Emerging Potential Agents against Malignant Pleural Mesothelioma: A Review of *in vitro* Studies

Malign Plevral Mezotelyoma Tedavisinde Potansiyel Ajanlar Üzerine Bir *in vitro* İnceleme

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ABSTRACT

Malignant pleural mesothelioma is a highly aggressive and therapy-resistant tumor with poor prognosis. Approximately 80% of MPM cases worldwide are associated with exposure to asbestos. Incidence of MPM has increased in the world. Most patients survive around 12 months in spite of given treatments. Since about 80% of MPM cases have been diagnosed in stage III/IV, they are no longer suitable for surgical intervention. Moreover, the conventional therapy strategies have failed to extend survival of MPM patients. Although the combination therapy, consisting of cisplatin and pemetrexed, has shown promising prognostic results and became the standard first-line treatment for mesothelioma, it has not yielded satisfactory outcomes regarding overall survival of patients. For these reasons, more effective therapy strategies are still needed. In this review, *in vitro* research studies that are related to inhibitors administrated on MPM cells are summarized. Results of *in vitro* studies are important for identification of potential therapeutic agents.

Key Words: Malignant pleural mesothelioma, apoptosis, inhibitors, preclinical, *in vitro*

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ÖZET

Malignant plevral mezotelyoma yüksek derece agresif ve tedaviye dirençli olan, prognozu kötü bir tümördür. Dünyadaki MPM vakalarının takriben %80'i asbest maruziyetiyle ilişkilidir. MPM'nin dünyada görülme sıklığı artmaktadır. Çoğu hasta verilen tedavilere rağmen yaklaşık 12 ay hayatta kalmaktadır. MPM vakalarının yaklaşık %80'i III/IV. aşamada teşhis edildiğinden, artık cerrahi müdahaleye elverişli değillerdir. Üstelik, geleneksel tedavi stratejileri de MPM hastalarının sağkalımını uzatmakta yetersiz kalmaktadır. Her ne kadar sisplatin ve pemetrekset içeren kombinasyon tedavi umut verici prognostik sonuçlar doğurmuş olsa da genel olarak sağkalım bakımından tatmin edici sonuçlar vermemiştir. Bu sebeplerden dolayı daha etkin tedavi stratejilerine olan ihtiyaç hala devam etmektedir. Bu derlemede, MPM hücreleri üzerinde uygulanan inhibitörlerle ilgili *in vitro* çalışmalar özetlenmiştir. *In vitro* çalışmaların sonuçları potansiyel terapötik ajanların belirlenmesi açısından önem arzetmektedir.

Anahtar Sözcükler: Malignant plevral mezotelyoma, apoptoz, inhibitör, preklinik, *in vitro*

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INTRODUCTION

Malignant mesothelioma is a primer malign tumor originating from mesothelium cells and settling into pleura, periton or pericardium, which are covered with a mesothelial membrane (1). Because of the etiological relationship, it most frequently originates from pleura (2). Furthermore, malignant pleural mesothelioma (MPM) is an aggressive tumor with poor prognosis and treatment resistance (1). While SV40 virus infection, genetic predisposition and radiation are among the risk factors of MPM, contact with asbestos and erionite are the primary risk factors (3). In addition, excluding tumors associated with asbestos exposure, all other etiologies account only for a small fraction of mesothelioma incidences. The second largest fraction stems from unknown etiologies (idiopathic) (4). During the last century, about 181 million tons of asbestos were produced, with a peak level at 1970s (5). Despite asbestos consumption has gradually been prohibited around the world and its production is very limited now, incidence of MPM has been increasing worldwide (6). According to the mortality database (1994-2008) of World Health Organization (WHO), worldwide age-adjusted mortality rate (AAMR) for mesothelioma was 4.9 in a million and this rate displayed an annual increase of 5.4% (7).

Mesothelioma has three main histological types: epithelioid, sarcomatoid (fibrous) and biphasic (mixed) (8). These types contain biological differences affecting clinical behavior of the tumor. Epithelioid is the most common (50 – 70%) and the least aggressive type. Sarcomatoid (10 – 20%) is the most aggressive type, and biphasic (20-35%) is a mixture of epithelioid and sarcomatoid.

Although surgery is the first choice for treatment of MPM, it can only be applied at earlier stages of the disease because of quick progression of the tumor throughout hemithorax. Single modality treatments, including surgery, radiotherapy and chemotherapy, remain incapable of extending MPM patients' survival. This situation has given rise to new research studies for multi-modality treatment of these patients (9). The chemotherapy, combining cisplatin and antifolate, has become the current first-line treatment standard for unresectable MPM. This treatment standard for MPM is effective only in 25-30% of patients, and median survival is 12 months (10). There is not any approved alternative regimen in case of failure of the first-line chemotherapy. Therefore, there is an immediate need for development of new treatment regimens.

Because systemic therapy is the only choice for most of the MPM patients, molecular and bio-pharmacologic research has been focused especially on identification of pathways taking part in tumor growth and propagation; and identification of new compounds counteractive to these mechanisms (9).

In this review, we focus on potential therapeutic agents used in *in vitro* studies with an intention to treat MPM, and their individual and combined activities on MPM cells. In case the findings of concerned preclinical investigations are supported by clinical investigations, these agents and/or their combination with one another or with conventional chemotherapeutics appear to be promising for development of novel and more efficient therapy alternatives.

1. Inhibitors Affecting Survival Pathways

1.1. PI3K/AKT and mTOR Inhibitors

Downstream effector mTOR-mediated PI3K (phosphoinositol-3-kinase)/AKT pathway mediates one of the most important oncogenic signals (11). Inhibition of AKT/mTOR signal may increase the sensitivity of MPM cells against cytotoxic agents. In a study testing PI3K inhibitor LY294002 on MPM cell lines, it was shown that PI3K/AKT signaling pathway exhibits an abnormal activity and plays a critical role in progression of cell cycle in MPM cell lines examined. Treatment with LY294002 caused arrest of G1 cell cycle and inhibition of cell proliferation (12). In another study, it was observed that temsirolimus blocks mTOR-mediated signals in *in vitro* cultures and creates a cytostatic effect on mesothelioma cell lines. Mesothelioma cells with intrinsic or acquired cisplatin resistance exhibited oversensitivity to temsirolimus. An apparent synergism was detected between mTOR inhibition and cisplatin (13). It was observed that, depending on their given concentrations, MEK (Mitogen-activated ERK kinase) and PI3K inhibitors (U0126 and LY29400, respectively) suppress MPM cell growth in human mesothelioma cells *in vitro* through apoptosis induction and cell cycle arrest at G1 stage. Moreover, use of combination of MEK and PI3K inhibitors exhibited an additive or synergetic inhibition effect on MPM cell growth compared to their individual treatment (14). Poly (ADP-ribose) polymerase 1 (PARP1) inhibitor CO-338 alone significantly reduced viability of MPM cells in a concentration-dependent manner and exhibited a synergistic effect together with cisplatin. It was observed that treatment of MPM cells with increased concentrations of PARP1 inhibitor for 24h resulted in cell cycle arrest in G2/M phases of cell cycle. It was indicated that there exists a correlation between AKT/mTOR axis regulated by PARP1 and SIRT1 (Sirtuin 1). PARP1 has been described as a gatekeeper for SIRT1, which plays a role in modulation of AKT activation (15). In another study, using six different MPM cell lines and nine selective AKT inhibitors (namely afuresertib, Akti-1/2, AZD5363, GSK690693, ipatasertib, MK-2206, perifosine, PHT-427 and TIC10), the effects of AKT inhibitors on MPM cell survival were examined. When IC_{50} values of the AKT inhibitors were compared, it was seen that afuresertib, which is an ATP-competitive specific AKT inhibitor, exhibits tumor-specific effects on MPM cells. Afuresertib treatment considerably increased caspase-3 and caspase-7 activities and apoptotic cell number in ACC-MESO-4 (epithelioid) and MSTO-211H (biphasic) cells. Besides, combined application of afuresertib and cisplatin on these cells suppressed cell viability (16).

It was previously shown that curcumin can inhibit cell growth, proliferation, angiogenesis, and metastasis. Because curcumin suppresses mTOR-mediated molecular pathways, it can be viewed as a new class of mTOR inhibitors (17). By various preclinical studies, it was proven that curcumin inhibits cell growth in a concentration- and time-dependent manner. Wang et al. set forth that after pretreatment with curcumin, cisplatin treatment enhances inhibition activity of cisplatin growth and stimulates apoptosis in MPM cell lines (18). In addition, Yamauchi et al. indicate that curcumin reduces cell viability in ACC-MESO-1 cells in a concentration-dependent manner, but does not induce apoptosis although inducing autophagosome formation (19). In one of our previous researches, we evaluated activities of everolimus (RAD001) and EF24 on the MPM cell line MSTO-211H and nonmalignant mesothelial (Met-5A) cells. Cisplatin treatment after pretreatment with EF24 or RAD001 enhanced the effects of cisplatin in compared to it individual application. It was indicated that pretreatment with EF24 or RAD001 may reduce cytotoxic effect of cisplatin on Met-5A cells and increase cell death response of MSTO-211H cells (20). Lastly, in another study conducted by Zhang et al. it was set forth that curcumin inhibits cell viability and stimulates apoptotic cell death in RN5 MPM cells. Following 5μM cisplatin treatment for 72 h, it was observed that approximately 50% of cells died. 20 μM curcumin has stimulated a similar effect. In this way, it has been set forth that cisplatin is more cytotoxic than curcumin in RN5 cells (21).

1.2. MAPK Pathway Inhibitors

The mitogen-activated protein kinase (MAPK) pathway plays a critical role in regulation of cell proliferation, growth, differentiation and survival. Dysregulation of MAPK pathway contributes to formation of various tumors, including MPM (22). JBIR-23, isolated from Streptomyces sp. AK-AB27, was tested on MPM cells. JBIR-23 treatment inhibited growth of all tested MPM cells in a concentration- and time-dependent manner. This compound showed its cytotoxic activity on MPM cells through promoting tubulin polymerization and G2/M arrest. In addition, it exerted apoptosis induction through a caspase-dependent pathway (23). In a study conducted by Kaku et al., treatment with DPPE (1,2-dipalmitoleoyl-sn-glycero-3-phosphoethanolamine) for 24 and 48 h reduced cell viability and induced apoptosis in MPM cells NCI-H28 in a concentration-dependent manner (24). In another study conducted by Tsuchiya et al., it was shown that DAPE (1,2-Diarachidonoyl-sn-glycero-3-phosphoethanolamine) also reduces cell viability of MPM cells NCI-H28 in a time- and concentration-dependent manner as well as inducing their caspase-independent apoptosis (25). Lastly, examination of the effects of MEK (mitogen-activated protein kinase) inhibitor trametinib and HA (hyaluronic acid) synthesis inhibitor 4-methylumbelliferone (4-MU) on MPM cells shown that trametinib and 4-MU reduce cell viability in a concentration-dependent manner and induce apoptosis (22).

1.3. Hedgehog Pathway Inhibitors

Hedgehog signals play a critical role in normal organ development and are dysregulated in various cancer types (26). The number of studies about hedgehog signal pathway inhibitors on MPM is very limited. In a study, it was observed that hedgehog signaling is upregulated in MPM tumors and the smoothened (SMO) inhibitor HhAntag concentration-dependently caused reduction of cell survival in MPM cells (27). In another study, the effects of SMO antagonists [SMO inhibitor GDC-0449 or the antifungal drug itraconazole (ITRA)] or Gli inhibitors [GANT61 or the anti-leukemia drug arsenic trioxide (ATO)] on eight different MPM cell lines were evaluated. These four hedgehog antagonists considerably suppressed MPM cell viability. More importantly, ITRA, ATO and GANT 61 significantly induced apoptosis in representative MPM cells (28).

1.4. HGF (Hepatocyte Growth Factor) – MET (HGF Receptor) Pathway Inhibitors

Activation of HGF-Met pathway, which plays a critical role in tissue development and regeneration, promotes cell growth, survival, migration and morphogenesis in normal cells (29).

It was stated that HGF-Met pathway exhibits aberrant activation in tumor cells in tumorigenesis, progression of invasive and metastatic diseases, and resistance against anticancer drugs (30). Effects of HGF antagonist NK4 on MPM cells were evaluated and it was concluded that NK4 inhibits MPM cell growth, Met receptor activation and migration. In the ninth day, 500 nM NK4 reduced the number of cells living in the culture by up to 55% (31). In another study, evaluating activity of tubulin and c-Met inhibitor tivantinib (ARQ197) in four different MPM cell lines, tivantinib, which is known to inhibit both c-Met activity and microtubule polymerization, caused inhibition of cell growth. Moreover, in case of simultaneous application of tivantinib and pemetrexed, it was seen that tivantinib synergically enhances anti-proliferative and proapoptotic activity of pemetrexed. This synergetic effect was associated with reduction of thymidylate synthase expression and inhibition of migration activity (32). Lastly, activities of MET/ALK inhibitor crizotinib, in combination with a pan-class I PI3K inhibitor, BKM120, and a PI3K/mTOR dual inhibitor, GDC-0980, on mesothelioma were inspected. MET/ALK inhibitor notably reduced cell migration and its combination with the other inhibitors led to a synergetic interaction. When BKM120 was applied alone or in combination with crizotinib, it induced G2-M arrest and apoptosis (33).

1.5. IGF-1R (Insulin-like growth factor 1 receptor) Pathway Inhibitors

It has been ascertained that IGF-1R pathway is a substantial regulator of tumorigenesis and growth in MPM cells (34). In a research assessing the activity of IGF-1R inhibitor NVP-AEW541 on cell growth and IGF-related pathways, it was shown that lower concentrations of NVP-AEW541 caused inhibition activity in MPM cell lines while its higher concentrations caused cytocidal activity (35). Another research study activity of another IGF-1R pathway inhibitor, namely AG1024, on MPM cell line NCI-H513. AG1024 inhibited cell growth and synergically enriched cytotoxic activity of cisplatin. Accordingly, it was noted that inhibition of IGF-1R pathway can be a good target for reduction of toxicity and chemoresistance of conventional anticancer agents for malignant mesothelioma patients (36).

1.6. Tyrosine Kinase Inhibitors

Dasatinib is a thiazole-based ATP competitive, dual Src/Abl kinase inhibitor. In a study carried out with four different MPM cell lines, the effects of dasatinib were tested. Except the epithelioid-type NCI-H2452, the other three cell lines appeared to be sensitive to this compound through cytotoxic effect. In the sensitive cell lines, dasatinib caused apoptosis and cell cycle arrest (37). The potential increase in the anti-tumor effect of PEM (Pemetrexed) when combined with dasatinib is researched on MPM cell lines MPP89, REN and MSTO-211H. PEM and dasatinib were applied individually, in combination, and in sequence. Dasatinib pretreatment sensitized PEM activity through SRC inhibition, impaired cell migration, and as a result increased PEM sensitivity. Moreover, pretreatment with dasatinib enhanced cellular response to PEM (38).

It has been seen that tyrosine kinase inhibitor imatinib mesylate induces cytotoxicity and apoptosis. After 48 h of incubation with 100 µM imatinib, cell viability notably decreased. Imatinib, when treated together with gemcitabine and pemetrexed, demonstrated a synergistic effect (39). Katz et al. examined the effects of Sorafenib treatment alone and in combination with tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) on six different human mesothelioma cell lines. While these MPM cells were sensitive to the multikinase inhibitor sorafenib, they showed resistance to TRAIL. It was observed that TRAIL is not active by itself, but it increases the cytotoxic effect of sorafenib. Hence, combining sorafenib therapy with TRAIL will be useful for obtaining a more efficient death signal (40). In the study conducted by Favoni et al., gefitinib treatment in the cell lines IST-Mes2 and ZL55 affected cell proliferation in a concentration- and time-dependent manner. Meanwhile, it inhibited both EGFR (epidermal growth factor receptor) and ERK (Extracellular signal-regulated kinase) 1/2 activation. While low concentrations of gefitinib caused mesothelioma cell cycle arrest through obstruction of EGFR activity, its high concentrations (> IC_{50}) triggered apoptosis (41). In another study, the effects of the combination of the multikinase inhibitor sorafenib and the mTOR (mammalian target of rapamycin) inhibitor everolimus were tested on seven different cell lines. It was observed that the combination of sorafenib and everolimus is effective in mTOR and ERM (ezrin/radixin/moesin) blockade, exhibiting synergistic effects on inhibition of the MPM cell proliferation, triggering ROS (reactive oxygen species) production (42). Pattarozzi et al., working with mesothelioma TIC (tumor-initializing cells or cancer stem cells) cultures, identified that the anti-tumor effects of sorafenib are basically attributed to a direct inhibition of FGFR1 (Fibroblast growth factor receptor) activity rather than downstream effectors, such as Raf/Ras/MEK/ERK pathway (43).

2. HDAC Inhibitors

The histone deacetylases (HDACs) are a very old and well-preserved group of enzymes that, in opposition to the effects of histone acetyl transferases (HATs), are responsible for removal of acetyl groups from lysine residues. Because of their deacetylase activity aimed at histones, they play a crucial role in epigenetic modulation of gene expression (44). HDACs, together with other regulatory proteins, serve an essential function in devising apoptosis of tumor cells. In general, HDAC inhibitors have been designed to govern acetylation-deacetylation process and to promote a variety of cellular functions, including apoptosis (45).

Hurwitz et al. test the effects of HDAC inhibitor Vorinostat (SAHA) on malignant mesothelioma using seven different MPM cell lines. Their study demonstrates that SAHA down-regulates FLIP (caspase 8 inhibitor) protein expression in all of the seven MPM cell lines. Also, they reported that SAHA treatment induced apoptosis through caspase 8 in all MPM cell lines except epithelioid-type cell line H2591 (46). Although individual treatment of inhibitors causes cell growth inhibition and apoptosis, their combined use with one another and/or conventional chemotherapeutics lead to more effective results in MPM cells. Nguyen et al. treat five different MPM cell lines with the HDAC inhibitor depsipeptide (DP) FK228 and cyclin-dependent kinase inhibitor Flavopiridol (FLA). In this study, it was identified that MPM cells show a broad range of sensitivity to the cytotoxic effects of DP. Exposing these cells to DP caused concentration-dependent growth inhibition. It was also reported that exposure of MPM cells to various FLA concentrations subsequent to removal of DP from these cells significantly increases the magnitude of growth inhibition in all of the mesothelioma cell lines except epithelioid-type cell line H2052 (47). Another study tests the effects of HDAC inhibitor valproic acid and 3-hydroxy-3-methylgrutaryl-CoA (HMG-CoA) reductase inhibitor lovastatin on the cell line ACC-MESO-1. Individual or combined treatment with lovastatin and/or valproic acid neither reduced cell viability nor induced apoptosis. Nonetheless, it was detected that these agents reduce cell invasion (48). It was shown that SAHA sensitizes MPM cells to SMAC mimetic compounds depending on its ability to down-regulate FLIP (49). Similarly, combined application of panobinostat and cisplatin results in a higher rate of cell death compared to individual treatment of cisplatin (50). Lastly, Gueugnon et al. evaluate anti-tumor potentials of four new HDAC inhibitors [two pan-HDAC inhibitor (ODH and NODH)] and two class I HDAC inhibitor (ODB and NODB), all featuring a potent histone H3 acetylation induction and derived from Trichostatin A compounds on three different MPM cells individually and by combining with cisplatin. Furthermore, they compare the results with the effects of SAHA, which is an approved HDAC inhibitor for cancer treatment, as a reference point. It was demonstrated that the effects obtained with micromolar concentrations of SAHA can similarly be obtained with nanomolar concentrations of the hydroxamate compound NODH. Moreover, they identify that treatment with HDAC inhibitor-cisplatin combination strongly increases cell deaths compared to the results obtained by their separate treatments (51).

HAT acetylates amino group of lysine residues in the tail region of histones. This believed to loosen chromatin by neutralizing the positive charge of lysine and, thus facilitating transcription. Recently several compounds, having the effect of HAT inhibitors, have been identified, some of which are shown to inhibit growth of cancer cells (52). A study carried out in our laboratory evaluates activities of HAT inhibitor anacardic acid (AA) and cisplatin, alone and in combination, on MPM cell line MSTO-211H (biphasic). The viability of cells treated with AA + cisplatin combination reported to be lower than the viability of cells treated only with cisplatin. Moreover, AA pretreatment leads to a more effective cellular death response by increasing sensitivity of the MPM cells to the conventional chemotherapy agent cisplatin (53).

3. HSP90 Inhibitors

Heat shock protein 90 (HSP90), which is a molecular chaperone, helps protein folding and maturation that control stability of various proteins related to reproduction and death of cancel cells, including many RTK (receptor tyrosine kinase) activated in MPM (54). Regarding the literature about the effects of HSP90 inhibitors on MPM, only two studies have been discovered. In a study, it was observed that a small molecule inhibitor of Hsp90, 17-Allilamino-17-demethoxygeldanamycin (17-AAG), causes cell cycle arrest and inhibition of cell proliferation. In addition, in all MPM cell lines, treated with 17-AAG, apoptosis induction was observed (55). Compared to individual inhibition of activated RTKs, multi-RTK inhibition by HSP90 inhibitor 17-AAG has a greater effect on proliferation and survival of mesothelioma cells (54).

4. COX-2 Inhibitors

Cyclooxygenase-2 (COX-2) is an inducible enzyme, catalyzing transformation of arachidonic acid to prostaglandins in response to proinflammatory or mitogenic signals. It is overexpressed in many solid tumors (56). The effects of the nonsteroidal anti-inflammatory compound indometacin and the selective COX-2 inhibitors NS-398 and celecoxib were tested on MPM cells. It was observed that these agents inhibit cell proliferation of the MPM cells MPP89, H-Meso and Ist-Mes1 in a concentration-dependent manner, as well as that celecoxib stimulates MPM cell apoptosis in a concentration- and time-dependent manner (57). In another study, it was shown that the agent obtained by combining one of the specific COX-2 inhibitors, DuP-697 or NS-398, with pemetrexed has at least 4 times increased cytotoxicity for the tested MPM cell lines (58). Another study tests the effects of COX-2 and EGFR inhibitors rofecoxib and gefitinib, respectively, alone and in combination. They are treated in a concentration- and time-dependent manner in five different MPM cell lines. In Ist-Mes-2 cell line, gefitinib and rofecoxib exhibited a synergistic effect in inhibition of cell growth. The other two cell lines, Ist-Mes-1 and MPP89, found to be more sensitive to individual treatment of the agents compared to their combined treatment. For this reason, gefitinib and rofecoxib exhibit effects specific to cell types (59).

5. Proteasome Inhibitors

Proteasome inhibitors have become potential therapeutic agents in treatment of various human cancers that resist conventional chemotherapy (60). There are several studies about the effects of proteasome inhibitors on MPM. In a study, the effects of proteasome inhibitor MG132 on two different MPM cell lines were tested. This study detected that a very low level of MG132 would induce MPM cell apoptosis in a caspase-dependent manner. In addition, it was shown that this agent inhibits MPM cell invasion (61). In another study the effects of WA (Withaferin A) on MPM cells were examined. In this study, it was seen that H2373 cells exhibit 52% inhibition of their growth in case of 1.25 µM concentration while the other cell lines exhibit 55-67% inhibition of cell growth in case of 5 µM concentration. In addition, WA has inhibited proteasomal chymotrypsin-like activity in MPM cells as well as triggering apoptosis (62). Cheriyan et al. analyze suppressive effects of DSF-Cu (copper-complexed disulfiram) on MPM cells and conclude that DSF-Cu inhibits cell proliferation in all cell lines analyzed. 1 µM concentration of DSF-Cu potently stimulated caspase-3 and caspase-7 in H2373 cells and caused 70% loss in cell viability in all of the MPM cells examined, except epithelioid-type H2595 cells. It was also reported that DSF-Cu partially suppresses MPM cell growth by inhibiting proteasome and activating caspase-9 through an intrinsic apoptosis signaling (63). Another study conclude that each tested MPM cell exhibited a distinctive sensitivity to the proteasome inhibitor bortezomib. Among these cells with distinctive sensitivities to bortezomib, the sensitive MPM cell lines exhibited less proteasome activity compared to the clones with bortezomib resistance (64).

Although individual treatment of proteasomal inhibitors inhibits cell growth and cause cell death of MPM cells, combining them with one another and/or with conventional chemotherapeutics lead to more effective results in MPM cells. In a study conducted by Gordon et al., it was identified that bortezomib displays a high level of cytotoxicity against MPM cells, causes cell cycle arrest at both G2/M and G1/S phases, and increases apoptosis in the tested MPM cell lines in a concentration- and time-dependent manner, except the biphasic cell line MS589. The same study also demonstrates that pretreatment with bortezomib increases cytotoxicity of cisplatin and pemetrexed in a concentration-dependent manner (65). Another study conducted by Wang et al. reveal that bortezomib decreases cell growth in MPM cells in a concentration- and time-dependent manner and causes G2/M cell cycle arrest. Moreover, bortezomib pretreatment exhibited a synergistic effect together with cisplatin (66). Proteasome inhibitors bortezomib and MG132 alone or in combination with TRAIL have been tested on cell lines comprised of three main histological types of MPM. Treatment with MG132 alone or bortezomib alone induced a limited apoptosis in MPM cells that correlated with a high level of Mcl-1 protein and hyperactive PI3K/Akt signaling. Besides, while TRAIL induced a limited apoptosis, treatment with a combination of TRAIL and MG132 or TRAIL and bortezomib triggered a potent apoptosis in all of the three MPM cell lines (67).

6. Targeting Sp1-related signaling pathway

For a variety of cancer cells, it was reported that expression level of Sp1 (specifity protein 1) is higher compared to that in normal cells (68). There are several studies about the role of Sp1 in MPM. Chae et al. state that quercetin reduces cell viability and increases apoptotic cell deaths in MSTO-211H. In addition to this, by interacting with Sp1, quercetin suppresses its protein and mRNA expression levels (69). Activities of resveratrol and hesperidin on MSTO-211H cell line were also tested. It was observed that resveratrol and hesperidin reduce cell viability, increase apoptotic cell deaths and Sub-G1 population, and significantly suppress Sp1 protein levels in MSTO-211H cells. It was also noted that hesperidin suppresses mesothelioma cell growth through Sp1 inhibition (70, 71). Another study shows that LCA (Licochalcone A) negatively modulates both cell growth and Sp1 expression and induces apoptosis via Sp1 in MSTO-211H and H28 cells (72. Exposure to mitramisina concentration-dependently decrease Sp1 in both cell lines. Mitramisin dramatically inhibited proliferation and clonogenity of MPM cells (73). Similarly, Manu A (Manumycin A) inhibited cell viability of MSTO-211H and H28 cells and protein and mRNA levels of Sp1 expression in a concentration-dependent manner (74).

7. TRAIL (Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand)

In a study conducted by Belyanskaya et al., sensitivity of 13 different cell lines or primary cultures to TRAIL and two different human agonistic monoclonal antibody directed to TRAIL-R1 (Mapatumumab) and TRAIL-R2 (Lexatumumab) have been examined. It was established that nine of these cell lines show sensitivity to TRAIL, most of the cell lines (46%) are more sensitive to lexatumumab than to mapatumumab while a small number of cell lines are more sensitive to mapatumumab than to lexatumumab. TRAIL-R2 promoted MPM cell apoptosis, mediated by death receptors, more than TRAIL-R1. In addition, combining cisplatin with matatumumab or lexatumumab synergistically inhibited cell growth and increased apoptotic cell deaths. Moreover, mapatumumab or lexatumumab treatment to cisplatin-pretreated MPM cells led to significantly high cytotoxic activities (75). In a recent study, Urso et al. (2017) examine activity of MDM2 inhibitor nutlin 3a individually and in combination with rhTRAIL on MPM cells. Nutlin 3a caused an accumulation at G1 phase of cell cycle in all the cell lines examined, excluding ZL55, and caused a synergistic increase in cell deaths in all cell lines containing functional p53 when simultaneously treated with rhTRAIL (76).

8. Other molecules used in combination with cisplatin

There are also other agents targeting different molecules/pathways. When combined with conventional chemotherapeutics, these agents enhance their effectiveness. Peroxisome proliferator-activated receptor-γ (PPAR-γ) agonist triglitazone concentration-dependently inhibited MPM cell growth *in vitro* and induced G1 cell cycle arrest and apoptosis. Triglitazone and cisplatin combination exhibited an additive inhibitor activity on MPM cell growth compared to individual treatment of these agents (77). In a study, dealing with optimization of gemcitabine-cisplatin protocols by using various cell lines obtained from different histological sub-types of MPM, it was found that exposition to cisplatin for 68h after pretreatment with gemcitabine for 4h exerts synergistic activity in both epithelioid and sarcomatoid sub-types of MPM and induces a potent S-phase arrest that correlated with double-strand breaks (78). Another study examines activity of glutathione S-transferase inhibitor NBDHEX alone and in combination with cisplatin on human MPM cell lines with epithelioid and biphasic characteristics. When NBDHEX was simultaneously treated with cisplatin, a synergistic activity was observed. In case of sequential treatment, an additive activity was observed. NBDHEX triggered caspase-dependent cell death in all mesothelioma cell lines. These findings suggest that NBDHEX activates an intrinsic apoptotic pathway (79). In Erβ-positive human MPM cells, Erβ agonist KB9520 has exhibited its highest activity at 10nM and reduced cell growth and viability in a concentration-dependent manner. Besides, exposition of REN cells to KB9520 prior to cisplatin treatment ensured synergistic inhibition of cell proliferation and survival. It was reported that pretreatment with 10 nM KB9520 causes 20 µM cisplatin treatment to be as effective as 100 µM cisplatin treatment alone (80). Hoda et al. shows that trabectedin, in a concentration-dependent manner, decreases MPM cell growth in both monolayer and multi-cellular spheroid cell cultures and shows synergistic activity when combined with cisplatin and Bcl-2 inhibitors. In addition, it induces apoptosis along with changes in the expressions of pro-apoptotic and anti-apoptotic regulators (81).

CONCLUSION

Chemotherapy has been continuing to be one of the primary therapy choices for prolonging survival and increasing life quality. Nonetheless, the recent developments in *in vitro* targeted therapy approaches for MPM therapy are promising. Based on the data derived from *in vitro* studies, combined treatments of many of these agents are expected to display a larger therapeutic potential than their individual treatments.

For assessment of activities of targeted agents, alone or in combination with other agents, there is a need for more *in vitro* and *in vivo* preclinical works. Based on developments in such studies, new molecules can be discovered as potential candidates for clinical studies.

Conflict of interest

No conflict of interest was declared by the authors.

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