The Emerging Role of Antifolates in the Treatment of Malignant Pleural Mesothelioma

Karim Fizazi, William J. John, and Nicholas J. Vogelzang

Clinicians have long regarded malignant pleural mesothelioma as a chemoresistant neoplasm and as a result no standard chemotherapy regimen has emerged. Antifolates such as methotrexate are among the most active compounds in mesothelioma, albeit based only on phase II data. Recently two antifolate-based combinations with apparently higher efficacy than older regimens have emerged: the pemetrexed/cisplatin regimen and the raltitrexed/oxaliplatin regimen. In two phase I trials with pemetrexed combined with either cisplatin or carboplatin responses occurred in five of 11 and nine of 29 patients, respectively. In a phase I trial of raltitrexed/oxaliplatin, six of 17 patients (35%) with mesothelioma achieved a partial response. In a phase II trial of raltitrexed/oxaliplatin, 14 objective responses were confirmed in 72 patients (25%) with malignant pleural mesothelioma. Indeed, responses were seen in cisplatin-refractory patients. Based on the promising results from these combination trials, two large phase III studies have begun. The first study was a multicenter, multinational trial sponsored by Eli Lilly and Company, which randomized more than 430 patients with malignant pleural mesothelioma to cisplatin with or without pemetrexed. That trial completed enrollment in February 2001 and is the largest trial ever conducted in mesothelioma. The second trial is being conducted by the European Organization for the Research and Treatment of Cancer (EORTC) and compares cisplatin with or without raltitrexed with planned accrual of 240 patients. In both trials, survival is the main endpoint. These trials will help to define the role of these new antifolates in malignant pleural mesothelioma.

Semin Oncol 29:77-81.

SIGNIFICANT THERAPEUTIC interest has focused on malignant pleural mesothelioma in recent years due to the increasing incidence in Western countries and due to its dismal survival rate.[1,2] Most patients with malignant pleural mesothelioma have locally advanced disease at presentation. Therefore, attempts at local control with surgery are restricted to a few candidates for pleurectomy or extrapleural pneumonectomy. Likewise, radiotherapy is rarely an option, although short-duration radiation therapy delivered to thoracoscopy scars prevents malignant seeding.[3] Many systemic therapeutic options have been developed in the past, yet no standard therapy has emerged.[4-6] Most agents have shown little activity but even "active" agents have only shown response rates of 15% to 20%, with median survivals of only 7 to 9 months.[4-6] Response assessment has been a concern, since bidimensional measurements are difficult to obtain. In spite of these concerns, some phase II reports have suggested that patients can expect a 40% to 50% clinical benefit with some drugs.[7-9] In the early 1990s, combining chemotherapy and immunotherapy yielded promising response rates, but the toxicity of this approach has precluded phase III development.[10] Therefore, most research efforts have focused on assessing the efficacy of new agents and new combinations. Although most chemotherapeutics have limited activity, for example, paclitaxel and irinotecan,[11-13] other agents including the antifolates have been more promising. This review discusses the design and results of trials with the older and newer antifolates.

HISTORICAL PERSPECTIVE OF ANTIMETABOLITES IN MESOTHELIOMA BEFORE THE MID-1990S

Although the role of antimetabolites (including the antifolates) has been assessed in mesothelioma, reliable data on monotherapy are scarce due to the relative rarity of the disease and the difficulties in assessing objective responses. For example, data on 5-azacytidine are available in only six patients treated in two trials,[14,15] while data on 5-dihydro-azacytidine (DHAC) alone and in combination with cisplatin are more reliable and suggest activity, including rare complete remissions.[16-18]

The activity of another antimetabolite, 5-fluorouracil (5-FU), has also been poorly assessed in three very small trials containing a total of 25 patients.[19-21] Although five patients (20%)

From the Institut Gustave Roussy, Villejuif, France; Eli Lilly and Company, Indianapolis, IN; and the University of Chicago Cancer Research Center, Chicago, IL.

Address reprint requests and to Karim Fizazi, MD, Department of Medicine, Institut Gustave Roussy, 39 rue Camille Desmoulins, 94800 Villejuif, France.

0093-7754/02/2901-0009$35.00/0

doi:10.1053/sonc.2002.30233

achieved a response to therapy (including four complete responses), only one partial response out of 20 was reported in the largest prospective trial reported to date.[21] There have been a number of case reports describing long-lasting responses with single-agent 5-FU or 5-FU–based combinations.[22-25] A single-center phase II trial assessed the cisplatin/5-FU combination plus etoposide and mitomycin C with a promising response rate of 38%.[26] However, that regimen induced myelosupression requiring colony-stimulating factors and the results require confirmation. Therefore, it is difficult to assess the efficacy of 5-FU (a thymidylate synthase [TS] inhibitor) in malignant pleural mesothelioma based on the available literature. A multicenter trial of the oral fluoropyrimidine, capecitabine, has been completed within the Cancer and Leukemia Group B (CALGB) and final results are pending.

Three trials have assessed the activity of the oldest antifolate, methotrexate, in mesothelioma with response rates of 2/6, 4/9, and 22/60 (37%), respectively.[27-29] This apparent efficacy of high-dose methotrexate plus leucovorin rescue did not lead to widespread use in malignant pleural mesothelioma. This technique is difficult to handle in adult patients whose median age is typically 70 years and in patients where pleural and peritoneal effusions complicate methotrexate pharmacokinetics.

Therefore, methotrexate analogs were developed and tested against mesothelioma. Dideazafolic acid (CB3717), a quinazoline antifolate which inhibits TS, was assessed in 17 patients with only one partial response.[30] Further trials of this compound were suspended due to unpredictable nephrotoxicity.

The CALGB has followed up this promising lead by performing a series of clinical trials using various antifolates in mesothelioma. Trimetrexate was the first agent administered in 52 patients, treated sequentially at two doses (6 mg/m^2 × 5 and 10 mg/m^2 × 3 days every 21 days). It resulted in a low (but definite) response rate (12%) and a reasonable 2-year survival rate of 18%.[31] The Food and Drug Administration (FDA) approved trimetrexate to treat *Pneumoncystis carinii* pneumonia. Surprisingly, further studies with trimetrexate in mesothelioma have not been initiated.

Edatrexate monotherapy (80 mg/m^2 intravenously weekly) yielded five responders in 20 patients (25%). However, this regimen was associated with a high incidence of serious side effects, including two lethal neutropenic fevers. The combination of edatrexate with leucovorin was better tolerated, although the response rate was only 16%, thus raising the question of an adverse role of leucovorin on the efficacy of edatrexate.[32] Since edatrexate is unlikely to be FDA-approved, newer antifolates and TS inhibitors continue to be developed.

Recently, reproducible efficacy has been reported by several groups using the combination of new-generation TS inhibitors (either pemetrexed or raltitrexed) and platinating agents (oxaliplatin, cisplatin, or carboplatin).

Pemetrexed/Cisplatin

Pemetrexed (Alimta, LY231514, Eli Lilly and Company, Indianapolis, IN), a recently developed antifolate/antimetabolite,[33] has shown promising activity in malignant pleural mesothelioma alone or in combination with cisplatin or carboplatin. Pemetrexed is an antifolate that inhibits several folate-dependent enzymes including TS, dihydrofolate reductase (DHFR), and GAR formyl transferase (GARFT). Given at a dose of 500 mg/m^2 intravenously every 3 weeks, pemetrexed has a broad range of antineoplastic activity in lung, colon, pancreas, and breast cancers.[34-36]

In a phase I trial of pemetrexed combined with cisplatin, five of 11 patients (45%) with malignant pleural mesothelioma had a confirmed response.[37] Based on these results, a randomized phase III trial of cisplatin (75 mg/m^2) plus pemetrexed (500 mg/m^2) every 3 weeks was compared to cisplatin monotherapy. This trial (called EMPHACIS: Evaluation of Mesothelioma in a Phase III Study of Alimta with Cisplatin) has reached the accrual goal of 430. This trial, the largest phase III trial ever conducted in malignant pleural mesothelioma, is currently undergoing analysis.

Another phase I study has combined pemetrexed with carboplatin in malignant pleural mesothelioma. The maximum tolerated dose of pemetrexed was 500 mg/m^2 with a carboplatin area under the curve (AUC) of 5.0. Among 29 enrolled patients, nine (31%) achieved a partial response and symptomatic improvement was documented in 14 (48%). The median survival duration was 13.6 months.[38] Finally, a phase II trial of single-agent pemetrexed (500 mg/m^2) has recently completed accrual of 62 patients. Nine responses

(14.5%) were observed and the median survival was 10.7 months.[39]

Because of sporadic and unpredictable episodes of neutropenia, diarrhea, stomatitis, and thrombocytopenia seen in early pemetrexed trials, Niyikiza et al analyzed toxicity as a function of baseline homocysteine levels.[40] They reasoned that the toxicity could be related to low baseline folate levels (a hypothesis which could be tested since homocysteine levels, reflecting folate, were measured in most patients on the phase II trials). Multivariate analysis found that high homocysteine levels (reflecting low folic acid levels/intake) and low albumin levels were most predictive of toxicity.[40] B_{12} and folate supplementation was then added to subsequent pemetrexed trials and found to significantly reduce pemetrexed toxicity.[41]

Raltitrexed/Oxaliplatin

TS catalyses the conversion of uracil monophosphate to thymidylate and is the only source of thymidylate for DNA replication. Several folate analogs, including the first antifolate TS inhibitor, CB3717, have been developed as TS inhibitors.[42] The Cancer Research Campaign Center for Cancer Therapeutics modified CB3717, leading to raltitrexed.[43] Raltitrexed is now approved in Australia, Canada, and Europe for the treatment of metastatic colorectal cancer.[44]

From 1997 to 1999, the Institut Gustave Roussy conducted a phase I trial of raltitrexed and oxaliplatin in advanced solid neoplasms.[45] This study was intended to develop an alternative to 5-FU/oxaliplatin in colorectal cancer, with 5-FU being replaced by raltitrexed, a TS inhibitor given on a once-every-3-week schedule. Patients with orphan neoplasms, including those with refractory mesothelioma, were enrolled into the study. After the first two patients with cisplatin-refractory mesothelioma obtained a partial response and significant clinical benefit, the trial was opened to patients with chemonaive malignant pleural mesothelioma.[10] Overall, six of 17 (35%) patients with mesothelioma achieved a partial response (35%), including four cisplatin-pretreated patients, whereas four other patients had a short-lived response that was not confirmed by a computed tomography scan 4 weeks later. Responses were reviewed by an independent radiologist. The median survival duration was 13 months and 17 months since inclusion in the study and since diagnosis, respectively. This outpatient combination was well tolerated with no alopecia and no significant hematologic toxicity.

Based on these encouraging results, a large phase II trial was initiated in France in malignant mesothelioma. The schedule was the same as that of the phase I trial: raltitrexed (3 mg/m^2) was given first as a 15-minute infusion and 45 minutes later oxaliplatin (130 mg/m^2) as a 2-hour infusion, every 3 weeks in the outpatient clinic. Responses were also reviewed by an independent radiologist. Accrual to this study was completed in 1999 and the raltitrexed/oxaliplatin regimen induced responses in 14 of 72 patients (response rate, 25%; 95% confidence interval [CI], 14% to 8%). Currently, the median survival from trial entry and from diagnosis is 6.5 months (95% CI, 5.4 to 7.7) and 12 months (95% CI, 10.1 to 15.3), respectively.[46,47] The final results, including an assessment of clinical benefit, are expected soon.

The promising efficacy of the raltitrexed/oxaliplatin combination has prompted the European Organization for Research and Treatment of Cancer (EORTC) to initiate a phase III randomized trial of cisplatin with or without raltitrexed. This study is ongoing with an accrual goal of 240 patients to detect a 50% increase in the median survival of patients treated with the combination regimen.

CONCLUSION

Recent results using the raltitrexed/oxaliplatin and pemetrexed/cisplatin or carboplatin regimens as chemotherapy for malignant pleural mesothelioma appear promising. These two regimens have in common the combination of a "third-generation" antifolate TS inhibitor and a platinum compound. Hopefully, the results of the two phase III trials comparing cisplatin alone versus cisplatin plus either raltitrexed (the EORTC trial) or pemetrexed (the EMPHACIS trial) will further define the role of these combinations in malignant pleural mesothelioma.

The molecular/cellular basis for the consistent activity of the antifolates in malignant pleural mesothelioma is unknown. However, recently, Bueno et al discovered that the human alpha folate receptor was consistently overexpressed in this disease. Using differential display analysis on freshly frozen RNA obtained from 61 normal lung, pleura, and mesothelioma specimens,[48] they found

that 44 (72%) of the mesothelioma patients had between two- and fourfold higher mRNA expression of the folate receptor compared to normal tissues. There was no correlation with histologic subtype. This finding suggests that folate receptor antagonist therapy in malignant pleural mesothelioma could benefit the majority of these patients.

REFERENCES

1. Peto J, Hodgson JT, Matthews FE, et al: Continuing increase in mesothelioma mortality in Britain. Lancet 345:535-539, 1995
2. Peto J, Decarli A, La Vecchia C, et al: The European mesothelioma epidemic. Br J Cancer 79:666-672, 1999
3. Boutin C, Rey F, Viallat JR: Prevention of malignant seeding after invasive diagnostic procedures in patients with pleural mesothelioma. A randomized trial of local radiotherapy. Chest 108:754-758, 1995
4. Ong ST, Vogelzang NJ: Chemotherapy in malignant pleural mesothelioma. A review. J Clin Oncol 14:1007-1017, 1996
5. Ryan CW, Herndon J, Vogelzang NJ: A review of chemotherapy trials for malignant mesothelioma. Chest 113:66S-73S, 1998
6. Alberts AS, Falkson G, Goedhals L, et al: Malignant pleural mesothelioma: A disease unaffected by current therapeutic maneuvers. J Clin Oncol 6:527-535, 1988
7. Middleton GW, Smith IE, O'Brien ME, et al: Good symptom relief with palliative MVP (mitomycin C,vinblastine and cisplatin) chemotherapy in malignant mesothelioma. Ann Oncol 9:269-273, 1998
8. Steele JP, Shamash J, Evans MT, et al: Phase II study of vinorelbine in patients with malignant pleural mesothelioma. J Clin Oncol 18:3912-3917, 2000
9. Steele JP, O'Doherty CA, Shamash J, et al: Phase II trial of liposomal daunorubicin in malignant pleural mesothelioma. Ann Oncol 12:497-499, 2001
10. Fizazi K, Caliandro R, Soulie P, et al: Combination raltitrexed (Tomudex)-oxaliplatin: A step forward in the struggle against mesothelioma? The Institut Gustave Roussy experience with chemotherapy and chemo-immunotherapy in mesothelioma. Eur J Cancer 36:1514-152, 2000
11. Vogelzang NJ, Herndon JE 2nd, Miller A, et al: High-dose paclitaxel plus G-CSF for malignant mesothelioma: CALGB phase II study 9234. Ann Oncol 10:597-600, 1999
12. Caliandro R, Boutin C, Perol M, et al: Phase II study of paclitaxel (Taxol) and cisplatin (CDDP) in advanced pleural malignant mesothelioma (MM). Lung Cancer 18:19, 1997 (abstr)
13. Kindler HL, Herndon JE, Vogelzang NJ, et al: CPT-11 in malignant mesothelioma: A phase II trial by the Cancer and Leukemia Group B (CALGB 9733). Proc Am Soc Clin Oncol 19:505a, 2000 (abstr)
14. Vogler WR, Arkun S, Velez-Garcia E: Phase I study of twice weekly 5-azacytidine (NSC-102816). Cancer Chemother Rep 58:895-899, 1974
15. Chahinian AP, Pajak TF, Holland JF, et al: Diffuse malignant mesothelioma. Prospective evaluation in 69 patients. Ann Intern Med 96:746-755, 1982
16. Dhingra HM, Murphy WK, Winn RJ, et al: Phase II trial of 5,6-dihydro-5-azacytidine in pleural malignant mesothelioma. Invest New Drugs 9:69-72, 1991
17. Vogelzang NJ, Herndon DC 2nd, Cirrincione C, et al: Dihydro-5-azacytidine in malignant mesothelioma. Cancer 79: 2237-2242, 1997
18. Samuels BL, Herndon JE 2nd, Harmon DC, et al: Dihydro-5-azacytidine and cisplatin in the treatment of malignant mesothelioma: A phase II study by the Cancer and Leukemia Group B. Cancer 82:1578-1584, 1998
19. Gerner RE, Moore GE: Chemotherapy of malignant mesothelioma. Oncology 30:152-155, 1974
20. Jara F, Takita H, Rao UNM: Malignant mesothelioma of pleura. Clinicopathologic observation. NY State J Med 10: 1885-1888, 1977
21. Harvey VJ, Slevin ML, Ponder BAJ, et al: Chemotherapy of diffuse mesothelioma. Phase II trials of 5-fluorouracil and Adriamycin. Cancer 54:961-964, 1984
22. Umsawasdi T, Dhingra HM, Charnsangavej C, et al: A case report of malignant pleural mesothelioma with long-term disease control after chemotherapy. Cancer 67:48-54, 1991
23. Colleoni M, Liessi G, Avventi C, et al: Response to chemotherapy of brain metastases from malignant pleural mesothelioma. Tumori 82:456-468, 1996
24. Takagi K, Fukushima Y, Kanou J, et al: A long-term survivor case of malignant mesothelioma treated by recombinant tumor necrosis factor-SAM2 (TNF-alpha mutein) and 5-fluorouracil (5-FU): A new therapeutic approach based on host-tumor relationship. Anticancer Res 18:4591-4600, 1998
25. Ito H, Imada T, Kondo J, et al: A case of malignant peritoneal mesothelioma showed complete remission with chemotherapy. Jpn J Clin Oncol 28:145-148, 1998
26. Kasseyet S, Astoul P, Boutin C: Results of a phase II trial of combined chemotherapy for patients with diffuse malignant mesothelioma of the pleura. Cancer 85:1740-1749, 1999
27. Dimitrov NV, Egner J, Balcueva E, et al: High dose methotrexate with citrouorum factor and vincristine in the treatment of malignant mesothelioma cancer. Cancer 50:1245-47, 1982
28. Djerassi I, Kim JS, Kassarov L, et al: Response of mesothelioma to large doses of methotrexate with CF rescue (HDMTX-CF) used alone or woth cisplatinum. Proc Am Soc Clin Oncol 4:191, 1985 (abstr)
29. Solheim OP, Saeter G, Finnanger AM, et al: High-dose methotrexate in the treatment of malignant mesothelioma of the pleura. A phase II study. Br J Cancer 65:956-960, 1992
30. Cantwell BM, Earnshaw M, Harris AL: Phase II study of a novel antifolate, N10-propargyl-5,8 dideazafolic acid (CB3717), in malignant mesothelioma. Cancer Treat Rep 70: 1335-1336, 1986
31. Vogelzang NJ, Weissman LB, Herndon JE 2nd, et al: Trimetrexate in malignant mesothelioma: A Cancer and Leukemia Group B phase II study. J Clin Oncol 12:1436-1442, 1994
32. Kindler HL, Belani CP, Herndon JE 2nd, et al: Edatrexate (10-ethyl-deaza-aminopterin) (NSC #626715) with or without leucovorin rescue for malignant mesothelioma. Sequential phase II trials by the cancer and leukemia group B. Cancer 86:1985-1991, 1999
33. Adjei AA: Pemetrexed: A multitargeted antifolate

agent with promising activity in solid tumors. Ann Oncol 10:1335-1341, 2000

34. Rusthoven JJ, Eisenhauer E, Butts C, et al: Multitargeted antifolate LY231514 as first-line chemotherapy for patients with advanced non-small-cell lung cancer: A phase II study. National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 17:1194, 1999

35. John W, Picus J, Blanke CD, et al: Activity of multitargeted antifolate (pemetrexed disodium, LY231514) in patients with advanced colorectal carcinoma: Results from a phase II study. Cancer 88:1807-1813, 2000

36. Miles DW, Smith IE, Coleman RE, et al: A phase II study of pemetrexed disodium (LY231514) in patients with locally recurrent or metastatic breast cancer. Eur J Cancer 37:1366-1371, 2001

37. Thödtmann R, Depenbrock H, Dumez H, et al: Clinical and pharmacokinetic phase I study of multitargeted antifolate (LY231514) in combination with cisplatin. J Clin Oncol 17: 3009-3016, 1999

38. Calvert AH, Hugues AN, Calvert PM, et al: Alimta in combination with carboplatin demonstrates clinical activity against malignant mesothelioma in a phase I trial. Proc Am Soc Clin Oncol 19:495a, 2000 (abstr)

39. Scagliotti G, Shin D, Kindler H, et al: Phase II study of ALIMTA (pemetrexed disodium, MTA) single agent in patients with malignant pleural mesothelioma. Eur J Cancer 37:S20, 2001 (suppl 6, abstr)

40. Niyikiza C, Baker S, Johnson R, et al: MTA (LY231514): Relationship of vitamin metabolite profile, drug exposure, and other patient characteristics to toxicity. Ann Oncol 9:126, 1998 (abstr)

41. Bunn P, Paoletti P, Niyikiza C, et al: Vitamin B12 and folate reduce toxicity of Alimta (pemetrexed disodium, LY231514, MTA), a novel antifolate/antimetabolite. Proc Am Soc Clin Oncol 20:76a, 2001 (abstr)

42. Jackman AL, Calvert AH: Folate-based thymidylate synthase inhibitors as anticancer drugs. Ann Oncol 6:871-881, 1995

43. Newell DR: Clinical pharmacokinetics of antitumor antifolates. Semin Oncol 26:74-81, 1999 (suppl 6)

44. Clarke SJ, Hanwell J, de boer M, et al: Phase I trial of ZD1694, a new folate-based thymidylate synthase inhibitor, in patients with solid tumors. J Clin Oncol 14:1495-503, 1996

45. Fizazi K, Ducreux M, Ruffié P, et al: A phase I, dose-finding and pharmacokinetic study of raltitrexed ('Tomudex') combined with oxaliplatin in patients with advanced cancer. J Clin Oncol 18:2293-2300, 2000

46. Fizazi K, Doubre H, Viala J, et al: The combination of raltitrexed ('Tomudex') and oxaliplatin is an active regimen in malignant mesothelioma: Results of a phase II study. Proc Am Soc Clin Oncol 19:2276, 2000 (abstr)

47. Fizazi K, Doubre H, Viala J, et al: Chimiothérapie par l'association raltitrexed-oxaliplatine chez des patients atteints de mésothéliome: Résultats préliminaires d'une étude de phase II. Rev Mal Resp 18:1S103-1S104, 2001

48. Bueno R, Appasani K, Mercer H, et al: The alpha folate receptor is highly activated in malignant pleural mesothelioma. J Thorac Cardiovasc Surg 121:225-233, 2001