FONDAZIONE Buzzi Unicem ONLUS

MESOTELIOMA PLEURICO

Bibliographic review Second semester 2013

January 2013

Elisa Roca (elisaroca@gmail.com)

Malignant Pleural Mesothelioma: from the bench to the bedside

Introduction

Malignant pleural mesothelioma (MPM) is a highly aggressive, rare form of cancer with a growing rate of incidence and an often unfavorable prognosis. Optimal management of this disease has not yet been defined due to the lack of an indisputedly effective therapy, although various scientific societies have proposed practical guidelines that are being applied in standard clinical practice. These guidelines emphasize the difficulty of diagnosing MPM and note the poor results of current treatments, thus emphasizing the need for innovative therapies and methods to monitor patients suffering from this disease.

Although the prognosis of MPM is often unfavorable and the prospects pessimistic, recent studies investigating the pathogenesis and biology of this disease have revealed some interesting findings, pointing to promising significant progress for the future treatment of these patients. Translational research in this disease is making great progress and different molecular oncogenic pathways leading to the growth and progression of MPM have been characterized and better defined, leading to exciting pharmaceutical developments. However, more in-depth analysis still needs to be done to further define the processes, including increased early mesothelial cell profileration to the progression of invasive mesothelioma. All this information will help define an effective, more personalized treatment for these cancer patients.

The purpose of this bibliographic review of the scientific literature is to provide an overview of the recent advances in our knowledge of the biology of MPM and their potential therapeutic-diagnostic applications. This article is written in a non-scientific style to make it more available and accessible to a varied audience. We therefore refer interested readers and experts to the chapter containing the references, which could prove useful to anyone who would like to learn more about the studies analyzed in this review.

New therapeutic approaches

The role of surgery and radiotherapy for the treatment of MPM is still controversial and further studies may eventually provide more information in this regard.

However, medical therapy is considered the standard treatment in clinical practice, and the combination of platinum-based chemotherapy with antimetabolites (pemetrexed/raltitrexed) in particular has been considered the best first-line therapy for patients with MPM (1,2). Results obtained thus far have been limited, however, especially in terms of survival.

The main goal is to increase knowledge about the pathogenesis of MPM to define and improve target therapies and new therapeutic agents currently under investigation. The purpose of this review of the scientific literature is to describe the main therapeutic approaches currently being investigated in preclinical and clinical studies.

Epithelial Growth Factor Receptor The epithelial growth factor receptor (EGFR) performs a role in the proliferation, differentiation, migration, adhesion and survival of cells (3) and is overexpressed in over 50% of MPM patients (4). The expression of the receptor in mesothelioma cells has led to the hypothesis that a therapy targeted against EGFR will inhibit it and prevent its uncontrolled and often harmful activity. This is why a number of studies have investigated the efficacy of EGFR inhibitors such as gefitinib and erlotinib in chemotherapy-naive patients. These studies have demonstrated that these drugs are not very effective as first-line therapy in MPM when they are administered as monotherapy, so not in conjunction with any standard chemotherapy (5, 6, 7). However, although the EGF receptor is overexpressed in mesothelioma, the reason why EGFR inhibitors are not very effective may be because mutations of this receptor are rare (8).

Some studies disagree about the correlation between the overexpression of EGFR in mesothelioma cells and the response to treatment with inhibitors of this receptor. Some research groups have proven that there is no relationship between the overexpression of EGFR and the clinical outcome of MPM patients (9,10), while others have shown that patients who overexpress the receptor may have a better outcome (11-14). These discrepancies confirm the need for further research to better define the results. In any case, it has been shown that overexpression of EGFR in MPM is more common in the epithelial histological subtype, which is associated with better patient survival but is not an independent prognostic marker (13,14).
Recent results indicate the presence of an important communication network between the EGFR pathways and other cellular signaling pathways. For example, some proteins such as PI3K and AKT which play a role in the EGFR signaling pathway, also act in other cellular growth pathways and interact with other factors such as c-MET and IGF-1 (15,17). The histological overexpression of the c-MET protein has been documented in MPM and also in some normal pleura samples. According to this rationale, c-MET inhibitors have been investigated in mesothelioma cell lines; preliminary results have shown a dose-dependent inhibition of tumor growth (18). This type of dose-dependent inhibition was also observed in MPM cell lines subjected to IGF receptor inhibitors (19). Moreover, the cytotoxic effect of cisplatin also increased when administered together with these inhibitors (20).
An important biological communication also exists between EGFR and cyclooxygenase 2 (COX-2) (21). COX2 is overexpressed in many solid tumors and so it is considered a potential therapeutic target (22-24). Immunohistochemical studies of this protein in MPM demonstrated that it was overexpressed in 59-100% of the tumor samples analyzed (25-27). They also showed that treating mesothelioma cell lines with COX2 inhibitors induces cytotoxicity and increases the effect of pemetrexed (28-29).

K-ras, BRAF and PI3KCA mutations

In the search for therapeutic targets, researchers have investigated the presence of genetic mutations associated with neoplastic pathogenesis, leading to studies of K-ras, BRAF and PI3KA gene mutations. Unfortunately, genetic mutations of K-ras were not seen in the initial studies (30-32), thus changing expectations about this protein as a potential therapeutic target.
Studies of BRAF gene mutations have shown that they are absent in various tissues and tumor cell lines (33); other authors (34) have studied different MPM cell lines to analyze the PI3ka gene, but no mutation has been seen.

PTEN

PTEN is a protein that has been investigated in MPM to evaluate a potential therapy that would interact with this pathogenetic pathway.
Recent studies of various mesothelioma samples have shown that there is a loss of expression of the protein and that the mutation of this protein expression can be considered a negative prognostic value. In fact, patients with a decreased or lack of PTEN expression had a worse prognosis, whereas those with no genetic mutation had a greater survival rate (35).
It was also observed that the loss of PTEN expression might result in increased AKT activity, another important factor associated with the pathogenesis of cancer (36, 34). The loss of PTEN expression, which activates AKT, may induce resistance to various biological treatments such as EGFR inhibitors or anti-EGFR monoclonal antibodies. Therefore, these mutations also have consequences on other pathogenetic pathways, demonstrating the complexity of the pathogenesis and the intersecting network between these biological factors.

VEGF / VEGF Receptors

VEGF receptors have also been studied in mesothelioma cells and preclinical studies have shown they are expressed in both tumor tissue and peripheral blood in MPM patients (37).
The rationale for using drugs that inhibit this biological pathway is because they are expressed in greater levels in MPM patients than in healthy subjects. Also, the increased levels of VEGF are associated with increased microvascular density and appear to be associated with an unfavorable prognosis (38) as well as the likelihood of disease progression (39-41).
Anti-VEGF antibodies that actively inhibit this factor have been investigated. Studies have also tested the efficacy of combined VEGF and EGF inhibitors, in which these combinations achieved disease stabilization in 50% of patients, progression-free survival of 2.2 months and a median survival of 5.8 months (42, 43).
Drugs currently being investigated include vatalanib and cediranib, which are VEGF receptor inhibitors with antitumor activity in a variety of solid tumors (44-47).
Semaxanib is another VEGF-1 receptor inhibitor, but it also acts on the PDGF receptor (PDGFR) and c-kit (48).
Another drug is thalidomide, which has been investigated in MPM patients with the following results: no partial or complete responses, 27.5% of patients were progression free after 6 months, and median overall survival of 7.6 months (49).
Sorafenib has shown limited activity in non-resectable MPM patients (50). However, it has also been studied in combination with doxorubicin, which confirmed that this combination is well tolerated thus justifying further clinical studies (51).
Sunitinib has been investigated in a Phase II study in MPM as second-line treatment after chemotherapy with platinum and antimetabolites, with the following results: partial response in 12% of patients; disease stabilization in 65% of patients; mean time to progression of 3.5 months and overall survival of 7 months (Nowak et al., IMIG 2011, unpubl. data).
Various Phase II studies have been conducted to determine the efficacy of imatinib mesylate in MPM patients refractory to chemotherapy or chemotherapy-naive patients (52-54). Combination studies between imatinib, cisplatin and pemetrexed are currently underway (55). New research is investigating the utility of these drugs, which appear to be active in MPM due to their ability to induce apoptosis of the tumor cells and by inhibiting various metabolic pathways such as AKT/PI3K, for example; the efficacy of these drugs has also been demonstrated due their ability to increase the sensitivity of the tumor to chemotherapy with gemcitabine or pemetrexed (56).

PDGF / PDGFR

The discovery that the PDGF receptor is highly expressed in mesothelioma cells has further defined the rationale for targeting treatment against this molecule (57).
The increased secretion of PDGF appears to be associated with thrombocythemia, which is considered a prognostic factor of adverse events that is seen in many MPM patients (58-59). In fact, high serum levels of PDGF in MPM patients appear to be a predictive factor of an unfavorable prognosis.
The expression of c-kit in MPM cells has also been shown in 26% of patients, prompting a number of clinical studies investigating imatinib in this disease (60).
Inhibition of PDGFR using imatinib combined with paclitaxel reduced interstitial fluid pressure, thereby enhancing the effect of the drugs and increasing in vitro efficacy (61). A partial response was seen in a Phase I study of imatinib in combination with gemcitabine (62). Dasatinib has shown cytotoxic effects in preclinical studies, leading to decreased migration and invasion in mesothelioma cells (63-64).

PI3K/AKT/mTOR Pathway

The PI3K/AKT/mTOR biological pathway is often aberrant in MPM, and various in vitro studies have shown that inhibiting this intracellular pathway may induce apoptosis in MPM cell lines (36, 65].
Sirolimus is a drug that has been approved as an immunosuppressant and which is currently used mainly in kidney transplantation and has an anti-proliferative effect on the PI3K/AKT/mTOR pathway.
Temsirolimus, a derivative of rapamycin, was investigated in a Phase I study but did not produce meaningful results (66). Studies investigating the combination of cisplatin and sirolimus are also underway, which have shown synergistic anti-tumor effects in MPM cell lines (67).

Mesothelin

Mesothelin is highly expressed in a number of cancer types, including ovarian, pancreatic, some squamous carcinomas and the epithelial subtype MPM (68, 69).
Overexpression of the membrane protein mesothelin in MPM and its limited distribution in normal tissue has raised interest in this protein as a potential anti-tumor target (70).
Preliminary studies have not yet produced meaningful results (71); however, a number of drugs with anti-mesothelin activity are currently being investigated (72). Synergistic effects from the combination of these new agents with chemotherapy have been observed (73) offering promising results.

Ribonucleases

Ribonucleases are proteins that act on cellular RNA. Ranpirnase belongs to this group of proteins and has been investigated for its potential to induce apoptosis of tumor cells and inhibit cellular growth and proliferation.
However, various treatment-related adverse events have been observed, such as renal insufficiency, allergic reactions, arthralgia and peripheral edema (73).

Asparagine-Glycine-Arginine-human

TNF has known anti-tumor activity which is activated by inducing apoptosis of tumor cells. Studies of systemic treatment with this drug have shown that it is highly toxic and so it must be administered in such low doses to avoid disabling side effects that it is rendered ineffective (75-76).
Researchers have investigated a molecule consisting of a TNF fused to a peptide (tumor-homing peptide asparagine-glycine-arginine (NGR)) which is capable of selectively binding to mesothelial cells and has shown good tolerability as well as promising responses (77).

HDACi

Histone dacetylase inhibitors (HDACi) have been shown to alter the growth of numerous cancerogenic cell types. These molecules, many of which are derived from natural sources, have shown that they can inhibit proliferation, induce differentiation, and induce apoptosis of tumor cells. Preliminary data from a Phase I study suggest that vorinostat has clinically significant activity in mesothelioma patients (78).
However, other studies have shown that this drug does not increase survival (79).
Vorinostat has also been investigated in combination with carboplatin and paclitaxel (80) and shown disease stabilization in some cases.
Belinostat is another drug that belongs to this group but has not proved to be superior to the other drugs (81).
However, in vitro studies have demonstrated increased efficacy of these inhibitors when they are administered in combination with other agents (82, 83).

CBP501 EIMC-A12

Cells constantly undergo control processes to verify whether they are free of mutations and can continue in their cell cycle and multiply, or whether there are anomalies, in which case their life cycle must stop, lead to apoptosis and destruction of the cells to prevent more extensive damage. There are actually check-points that the cells must pass to obtain "permission" to proceed in their cellular cycle. Although they are anomalous, tumor cells can overcome these controls and can escape from being destroyed.
Drugs that act on these checkpoints have been defined to block the cell cycle of tumor cells which otherwise would continue proliferating and multiplying (84). Studies have also documented partial responses to treatment with these drugs when administered in combination with cisplatin (20), by enhancing the chemotherapy induced by these drugs.

Immunotherapy and Gene Therapy

Immunotherapy is another treatment that has contributed to significant advances and is currently being studied. An example of this treatment is the systemic administration of IL-2, which unfortunately had only limited efficacy and some side effects (85-86). Intrapleural administration of IL-2 has also been investigated and found to be well tolerated with objective responses, although further studies are needed to evaluate whether it offers more benefits than conventional treatment (87). Studies are also investigating systemic therapy with IL-2 by gene transfer of endogenous IL-2 as well as artificial regulation (88). Rapamycin is a natural macrolid that has been approved as an immunosuppressant and appears to have anti-proliferative effects by inhibiting some kinases such as mTOR. Synthetic derivatives of rapamycin known as "rapalogs" have been developed to improve the pharmacological properties of this macrolide; several examples are everolimus, temsirolimus and deforolimus.
Bortezomib is a potent proteasome inhibitor that has shown interesting cytotoxic effects in vitro and in vivo (89-90). Several studies are currently underway based on promising preclinical data (91). Studies are evaluating the combination of interferon and various standard chemotherapy regimens, which have shown variable response rates to the treatment (92-95).
Vaccine therapies have also been studied, aiming to stimulate immune activity against tumor cells in MPM patients.
Some very interesting studies aimed at activating the immunostimulant ability of dendritic cells have also demonstrated variable but promising results (97-99).

Intrapleural therapy

The pleural cavity provides easy access for therapeutic molecules and intrapleural administration of drugs active in this disease could certainly offer excellent therapeutic prospects (100).
Various studies have evaluated the intracavitary administration of chemotherapy even after surgical resection, with the goal of enhancing local control of the disease (101-103). Results have shown a 50% relapse of the disease after resection together with intrapleural chemotherapy, but further studies are needed to confirm these results that could probably show better responses. Studies are also evaluating the intrapleural administration of recombinant viruses to try to sensitize tumor cells to drugs administered later (104-106).
Anti-mesothelin agents have also been injected into the pleural cavity (107-112), with the aim of inducing an immune response that could also act against tumor cells (113).

Conclusion

It is clear that clinicians, pathologists (114) and basic researchers must collaborate constantly to improve the treatment of rare but very aggressive diseases which often have an unfavorable prognosis such as MPM.
Numerous studies have been conducted over the last few years to investigate targeted molecular therapy and

the biological pathways involved in the pathogenesis of this disease.
We need to gain a better understanding of the basic mechanisms of the development of this cancer in order to sufficiently understand the biomolecular pathways that play a role in cancerogenesis and so more effectively inhibit them. All these new studies, including those currently underway, have contributed to new advances or encouraging findings. However, further studies and more in-depth analyses carefully conducted and controlled will be able to confirm the results obtained thus far, as well as provide new information in order to achieve an effective therapy.

References

1. Pinto C, Ardizzoni A, Betta PG, et al: Export opinions of the First Italian Consensus Conference on the Management of Malignant Pleural Mesothelioma. Am J Clin Oncol 2011; 34: 99–109.
2. Scherpereel A, Astoul P, Baas P, et al: Guidelines of the European Respiratory Society and the European Society of Thoracic Surgeons for the management of malignant pleural mesothelioma. Eur Respir J 2010; 35: 479–495.
3. Yarden Y: The EGFR family and its ligands in human cancer. Signalling mechanisms and therapeutic opportunities. Eur J Cancer 2001; 37(suppl 4):S3–S8.
4. Destro A, Ceresoli GL, Falleni M, et al: EGFR overexpression in malignant pleural mesothelioma. An immunohistochemical and molecular study with clinico-pathological correlations. Lung Cancer 2006; 51: 207–215.
5. Herndon JE, Green MR, Chahinian AP, et al: Factors predictive of survival among 337 patients with mesothelioma treated between 1984 and 1994 by the Cancer and Leukemia Group B. Chest 1998; 113: 723–731.
6. Govindan R, Kratzke RA, Herndon JE 2nd, et al: Gefitinib in patients with malignant mesothelioma: a phase II study by the Cancer and Leukemia Group B. Clin Cancer Res 2005; 11: 2300–2304.
7. Garland LL, Rankin C, Gandara DR, et al: Phase II study of erlotinib in patients with malignant pleural mesothelioma: a Southwest Oncology Group Study. J Clin Oncol 2007; 25: 2406–2413.
8. Cortese JF, Gowda AL, Wali A, et al: Common EGFR mutations conferring sensitivity to gefitinib in lung adenocarcinoma are not prevalent in human malignant mesothelioma. Int J Cancer 2006; 118: 521–522.
9. Destro A, Ceresoli GL, Falleni M, et al: EGFR overexpression in malignant pleural mesothelioma. An immunohistochemical and molecular study with clinico-pathological correlations. Lung Cancer 2006; 51: 207–215.
10. Gaafar R, Bahnassy A, Abdelsalam I, et al: Tissue and serum EGFR as prognostic factors in malignant pleural mesothelioma. Lung Cancer 2010; 70: 43–50.
11. Okuda K, Sasaki H, Kawano O, et al: Epidermal growth factor receptor gene mutation, amplification and protein expression in malignant pleural mesothelioma. J Cancer Res Clin Oncol 2008; 134: 1105–1111.
12. O'Byrne KJ, Edwards JG, Waller DA: Clinico- pathological and biological prognostic factors in pleural malignant mesothelioma. Lung Cancer 2004; 45(suppl 1):S45–S48.
13. Dazzi H, Hasleton PS, Thatcher N, et al: Malignant pleural mesothelioma and epidermal growth factor receptor (EGF-R). Relationship of EGF-R with histology and survival using fixed paraffin embedded tissue and the F4, monoclonal antibody. Br J Cancer 1990; 61: 924–926.
14. Edwards JG, Swinson DE, Jones JL, et al: EGFR expression: associations with outcome and clinicopathological variables in malignant pleural mesothelioma. Lung Cancer 2006; 54: 399–407.
15. Kono SA, Marshall ME, Ware KE, et al: The fibroblast growth factor receptor signalling pathway as a mediator of intrinsic resistance to EGFR-specific tyrosine kinase inhibitors in non-small cell lung cancer. Drug Resist Updat 2009; 12: 95–102.
16. Eyzaguirre A, Buck E, Iwata K, et al: Mechanisms of resistance to EGFR tyrosine kinase inhibitors: implications for patient selection and drug combination strategies. Target Oncol 2008; 3: 235–243.
17. Engelman JA, Janne PA: Mechanisms of acquired resistance to epidermal growth factor receptor tyrosine kinase inhibitors in nonsmall cell lung cancer. Clin Cancer Res 2008; 14: 2895–2899.
18. Jagadeeswaran R, Ma PC, Seiwert TY, et al: Functional analysis of c-Met/hepatocyte growth factor pathway in malignant pleural mesothelioma. Cancer Res 2006; 66: 352–361.
19. Whitson BA, Jacobson BA, Frizelle S, et al: Effects of insulin-like growth factor-1 receptor inhibition in mesothelioma. Thoracic Surgery Directors Association Resident Research Award. Ann Thorac Surg 2006; 82: 996–1001.
20. Kai K, D'Costa S, Sills RC, et al: Inhibition of the insulin-like growth factor 1 receptor pathway enhances the antitumor effect of cisplatin in human malignant mesothelioma cell lines. Cancer Lett 2009; 278: 49–55.
21. Dannenberg AJ, Lippman SM, Mann JR, et al: Cyclooxygenase-2 and epidermal growth factor receptor: pharmacologic targets for chemoprevention. J Clin Oncol 2005; 23: 254–266.
22. Hull MA: Cyclooxygenase-2: how good is it as a target for cancer chemoprevention? Eur J Cancer 2005; 41: 1854–1863.
23. Amir M, Agarwal HK: Role of COX-2 selective inhibitors for prevention and treatment of cancer. Pharmazie 2005; 60: 563–570.
24. Gasparini G, Longo R, Sarmiento R, Morabito A: Inhibitors of cyclo-oxygenase 2: a new class of anticancer agents? Lancet Oncol 2003; 4: 605–615.
25. Baldi A, Santini D, Vasaturo F, et al: Prognostic significance of cyclooxygenase-2 (COX-2) and expression of cell cycle inhibitors p21 and p27 in human pleural malignant mesothelioma. Thorax 2004; 59: 428–433.
26. Edwards JG, Faux SP, Plummer SM, et al: Cyclooxygenase- 2 expression is a novel prognostic factor in malignant mesothelioma. Clin Cancer Res 2002; 8: 1857–1862.
27. O'Kane SL, Cawkwell L, Campbell A, Lind MJ: Cyclooxygenase-2 expression predicts survival in malignant pleural mesothelioma. Eur J Cancer 2005; 41: 1645–1648.
28. Catalano A, Graciotti L, Rinaldi L, et al: Preclinical evaluation of the nonsteroidal antiinflammatory agent celecoxib on malignant mesothelioma chemoprevention. Int J Cancer 2004; 109: 322–328.
29. O'Kane SL, Eagle GL, Greenman J, et al: COX-2 specific inhibitors enhance the cytotoxic effects of pemetrexed in mesothelioma cell lines. Lung Cancer 2010; 67: 160–165.
30. Kitamura F, Araki S, Tanigawa T, et al: Assessment of mutations of Ha- and Ki-ras oncogenes and the p53 suppressor gene in seven malignant mesothelioma patients exposed to asbestos-PCR-SSCP and sequencing analyses of paraffin-embedded primary tumors. Ind Health 1998; 36: 52–56.
31. Kitamura F, Araki S, Suzuki Y, et al: Assessment of the mutations of p53 suppressor gene and Ha- and Ki-ras oncogenes in malignant mesothelioma in relation to asbestos exposure: a study of 12 American patients. Ind Health 2002; 40: 175–181.
32. Ni Z, Liu Y, Keshava N, et al: Analysis of Kras and p53 mutations in mesotheliomas from humans and rats exposed to asbestos. Mutat Res 2000; 468: 87–92.
33. Dote H, Tsukuda K, Toyooka S, et al: Mutation analysis of the BRAF codon 599 in malignant pleural mesothelioma by enriched PCR-RFLP. Oncol Rep 2004; 11: 361–363.
34. Suzuki Y, Murakami H, Kawaguchi K, et al: Activation of the PI3K-AKT pathway in human malignant mesothelioma cells. Mol Med Rep 2009; 2: 181–188.
35. Opitz I, Soltermann A, Abaecherli M, et al: PTEN expression is a strong predictor of survival in mesothelioma patients. Eur J Cardiothorac Surg 2008; 33: 502–506.
36. Altomare DA, You H, Xiao GH, et al: Human and mouse mesotheliomas exhibit elevated AKT/PKB activity, which can be targeted pharmacologically to inhibit tumor cell growth. Oncogene 2005; 24: 6080–6089.
37. Ohta Y, Shridhar V, Bright RK, et al: VEGF and VEGF type C play an important role in angiogenesis and lymphangiogenesis in human malignant mesothelioma tumours. Br J Cancer 1999; 81: 54–61.
38. Dowell J, Kindler H: Antiangiogenic therapies for mesothelioma. Hematol Oncol Clin North Am 2005; 19: 1137–1145.
39. Yasumitsu A, Tabata C, Tabata R, et al: Clinical significance of serum vascular endothelial growth factor in malignant pleural mesothelioma. J Thorac Oncol 2010; 5: 479–483.

40. König JE, Tolnay E, Wiethege T, Müller KM: Co-expression of vascular endothelial growth factor and its receptor flt-1 in malignant pleural mesothelioma. Respiration 2000;67:36–40.
41. Klabatsa A, Sheaff MT, Steele JP, et al: Expression and prognostic significance of hypoxia- inducible factor 1alpha (HIF-1 alpha) in malignant pleural mesothelioma (MPM). Lung Cancer 2006; 51: 53–59.
42. Jackman DM, Kindler HL, Yeap BY, et al: Erlotinib plus bevacizumab in previously treated patients with malignant pleural mesothelioma. Cancer 2008; 113: 808–814.
43. Jahan T, Gu L, Kratzke R, et al: Vatalanib in malignant mesothelioma: a phase II trial by the Cancer and Leukemia Group B (CALGB 30107). Lung Cancer 2011, E-pub ahead of print.
44. Mitchell CL, O'Connor JP, Roberts C, et al: A two-part phase II study of cediranib in patients with advanced solid tumours: the effect of food on single-dose pharmacokinetics and an evaluation of safety, efficacy and imaging pharmacodynamics. Cancer Chemother Pharmacol 2011; 68: 631–641.
45. Drevs J, Siegert P, Medinger M, et al: Phase I clinical study of AZD2171, an oral vascular endothelial growth factor signaling inhibitor, in patients with advanced solid tumors. J Clin Oncol 2007; 25: 3045–3054.
46. Matulonis UA, Berlin S, Ivy P, Tyburski K, et al: Cediranib, an oral inhibitor of vascular endothelial growth factor receptor kinases, is an active drug in recurrent epithelial ovarian, fallopian tube, and peritoneal cancer. J Clin Oncol 2009; 27: 5601–5606.
47. Garland L, Chansky K, Wosniak A, et al: Phase II study of cediranib in patients with malignant pleural mesothelioma: SWOG S0509. J Thorac Oncol 2011; 6: 1938–1945.
48. Morabito A, De Maio E, Di Maio M, et al: Tyrosine kinase inhibitors of vascular endothelial growth factor receptors in clinical trials: current status and future directions. Oncologist 2006; 11: 753–764.
49. Baas P, Boogerd W, Dalesio O, et al: Thalidomide in patients with malignant pleural mesothelioma. Lung Cancer 2005; 48: 291– 296.
50. 97 Dubey S, Jänne PA, Krug L, et al: A phase II study of sorafenib in malignant mesothelioma: results of Cancer and Leukemia Group B 30307. J Thorac Oncol 2010; 5: 1655–1661.
51. Richly H, Henning BF, Kupsch P, et al: Results of a phase I trial of sorafenib (BAY43- 9006) in combination with doxorubicin in patients with refractory solid tumours. Ann Oncol 2006; 17: 866–873.
52. Millward M, Parnis F, Byrne M, et al: Phase II trial of imatinib mesylate in patients with advanced pleural mesothelioma (abstract 912). Proc Am Soc Clin Oncol 2003; 22: 912.
53. Villano J, Husain A, Stadler M, Hanson L, Vogelzang N, Kindler H, et al: A phase II trial of imatinib mesylate in patients (pts) with malignant mesothelioma (MM). J Clin Oncol 2004; 22: 14.
54. Mathy A, Baas P, Dalesio O, et al: Limited efficacy of imatinib mesylate in malignant mesothelioma: a phase II trial. Lung Cancer 2005; 50: 83–86.
55. Bertino P, Porta C, Barbone D, et al: Preliminary data suggestive of a novel translational approach to mesothelioma treatment: imatinib mesylate with gemcitabine or pemetrexed. Thorax 2007; 62: 690–695.
56. Porta C, Mutti L, Tassi G: Negative results of an Italian Group for Mesothelioma (G.I.Me.) pilot study of single-agent imatinib mesylate in malignant pleural mesothelioma. Cancer Chemother Pharmacol 2007; 59: 149–150.
57. Vogelzang NJ, Porta C, Mutti L: New agents in the management of advanced mesothelioma. Semin Oncol 2005; 32: 336–350.
58. Filiberti R, Marroni P, Neri M, et al: Serum PDGF-AB in pleural mesothelioma. Tumour Biol 2005; 26: 221–226.
59. Edwards JG, Cox G, Andi A, et al: Angiogenesis is an independent prognostic factor in malignant mesothelioma. Br J Cancer 2001; 85: 863–868.
60. Arber DA, Tamayo R, Weiss LM: Paraffin section detection of the c-kit gene product (CD117) in human tissues: value in the diagnosis of mast cell disorders. Hum Pathol 1998; 29: 498–504.
61. Pietras K, Rubin K, Sjöblom T, et al: Inhibition of PDGF receptor signaling in tumor stroma enhances antitumor effect of chemotherapy. Cancer Res 2002; 62: 5476– 5484.
62. Ali Y, Lin Y, Gharibo MM, et al: Phase I and pharmacokinetic study of imatinib mesylate (Gleevec) and gemcitabine in patients with refractory solid tumors. Clin Cancer Res 2007; 13: 5876–5882.
63. Tsao AS, He D, Saigal B, et al: Inhibition of c-Src expression and activation in malignant pleural mesothelioma tissues leads to apoptosis, cell cycle arrest, and decreased migration and invasion. Mol Cancer Ther 2007; 6: 1962–1972.
64. Dudek A, Pang H, Kratzke A: A phase II study of dasatinib (D) in patients (pts) with previously treated malignant mesothelioma. J Natl Cancer Inst 2010; 28: 15.
65. Ramos-Nino ME, Testa JR, Altomare DA, et al: Cellular and molecular parameters of mesothelioma. J Cell Biochem 2006; 98: 723– 734.
66. Raymond E, Alexandre J, Faivre S, et al: Safety and pharmacokinetics of escalated doses of weekly intravenous infusion of CCI779, a novel mTOR inhibitor, in patients with cancer. J Clin Oncol 2004; 22: 2336–2347.
67. Hartman ML, Esposito JM, Yeap BY, et al: Combined treatment with cisplatin and sirolimus to enhance cell death in human mesothelioma. J Thorac Cardiovasc Surg 2010; 139: 1233–1240.
68. Chang K, Pai LH, Pass H, et al: Monoclonal antibody K1 reacts with epithelial mesothelioma but not with lung adenocarcinoma. Am J Surg Pathol 1992; 16: 259–268.
69. Chang K, Pastan I: Molecular cloning of mesothelin, a differentiation antigen present on mesothelium, mesotheliomas, and ovarian cancers. Proc Natl Acad Sci USA 1996; 93: 136–140.
70. Hassan R, Bera T, Pastan I: Mesothelin: a new target for immunotherapy. Clin Cancer Res 2004; 10: 3937–3942.
71. Hassan R, Schweizer C, Lu KF, et al: Inhibition of mesothelin-CA-125 interaction in patients with mesothelioma by the antimesothelin monoclonal antibody MORAb- 009: implications for cancer therapy. Lung Cancer 2010; 68: 455–459.
72. Greillier L, Baas P, Welch JJ, et al: Biomarkers for malignant pleural mesothelioma: current status. Mol Diagn Ther 2008; 12: 375– 390.
73. Hassan R, Broaddus VC, Wilson S, et al: Anti-mesothelin immunotoxin SS1P in combination with gemcitabine results in increased activity against mesothelin-expressing tumor xenografts. Clin Cancer Res 2007; 13: 7166–7171.
74. Mikulski SM, Costanzi JJ, Vogelzang NJ, et al: Phase II trial of a single weekly intravenous dose of ranpirnase in patients with unresectable malignant mesothelioma. J Clin Oncol 2002: 20: 274–281.
75. Mittelman A, Puccio C, Gafney E, et al: A phase I pharmacokinetic study of recombinant human tumor necrosis factor administered by a 5-day continuous infusion. Invest New Drugs 1992; 10: 183–190.
76. Lejeune FJ, Lienard D, Matter M, et al: Efficiency of recombinant human TNF in human cancer therapy. Cancer Immun 2006; 6: 6.
77. Gregorc V, Zucali PA, Santoro A, et al: Phase II study of asparagine-glycine arginine- human tumor necrosis factor alpha, a selective vascular targeting agent, in previously treated patients with malignant pleural mesothelioma. J Clin Oncol 2010; 28: 2604– 2611.
78. Kelly WK, O'Connor OA, Krug LM, et al: Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. J Clin Oncol 2005; 23: 3923–3931.
79. Paik PK, Krug LM: Histone deacetylase inhibitors in malignant pleural mesothelioma: preclinical rationale and clinical trials. J Thorac Oncol 2010; 5: 275–279.
80. Ramalingam SS, Parise RA, Ramanathan RK, et al: Phase I and pharmacokinetic study of vorinostat, a histone deacetylase inhibitor, in combination with carboplatin and paclitaxel for advanced solid malignancies. Clin Cancer Res 2007; 13: 3605– 3610.

81. Ramalingam SS, Belani CP, Ruel C, et al: Phase II study of belinostat (PXD101), a histone deacetylase inhibitor, for second line therapy of advanced malignant pleural mesothelioma. J Thorac Oncol 2009; 4: 97–101.
82. Marks PA, Richon VM, Miller T, et al: Histone deacetylase inhibitors. Adv Cancer Res 2004; 91: 137–168.
83. Scherpereel A, Berghmans T, Lafitte JJ, etal: Valproate-doxorubicin: promising therapy for progressing mesothelioma. A phase II study. Eur Respir J 2011; 37: 129–135.
84. Shapiro GI, Tibes R, Gordon MS, et al: Phase I studies of CBP501, a G2 checkpoint abrogator, as monotherapy and in combination with cisplatin in patients with advanced solid tumors. Clin Cancer Res 2011; 17: 3431–3442.
85. Mulatero CW, Penson RT, Papamichael D, et al: A phase II study of combined intravenous and subcutaneous interleukin-2 in malignant pleural mesothelioma. Lung Cancer 2001; 31: 67–72.
86. Nowak AK, Lake RA, Kindler HL, et al: New approaches for mesothelioma: biologics, vaccines, gene therapy, and other novel agents. Semin Oncol 2002; 29: 82–96.
87. Astoul P, Picat-Joossen D, Viallat JR, et al: Intrapleural administration of interleukin- 2 for the treatment of patients with malignant pleural mesothelioma: a phase II study. Cancer 1998; 83: 2099–2104.
88. Caminschi I, Venetsanakos E, Leong CC, et al: Interleukin-12 induces an effective antitumor response in malignant mesothelioma. Am J Respir Cell Mol Biol 1998; 19: 738– 746.
89. Fennell DA, Chacko A, Mutti L: BCL-2 family regulation by the 20S proteasome inhibitor bortezomib. Oncogene 2008; 27: 1189– 1197.
90. Sartore-Bianchi A, Gasparri F, Galvani A, et al: Bortezomib inhibits nuclear factorkappa B-dependent survival and has potent in vivo activity in mesothelioma. Clin Cancer Res 2007; 13: 5942–5951.
91. Gordon GJ, Mani M, Maulik G, et al: Preclinical studies of the proteasome inhibitor bortezomib in malignant pleural mesothelioma. Cancer Chemother Pharmacol 2008; 61: 549–558.
92. 92.Trandafir L, Ruffié P, Borel C, et al: Higher doses of alpha-interferon do not increase the activity of the weekly cisplatin-interferon combination in advanced malignant mesothelioma. Eur J Cancer 1997; 33: 1900– 1902.
93. Upham JW, Musk AW, van Hazel G, et al: Interferon alpha and doxorubicin in malignant mesothelioma: a phase II study. Aust NZ J Med 1993; 23: 683–687.
94. Parra HS, Tixi L, Latteri F, et al: Combined regimen of cisplatin, doxorubicin, and alpha- 2b interferon in the treatment of advanced malignant pleural mesothelioma: a phase II multicenter trial of the Italian Group on Rare Tumors (GITR) and the Italian Lung Cancer Task Force (FONICAP). Cancer 2001; 92: 650–656.
95. Halme M, Knuuttila A, Vehmas T, et al: High-dose methotrexate in combination with interferons in the treatment of malignant pleural mesothelioma. Br J Cancer 1999; 80: 1781–1785.
96. Bretti S, Berruti A, Dogliotti L, et al: Combined epirubicin and interleukin-2 regimen in the treatment of malignant mesothelioma: a multicenter phase II study of the Italian Group on Rare Tumors. Tumori 1998; 84: 558–561.
97. Hegmans JP, Hemmes A, Aerts JG, et al: Immunotherapy of murine malignant mesothelioma using tumour lysate-pulsed dendritic cells. Am J Respir Crit Care Med 2005; 171: 1168–1177.
98. Hegmans JP, Hemmes A, Hammad H, et al: Mesothelioma environment comprises cytokines and T-regulatory cells that suppress immune responses. Eur Respir J 2006; 27: 1086–1095.
99. Hegmans JP, Veltman JD, Lambers ME, de Vries IJ, Figdor CG, Hendriks RW, Hoogsteden HC, Lambrecht BN, Aerts JG: Consolidative dendritic cell-based immunotherapy elicits cytotoxicity against malignant mesothelioma. Am J Respir Crit Care Med 2010; 181: 1383–1390.
100. Haas AR, Sterman DH: Novel intrapleural therapies for malignant diseases. Respiration 2012;83:277–292.
101. Tilleman TR, Richards WG, Zellos L, et al: Extrapleural pneumonectomy followed by intracavitary intraoperative hyperthermic cisplatin with pharmacologic cytoprotection for treatment of malignant pleural mesothelioma: a phase II prospective study. J Thorac Cardiovasc Surg 2009; 138: 405–411.
102. Sterman DH, Treat J, Litzky LA, et al: Adenovirus- mediated herpes simplex virus thymidine kinase/ganciclovir gene therapy in patients with localized malignancy: results of a phase I clinical trial in malignant mesothelioma. Hum Gene Ther 1998; 9: 1083–1092.
103. Molnar-Kimber KL, Sterman DH, Chang M, et al: Impact of preexisting and induced humoral and cellular immune responses in an adenovirus-based gene therapy phase I clinical trial for localized mesothelioma. Hum Gene Ther 1998; 9: 2121–2133.
104. Sterman DH, Recio A, Vachani A, et al: Long-term follow-up of patients with malignant pleural mesothelioma receiving high-dose adenovirus herpes simplex thymidine kinase/ganciclovir suicide gene therapy. Clin Cancer Res 2005; 11: 7444– 7453.
105. Sterman DH, Recio A, Carroll RG, et al: A phase I clinical trial of single-dose intrapleural IFN-beta gene transfer for malignant pleural mesothelioma and metastatic pleural effusions: high rate of antitumor immune responses. Clin Cancer Res 2007; 13: 4456– 4466.
106. Hassan R, Ho M: Mesothelin targeted cancer immunotherapy. Eur J Cancer 2008; 44: 46–53.
107. Hassan R, Zhang J, Pastan I: Antibodybased treatment for mesothelioma: clinical trials and laboratory studies. Lung Cancer 2006; 54:S13.
108. Hassan R, Bullock S, Premkumar A, et al: Phase I study of SS1P, a recombinant antimesothelin immunotoxin given as a bolus I.V. infusion to patients with mesothelinexpressing mesothelioma, ovarian, and pancreatic cancers. Clin Cancer Res 2007; 13: 5144–5149.
109. Li Q, Verschraegen CF, Mendoza J, et al: Cytotoxic activity of the recombinant antimesothelin immunotoxin, SS1(dsFv)PE38, towards tumor cell lines established from ascites of patients with peritoneal mesotheliomas. Anticancer Res 2004; 24: 1327–1335.
110. Armstrong DK, Laheru D, Ma WW, et al: A phase I study of MORAb-009, a monoclonal antibody against mesothelin in pancreatic cancer, mesothelioma, and ovarian adenocarcinoma (abstract). J Clin Oncol 2007; 25: 615s.
111. Brockstedt DG, Giedlin MA, Leong ML, et al: Listeria-based cancer vaccines that segregate immunogenicity from toxicity. Proc Natl Acad Sci USA 2004; 101: 13832–13837.
112. Thomas AM, Santarsiero LM, Lutz ER, et al: Mesothelin-specific CD8(+) T cell responses provide evidence of in vivo crosspriming by antigen-presenting cells in vaccinated pancreatic cancer patients. J Exp Med 2004; 200: 297–306.
113. Hassan R, Ebel W, Routhier EL, et al: Preclinical evaluation of MORAb-009, a chimeric antibody targeting tumor associated mesothelin. Cancer Immun 2007; 7: 20.
114. Jantz MA, Antony VA: Pathophysiology of the pleura. Respiration 2008;75:121–133.
115. Froudarakis ME: Pleural diseases in the molecular era – time for more answers: introduction. Respiration 2012;83:2–4.