Research Paper *IJMSRR*
*Impact Factor :**3.029*** *E- ISSN - 2349-6746*
ISSN -2349-6738

ROLE OF ONCOGENES IN MALIGNANT PLEURAL MESOTHELIOMA: THERAPEUTIC IMPLICATIONS.

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Abstract
Mesothelioma is an aggressive cancer affecting the membrane lining of the lungs and abdomen. Mesothelioma typically diagnosed at advanced stage (III and IV), to date there is no early diagnostic method. World Health Organization (WHO) determined that all types of asbestos can cause cancer in humans. The incidents of malignant pleural mesothelioma (MPM) are expected to increase in Western Europe. The frequency of MPM is 1.25/100,000 in Great Britain and 1.1/100,000 in Germany. The occurrence of MPM is significantly higher in men when compare to women. MPM is largely unresponsive to conventional chemotherapy and most of the patients died within 10-17 months of initial diagnosis. Over-expression of many oncogenes and signature miRNAs is associated with malignant pleural mesothelioma. It's a significant approach for early diagnosis and novel therapeutic reagents. The prognosis of patients with malignant mesothelioma is usually poor. However, there is currently no known cure for mesothelioma and the new approaches for the treatment of MPM are very much essential.

INTRODUCTION

Malignant pleural mesotheliomas (MPM), is asbestos-induced aggressive tumor, arise most often from the mesothelial cells that line the pleura. More than 90% of cases reported in pleura compared with 4-7% in peritoneum and less than 1% in pericardium and tunica vaginalis testis (Henderson *et al*., 1992; Mesothelioma in Australia, 2011).The prognosis of MPM is extremely very poor because the diagnosis, staging and treatment of the disease remain difficult and complex. The median survival time is less than 12 months (Robinson *et al*., 2005). Histologically, MPM are of three types: (i) sarcomatoid type, appearing as a spindle cell carcinoma resembling fibrosarcoma, (ii) epithelial type, consisting of cuboidal, columnar or flattened cells forming a tubular and papillary structure resembling adenocarcinoma and, (iii) biphasic type, containing both epithelial and sarcomatoid (mixed) patterns (SukheshRao, 2009).

The first study was conducted the relationship between asbestos and the development of MPM in South Africa. The association of mesothelioma with asbestos exposure was well established with an etiological fraction above 80% (McDonald and McDonald, 1996), and the SV40 viral infection was also an important etiologic cofactor in malignant mesothelioma. Asbestos fibers are bio persistent that can be detected in the lung several years after inhalation (an average latency of mesothelioma was 42.8 years) (Dodson *et al*., 1990; Alessandro *et al*., 2012). Workers were continuously exposed by asbestos finding a shorter latency some early study reports shorter latency periods 20-30 year with heavy asbestos exposure (Bianchi and Bianchi *et al*., 2007).According to the World Health Organization (WHO) all types of asbestos can cause cancer in human, and upgraded its global estimate of ARD to 107,000 annual deaths in 2010 (WHO, 2006; Asbestos, 2010). The protein kinase C (PKC-β1 and -β2 isoforms) and vascular endothelial growth factor receptor (VEGFR)-2 are excellent combinatorial therapeutic targets for different types of mesothelioma(Sivakumar*et al*., 2011).Mesothelioma may arise in genetically predisposed host with autosomal transmitted gene in concert with asbestos exposure and familial mesothelioma was reported in siblings(i.e. a brother and sister, and identical twin brothers) (Martenssone*t al.*, 1984; Hammar*et al.*, 1989).

OCCURRENCE

Incidences of MPM reach 100 cases/million/year in occupationally exposed populations and 1 case/million/year in the generalpopulation (Porret*et al.*, 2007). Mesothelioma mainly occursin Australia because it is the only largest consumer of asbestos around the world (Nico*et al.*, 2013) and also was reported in United States (Price, 1997; Weill *et* al., 2004).Global mesothelioma incidences significantly higher than mortality registries, however no clear reports from developing countries(Park *et al*., 2011). The hidden burden of the disease approximates 39,000 cases in the 15-year period to 2008, predominantly in Russia, Kazakhstan, China, India and Thailand (Benjamin and Robinson, 2012)

INDIA

A retrospective study in India only 15 cases were reported over a 25-year period (Kini*et al*., 1992). In 2001, Nadgouda et al.

were reported only three cases over a 10-year period. Whether this is because of lesser number of cases or lack of awareness and diagnostic methods since it is difficult to predict.

WORLDWIDE

Worldwide malignant mesothelioma incidence has been rising since middleof 20thcentury in developed countriesabout 88% and 12% in developing countries because less exposure to asbestos, lack of awareness and diagnosis. The incidents of MPM are expected to increase in Western Europe (McElvenny*et al*.,2005; Hodgson *et al*.,2005), United States (Larson *et al*., 2007), Japan (Robinson *et al*.,2005), Australia (Leigh *et al*., 2002), India (Joshi *et al*., 2003), China, Indonesia and Vietnam (Pass *et al*., 2004). In Europe, it is rated about 20 per million with large intercountry variation (Bianchi and Bianchi, 2007; Lianes*et al.*, 2011). The frequency of MPM is 1.25/100,000 in Great Britain and 1.1/100,000 in Germany (Stahel*et al*., 2010).The ratio ofoccurrence is predominantly in men than women (Weill *et al*., 2004; Robinson and lake, 2005).

MORTALITY RATE

Every year around 43,000 people are dying worldwide by mesothelioma (Driscoll *etal*., 2005). The Increases of MPM hasin wide range of countries, approximately 10,000 annually in Australia, Japan, North America and Western Europe (Peto*et al*., 1995; Anonymous, 1997; Tse*et al*., 2010). Delgermaaet alextracted the numbers of malignant mesothelioma deaths recorded in the WHO mortality database between 1994 and 2008by the use of ICD-10 category C45 or any subcategory. During this time period 92, 253 mesothelioma deaths were reported in 83 countries (Vanya *et al*., 2011). The pleura anatomically accounted for 41.3% of all mesothelioma deaths, the peritoneum and pericardium accounted for 4.5% and 0.3% of deaths respectively, and unspecified sitesare 43.1%. Mesothelioma deaths were analyzed by continent based: In Europe almost 50,000 deaths (estimated 54.0% of all deaths worldwide) and in outside Europe the America and Asia, which accounted for 25.9% and 13.0% respectively. Analysis of age-adjusted mortality rate of mesothelioma is 4.9 per million, a mean age at death of 70 years and male to female ratio of 3.6:1 (Delgermaa *et al.*, 2011).

DIAGNOSIS AND STAGING OF MPM

A complete clinical diagnostic method of MPM is generally difficult and frequently occurs at a late stage. The latency period of mesothelioma is time elapsed between first exposure to asbestos and the diagnosis of disease is long.The chest X-ray or Computed tomography (CT) scan imaging studies inthe thoracocentesis with aspiration of pleural effusion fluid is usually the first-line pathological assessment of mesothelioma. Tissue biopsy is the primary investigation for diagnosis of many centers but some patientsare unable to tolerate the surgical procedure due to their poor physical condition(van *et al*., 2013).The fine needle aspiration use CT imaging procedure to locate abnormal tissue or fluid in the lung and small incisionis made in the skin where the biopsy needle is inserted into the abnormal tissue or fluid, and a sample is removed. Fine Needle Aspiration (FNA) biopsy (about 30%) and percutaneous pleural biopsy has a low diagnostic yield (about 30%) and this procedure not routinely recommended in malignant mesothelioma diagnosis (British Thoracic Society Standards of Care Committee, 2007; Scherpereel *et al*., 2010).Thoracoscopy-guided biopsy and CT-guided core biopsies have high diagnostic yields of about 80-90% or more (Maskell*et al*., 2003; Scherpereel *et al*., 2010) because it's high sensitivity and low complication rates. CT-guidedcore biopsy is suitable for diagnosis of pleural thickening or a nodular/mass lesion, high diagnostic yield and few complications occurred in the procedure (Maskell*et al*., 2003; Metintas*et al*., 2010). In 2010, Guidelines from the European Respiratory Society (ERS) and the European Society of Thoracic Surgeons (ESTS), the thoracoscopy was a preferred technique for inspection of the pleura and large biopsy (Scherpereel*et al*., 2010). Video-assisted thoracoscopy (VAT) is the best in biopsy technique and cytology it has low complication rate and a reliable diagnostic tool for experienced cytopathologists. A current definitive clinic pathological diagnosis of MPM is neo plastic invasion for example, infiltration into sub pleural fat, chest wall skeletal muscle, rib or lung by histological examination or by imaging studies (Hammar*et al*., 2008; Husain *et al*., 2009). Epigenetic profiles (Goto*et al*., 2009) and down-regulated miRNAs(Gee *et al*., 2010) have been suggested, diagnostic tool for malignant mesothelioma. Serum mesothelin is the best available biomarker of malignant pleural mesothelioma to examine in early diagnosis (Kevin *et al*., 2012).

SYMPTOMS AND CAUSES

In 2006, World Health Organization (WHO) determined that all types of asbestos cancause cancer in humans. Sometimes the signs and symptoms may be caused by the fluid, malignant mesothelioma includebreathing trouble, Cough, Pain under the rib cage, Pain or swelling in the abdomen, Lumps in the abdomen, Constipation, problems with blood clots, Weight loss, Feeling very tired. In 90% of cases with pleural mesothelioma having dyspnea is the first symptom (Scherpereel*et al*., 2010),pleural effusion lead to cause breathlessness(Yates *et al*., 1997), chest pain, coughand weight loss (Churg*et al*., 2004).The symptoms

of phrenic nerve palsy, irritativecough, paraneoplastic phenomena and spontaneous pneumothorax was rarer in mesothelioma (Neumann *et al*., 2001).

TREATMENT

Mesothelioma is a rare cancer that was treated in specialized centers and care by way of either curative or palliative intent, as well as pain control. The mesothelioma expertise of oncologists, thoracic surgeons, pathologists, imaging specialists, and scientists, who clinical interest of comprehensive and multidisciplinary focus of disease developing novel treatment protocols that extend patient lives.The new approaches for the treatment of malignant pleural mesothelioma (MPM) are very essential (Ramasamy*et al*.,2006). The goals of treatment for cancer are to prolong life and to improve the quality of life (Volker *et al*., 2013).MPM is resistant to treatment with classic anticancertreatments such as surgery, chemotherapy and radiotherapy. Recently some progress has been made with combination chemotherapy with multimodal treatment, which involves various combinations of chemotherapy, surgery and radiotherapy.However, median overall survival for patients with malignant mesothelioma hasremained modest (around seven months) as shown in recentpopulation based updates (Milano and Zhang, 2010;Musk*et al*., 2011).

SURGERY

Surgery means total resection of the tumor in mesothelioma and they are not totally resectable some residual tumor tissue is generally left behind. Adjuvant chemotherapy asgiven after the surgery forachieves elimination of remaining tumor cells (Rice, 2011).There are two type of surgery for MPM;Pleurectomy/decortications (P/D) and Extrapleuralpneumectomy(EPP). In stage I, stage II and stage III cancer can be removed by surgery and advancedstage IV, cancer cannot be removed by surgery because this stage cancer may have spread to lymph nodesanywhere in the chest.

PLEURECTOMY/DECORTICATION (P/D)

Pleurectomy and Decortication are a Surgery to remove part of the covering of the lungs and lining of the chest.Some mesothelioma surgeons refers P/D as a surgical procedure that aims to remove all macroscopic tumor from the affected hemithorax and others converse to this resection of only the parietal and visceral pleura(Nico van *et al*., 2013). P/D with en bloc resection of the parietal and visceral pleura as an effective method of preventing pleural effusion (Rice, 2011),however P/D has limitations as it does not remove the tumor completely (Maasilta, 1991). Patients who receive P/D alone often experience with local recurrence as the first site and less frequently distant recurrence; the local and distant recurrence rates are 64% to 72% and 10% to 36% respectively (Anne *et al*., 2009).P/D has a lower mortality (1.5%–5%) compared to EPP, and a significant effect on median survival (10 to 17 months) has been observed, but there is no significant effect on long-term survival (Soysal*et al*., 1997).MPM centers in Europe, some in North America and Japan are currently performing P/D with curative plan. Most hospitals has been reported equal or even better survival of after P/D than after EPP (Flores *et al*., 2008; Lang *et al*., 2012), conversely patients who undergo P/D have moreopportunities for additional therapy after recurrence compared with patients who undergo EPP (Bolukbas *et al*.,2012).Others use the term P/D to describe apalliative procedure for pain, symptom control and to improve respiratory function (Soysal*et al*., 1997).

EXTRAPLEURAL PNEUMECTOMY (EPP)

Surgical procedure of EPP has been well standardized with *en bloc* resection of the parietal and visceral pleura with the ipsilateral lung, pericardium and diaphragm.A number of specialized centers in the North America, Europe and Australia has been accepted the procedure of EPP for early stage mesothelioma (Weder *et al*., 2007;Yan *et al*., 2011). MPM patients who receive the EPP alone, median survival time is less than two years, but less significantly 10–20% of patients with average 5 year survival rates(Rusch*et al*., 1991; Van Ruth *et al*., 2003).Selection of EPP in MPM studies, one phase III study (Treasure *et al*., 2011) and several phase II studies has been reported till date (Weder *et al*., 2007;Federico*et al*., 2013). Sharif *et al*. aiming to compare the results of after EPP with palliative treatment approaches noted that the extension of survival achieved with EPP in patients with epithelioid histology(Sharif *et al*., 2011).Regarding long-term oncological outcome, initial analysis of the International Association for the Study of Lung Cancer (IASLC) reported a survival advantage in patients undergoing EPP compared to P/D. Italian guidelines recommend EPP to achieve adequate local control of MPM (Pinto *et al*., 2013).

MULTIMODALITY TREATMENT (MTM)

Trymodality therapy (that is combines chemotherapy with EPP and radiotherapy)comes under the multimodality treatment (Sugarbaker and Garcia, 1997).Usually the induction chemotherapy is administered followed by surgery and then by hemithoracic radiotherapy, however the treatment progress extends of six months ormore. Multimodality therapy guided to improve the prognostic factors of patients with good performance status, decrease the volume of disease, epithelioid

histology and the absence of significant co-morbidities(Sugarbaker and Norberto 1998; Flores *et al*., 2006; Nico van *et al*., 2013).EPP within Treasure a multimodality protocol offers additional benefit over induction chemotherapy and postoperative radiation therapy (*et al*., 2011).SomephaseI study of MTMprolong the median survival time (22 months) of patients (Sugarbaker*et al*., 1996), and one multimodality trialed to a higher average of 3-year survival rate than theunimodal treatment (Sienel *et al*., 2008).

RADIATION THERAPY

Radiation therapy can be given in post-operative consolidate treatment and this is applied to the sites of chest drain insertion, in order to prevent the tumor growth. MPM is a radio-resistant neoplasm (Andrew *et al*., 2013). There are two types of radiation therapy external radiation therapy (uses a machine outside the body to send radiation toward the cancer) and Internal radiation therapy (uses a radioactive substance sealed in needles, seeds, wires, or catheters that are placed directly into or near the cancer). The radiation therapy is given depends on the stage and type of the cancer. Radiotherapy in MPM cases can be given in a single modality, multymodality and the palliative radiotherapy. Radiotherapy will provide only symptomatic benefit but there is no studies have shown in improvement on survival time (Waite and Gilligan, 2007). Guidelines recommended the Prophylactic radiotherapy can be given only after EPP in clinical trial settings (Scherperee l*et* al., 2010). A recent study from the UK of 54 patients under taken modern radiotherapy technologies with follow-up CT scans, found a 54% response for relief of chest pain (Nico van, 2013). Palliative radiotherapy in MPM patients induces a response rate comparable to chemotherapy (Jenkins *et al*., 2011). High-dose external beam irradiation and intrapleural administration of radioactive isotopes promote long term survival rate (De Graaf-Strukowska *et al*., 1999), but high radiation treatment would cause collateral damage to the heart and lungs (Dhalluin and Scherpereel, 2011).

CHEMOTHERAPY

Chemotherapy in MPM patients there are two options resectable and unresectable tumors. This is given single agent or mostly in combination drugs which improve the response and survival rate. In MPM studies there are many phase II trials conducted by chemotherapy (Ellis *et al*., 2006). In many studies of preoperative chemotherapy treatment in MPM risks become lesser (Flores *et al*., 2006;Rea*etal*., 2007).Nowadays many studies are going on combined chemotherapy because there is no complete prognostic treatment in Mesothelioma. Because single chemotherapy drugs response rates of only 15% have been reported. Two studies states combination chemotherapy cisplatin and pemetrexed or raltitrexed which increase overall survival time (Vogelzang *et al*., 2003;van Meerbeeck *et al*., 2005). Median overall survival of patients given cisplatin-pemetrexed (12.1 months) and cisplatin-raltitrexed (11.4 months) it was significantly higher than patients who receiving cisplatin alone (9.3 and 8.8 months respectively). Izaet al.(2014) concluded that the combination of cisplatin with the natural compound PEITC induces a strong MPM cell death and therefore this combination could represent a promising strategy for the treatment of MPM. MPM is a highly aggressive tumor that is largely unresponsive to conventional chemotherapy and most of the patients died within 10-17 months of initial diagnosis (Sivakumar *et al*., 2011).A recent 2014 study shown one Italian phase II study of Gemcitabine and Carboplatin combined therapy in cases with pleural mesothelioma median survival of 66 weeks (Ceresoli *et al*., 2006; Lee *et al*., 2009).

OTHER NEW TARGETED THERAPY

Many clinical researches focused on molecular targeted therapies give us confidence that survival of mesothelioma patients will continue to improve as they have in the past.Growth factors or proteins are plays an important role in malignant transformation of mesothelial cells. Some molecular studies in malignant mesothelioma confirmed that vascular endothelial growth factor(VEGF),platelet-derived growth factor receptor beta (PDGFR beta) and the epidermal growth factor receptor family are frequently activate the tumor genesis (Nico van *et al*., 2013). Protein kinase C beta (PKCß) was overexpressed in MPM, Enzastaurin and combination with cisplatin inhibits PKC ß and suppresses the tumor growth (Leonardo *et al*., 2008). Another study the combinatorial therapeutic targets protein kinase C (PKCß1and ß2 isoforms) and vascular endothelial growth factor receptor (VEGFR)-2 are treated with enzastaurin and KPN633 which was strongly inhibit growth of tumor (Sivakumar *et al*., 2011). Some clinical trials shows single-agent angiogenesis inhibitors treatment such as bevacizumab, a recombinant humanized monoclonal antibody or other antiangiogenic agents SU5416, vatalanib, thalidomide and sorafenib which shown significant activity againsed mesothelioma ,further more research is needed to comparisons with other agents (Kindler, 2008). Nowadays several ongoing studies on bevacizumab in combination with pemetrexedand cisplatin and expected for therapy of MPM patients. A phase I trialshown HDAC has a partial response (Krug *et al*., 2006) and EphA2 as a novel potential molecular target in MPM (Nasreen *et al*., 2012). One *in vitro* and *in vivo* experiments shows Met and HGF inhibits the c-Met kinase (Mukohara *et al*., 2005).Biomarkers in MPM are important for positive outcomes of targeted agents in clinical trials. The first study of biomarkers suggests that serum mesothelin as a biomarker of mesothelioma (Robinson *et*

al., 2003). However, the mesothelin limitation is its poor sensitivity which makes difficult to achieve early diagnosis of mesothelioma(Grigoriu*et al*., 2009). Shahid conclude that serum miRNAs in MPM as a biomarker and its joined with KIF14 in MPM will be important for early diagnosis and novel therapeutic reagents of MPM (Shahid *et al*., 2014)

PALLIATIVEAND SUPPORTIVE TREATMENT

Malignant mesothelioma has a poor overall prognosis and high symptom burden (Nowak*et* al., 2004); however fatigue, dyspnoea, chest pain cough and pleural effusion are the symptoms. For this, palliative and supportive care is important for patients, it should start at that time of diagnosis, and less number of articles has been shown about psychosocial and supportive care issues of patients with mesothelioma (Nico van, 2013). One study compare non-small cell lung cancer patients, who received early palliative care or standard (late) palliative care but early palliative care led to improve the life and survival quality than standard (late) palliative care.(Temel *et al*., 2010;Waller *et al*., 2012).Control of Pain assessment with MPM patients follows the principles of cancer pain management, as MPM patients with pain were complex in nature(Ahmedzai *et al*., 2012). Palliative radiotherapy and chemotherapy has been reported an effective pain relief in MPM cases, however the combination chemotherapy would give symptom relief (Vogelzang *et al*., 2003; Van *et al*., 2005) such as shortness of breath. Recurrence of pleural effusion was managed by drain and indwelling plural catheters for recurrence of pleural effusion is more difficult (Scherpereel, 2010; Suzuki *et al*., 2011).

PROGNOSIS

Malignant pleural mesothelioma patients have poor prognosis, up to date there is no complete prognosis treatment, only option for this disease is extend of survival time and pain control palliative and supportive care. Median survival times varying from 4 to 12 months (Scherpereel *et* al., 2010) and only 12% of patients live longer than one year. Surgery, radiotherapy and chemotherapy have failed for treatment of MPM, nowadays combination chemotherapy and multimodality therapies are improve the long survival time.

CONCLUSION

Asbestos causes mesothelioma. Malignant pleural mesothelioma (MPM) continues to be a challenge. The prognosis of patients with malignant mesothelioma is usually poor However palliative treatment, supportive and cancer pain management is care for improve patient's performance. The diagnosis and treatment of patients with malignant pleural mesothelioma requires a multidisciplinary approach. Currently multimodality treatment, molecular targeted agents and biomarkers to improve patient's survival and quality of life. To improve the effect of treatment, an early diagnosis of malignant mesothelioma is of great value. Currently, there is no remedy for mesothelioma and the new approaches for the treatment of malignant pleural mesothelioma are very essential.

RECOMMENDATION

Diagnosis

- Thoracoscopy-guided biopsy and CT-guided core biopsies is recommended diagnosis method of MPM and its have high diagnostic yields.
- Video-assisted thoracoscopy (VAT) is the best biopsy technique and cytology, and it has low complication rate and a reliable diagnostic tool for experienced cytopathologists.
- Serum mesothelin and miRNAs is suggested to the best biomarker of malignant pleural mesothelioma to examine in early diagnosis.

Surgery

The procedure of EPP for early stage mesothelioma and it has been accepted by specialized centers in the North America, Europe and Australia.

Multimodality treatment

Multimodality treatment (chemotherapy with EPP and radiotherapy) is recommended for treatment of MPM, which decrease the volume of disease and improve the prognostic factors of patients.

Chemotherapy

Combination chemotherapy cisplatin with pemetrexed or raltitrexed and cisplatin with the natural compound PEITC suggested of hopeful strategy for the treatment of MPM

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