase II first line
	Cetuximab	EGFR	MAb against EGFR	Single arm phase II first line + platinum / pemetrexed
	Imatinib	PDGFR	MAb against PDGFR	Single arm phase I first line + platinum / pemetrexed
	Dasatinib	PDGFR	MAb against PDGFR	Single arm phase II first line + gemcitabine
	Cixutumumab	IGFR	MAb against IGFR	Single arm phase II in pretreated pts
	Sorafenib, Sunitinib	Multiple growth factors	RTK	Single arm phase II in pretreated pts

Table 4. Non-FDA approved kinase inhibitor drugs [17-26]

Drug	Clinical trial identifier number	Phase	Study design	Target
Vandetanib	NCT00597116	Phase II	Randomized, Open Label, Efficacy Study	VEGFR2, EGFR
Imatinibmesylate	NCT02303899	Phase II	Efficacy Study, Open Label	Bcr-Abl, PDGFR
Defactinib	NCT01870609	Phase II	Randomized, Efficacy Study, Double blind	FAK
Tivantinib	NCT01861301	Phase II	Open Label, Efficacy Study	Mesothelin
Gefitinib	NCT00787410	Phase II	Non- Randomized, Open Label, Safety/Efficacy Study	EGFR
Erlotinib	NCT00039182	Phase II	Open Label, Safety/Efficacy Study	EGFR
Dasatinib	NCT00652574	Phase I	Open Label, Safety/Efficacy Study	BCR-ABL kinase
Axitinib	NCT01211275	Phase I, II	Randomized, Open Label, Safety/Efficacy Study	VEGF
Alisertib	NCT02293005	Phase II	Open Label, Safety/Efficacy Study	Aurora A kinase
Trametinib	NCT01938443	Phase I	Randomized, Open Label, Safety Study	MEK 1 and 2

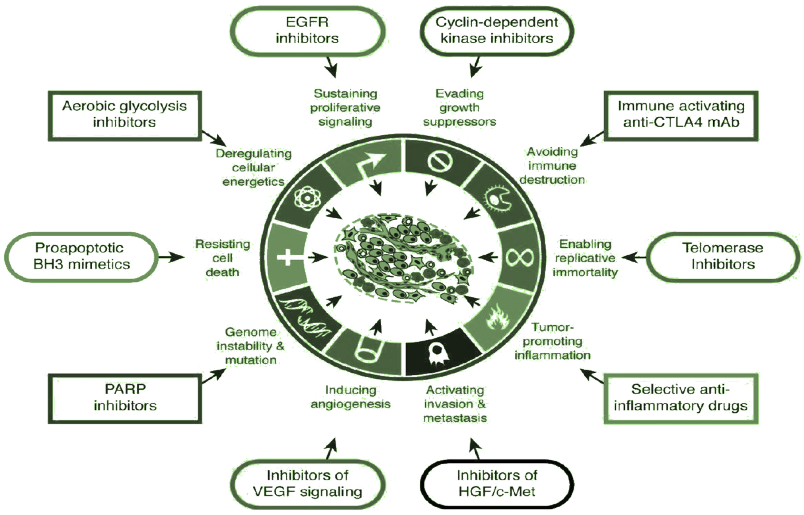

Figure 1. Hallmark of cancer with their targets [16]

Table 5. Non-FDA approved MAB drugs [27-31]

Drug	Clinical trial identifier number	Phase	Study design	Target
Cetuximab	NCT00996567	Phase II	Non-Randomized, Open Label, Efficacy Study	EGFR
Bevacizumab	NCT00407459	Phase II	Non-Randomized, Open Label, Safety/Efficacy Study	VEGF
Tremelimumab	NCT01655888	Phase II	Safety/Efficacy Study, Open Label	CTLA4
Amatuximab	NCT02357147	Phase II	Randomized, Double Blind, Safety/Efficacy Study	ADCC
BMS-986148	NCT02341625	Phase I, II	Non-Randomized, Open Label, Safety/Efficacy Study	Cancer cells

Table 6. Non-FDA approved proteasome inhibitor drugs [32]

Drug	Clinical trial identifier number	Phase	Study design	Target
Bortezomib	NCT00513877	Phase II	Non-Randomized, Open Label	NF-kaapa B, Proteasome inhibitor

Table 7. Non-FDA approved vaccines [33-36]

Vaccines	Clinical trial identifier number	Phase	Study design	Target
WT-1 analogue peptide vaccine	NCT01890980	Phase II	Randomized, Double Blind, Safety/Efficacy Study	CTL
TroVax	NCT01569919	Phase II	Open Label, Safety/Efficacy Study	Cancer cells
H1299 Lysate Vaccine	NCT02054104	Phase I, II	Randomized, Open Label, Efficacy Study	CTL
K562	NCT01143545	Phase I	Safety Study, Open Label	Cancer cells

Table 8. Non-FDA cytokine drugs [37]

Drug	Clinical trial identifier number	Phase	Study design	Target
NGR-hTNF	NCT01358084	Phase II	Randomized, Double Blind, Safety/Efficacy Study	CD13

Table 9. Non-FDA gene therapy [38]

Drug	Clinical trial identifier number	Phase	Study design	Target
TargomiRs	NCT02369198	Phase I	Open Label, Safety/Efficacy Study	EGFR

the restoration of expression of the miR-16 family. This leads to the downregulation of the expression of tumor-promoting genes and the inhibition of tumor cell growth. In addition, restoration of miR-16 expression sensitizes the tumor cell to certain chemotherapeutic agents. miR-16, a family of micro RNAs, is critical to the regulation of gene expression and appears to have a tumor suppressor function; its expression is downregulated in various cancer cell types (Table 9).

Conclusion

The diagnosis of malignant pleural mesothelioma is a vital clinical challenge for physicians because the incidence of this aggressive tumor is growing. Though insufficient biopsy material so as to require perfect facts of invasion and lack of different typical morphologic features of malignancy with other cytological abnormalities that build perfect diagnosis of malignant pleural mesothelioma and to discover a novel and efficient diagnostic marker for malignant pleural mesothelioma, will be of enormous significance for its prognosis and treatment. During the last decade, various targeted agents have been explored in malignant pleural mesothelioma, and in some of them; the preclinical rationale was very weak for exploring clinical activity. Malignant pleural mesothelioma is characterized via a composite genomic modification, through the defeat of chromosomal loci encoding for

different tumor suppressor genes such as TP53, NF2, p14, and p16. These types of genomic changes are very ordinary but, unluckily, these are not appropriate to be targeted through the available drugs. The deregulations in angiogenesis, apoptosis, and GFR pathway have been established, and these modifications may be agreeable to the intervention. Various clinical trials have tested different targeted agents focused against these pathways and receptors in order to inhibit the growth of mesothelial cell. There are some drugs which consistently revealed their activity in malignant pleural mesothelioma, but these drugs are under clinical trials.. The recent activities have increased our understanding of the tumor microenvironment, various immunotherapeutic modalities or combination therapy (like chemotherapy with immunotherapy). Additionally, the effects of such modalities in combination with immunotherapy in cancer patients are still exploratory phase. The complete perspective of immunotherapy treatment has not been realized and/or utilized. Proper preclinical and clinical designs are the important pillars in understanding the future of immunotherapy in treating cancer patients.

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