The role of pemetrexed in recurrent epithelial ovarian cancer: A scoping review

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Abstract

Ovarian cancer is the leading cause of mortality among gynecologic malignancies, with most cases diagnosed at an advanced stage. Despite an initial response, most develop a recurrence and subsequent resistance to standard therapies. Pemetrexed (Alimta™) is a new generation multi-targeted antifolate initially approved for the treatment of malignant pleural mesothelioma. In recent years, it has shown promise in the treatment of recurrent epithelial ovarian cancer. In this review, we outline the current literature and discuss the future of pemetrexed in the setting of recurrent epithelial ovarian cancer.

Introduction

Ovarian cancer is the leading cause of mortality among gynecologic malignancies, with more than 22,000 new diagnoses and 14,000 deaths estimated to occur in 2017.[1] Most cases are diagnosed at advanced stages, which carry worse prognoses.[2] Initial treatment consists of a combination of surgery and chemotherapy, to which most patients experience an objective response.[3] Despite an initial response, most patients recur. Those who develop recurrence more than six months after therapy are classified as *platinum-sensitive*, while those who develop recurrence before six months are deemed *platinum-resistant*. Prognosis for platinum-resistant disease is poor. Available treatment options for platinum resistant disease include paclitaxel, pegylated liposomal doxorubicin, gemcitabine, and topotecan. Response rates for platinum-resistant disease are poor.[4-9] Novel therapeutic approaches are needed to improve outcomes for patients with recurrent platinum resistant epithelial ovarian cancer.

Pemetrexed is a new generation multi-targeted antifolate agent which was initially approved by the FDA in 2004 for the treatment of malignant pleural mesothelioma in combination with cisplatin.[10] It has also demonstrated activity against several tumor types, including ovarian cancer, both as a single agent and when combined with other cytotoxic agents.[11-12]

Recent guidelines from the National Comprehensive Cancer Center Network (NCCN) include pemetrexed as a single agent for women with recurrent ovarian cancer who demonstrate platinum resistant disease.[13]

The purpose of this scoping review is to address the gaps in the published literature regarding the efficacy of pemetrexed, alone and in combination, as a treatment option for women with recurrent ovarian cancer.

Research methods

Scoping reviews are conducted in order to map the key concepts in an area of research and identify the sources and types of available evidence. We used the five-step method for scoping reviews developed by Arksey and O'Malley.[14]

1. *The research question*. Our research question is: what is the current state of pemetrexed as therapy in the setting of recurrent ovarian cancer? As of this writing, multiple systematic reviews are published discussing pemetrexed, its clinical activity and toxicity profile in recurrent ovarian cancer. We believe a review of the available clinical trials and existing literature would add a greater understanding of pemetrexed and underscore the need for further investigation of it as treatment of recurrent ovarian cancer.

2. *Identify relevant studies*. We performed an electronic literature search using the following databases and web-based searches: MEDLINE, Cochrane Library, ClinicalTrials.gov, Canadian Clinical Trials and Cancer Trials, Australian Clinical Trials, WHO ICTRP, and Google Scholar. We used the MeSH terms 'ovarian neoplasms', 'pemetrexed,' 'fallopian tube neoplasms' while using MEDLINE. In other search engines, we used combinations of 'ovarian cancer', 'primary peritoneal cancer', 'pemetrexed',

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'Alimta', 'multitargeted antifolate', and 'LY231514'. We only included English-language publications and studies with humans as subjects. This strategy yielded 26 results. These search results are current as of November 24, 2017.

3. *Study selection.* Studies were initially selected if the topic was pemetrexed therapy in ovarian cancer, making sure to filter out research pertaining to the topics of mesothelioma and lung cancer, as the bulk of pemetrexed literature pertains to these diseases. We included studies that had results pertaining to pemetrexed and its effects in the setting of recurrent ovarian cancer. Duplicate results, studies without dose schedules, and trials without evidence were excluded. Two members of the research team independently applied inclusion and exclusion criteria. Of the 26 results, ten were excluded for not meeting criteria. The primary reasons for exclusion were that the studies did not have available results or were about unrelated topics. Of the remaining 16 results, five were phase I trials, five were phase II trials, five were systematic reviews, and one was an expert commentary.

4. *Charting the data*. We recorded the following data from the selected studies on a data extraction sheet: author, year of publication, Clinical Trials Identifier (if applicable), treatment regimen (if applicable), study design, study population and size (if applicable), and study outcome.

5. *Collating, summarizing, and reporting results*. Drafts of this manuscript were circulated and edited based on feedback from the study team until it appropriately reflected the results of the literature search.

Results

We identified 16 studies meeting criteria. They are listed in Tables 1-4.[4,20-28, 31-36]

Table 1. Phase I studies.

Author	Year	Study population	Study size	Treatment*	Conclusion
Misset[20]	2004	Locally advanced or metastatic solid tumors	45 (including 3 ovarian)	Escalating dose pemetrexed and oxaliplatin without supplementation, 21-day cycle	MTD of pemetrexed was not reached. The recommended phase II dose was 500 mg/m^2 plus oxaliplatin 120 mg/m^2
Hensley[21]	2008	Solid tumor cohort and recurrent OC cohort	54 (including 30 ovarian)	Escalating dose pemetrexed + gemcitabine, 14-day cycle	In OC patients, the MTD for pemetrexed was 600 mg/m^2
Sehouli[22]	2010	Platinum sensitive recurrent OC	20	Escalating dose pemetrexed + escalating dose carboplatin, 21-day cycle	MTD was not reached for either medication. The recommended phase II dose for pemetrexed was 500 mg/m^2 and carboplatin AUC 6
Richards[23]	2011	Refractory OC, breast cancer, peritoneal cancer	29 (including 16 ovarian, 3 primary peritoneal, 10 breast)	Escalating dose pemetrexed (days 1, 15) + escalating dose PLD (day 1), 28-day cycle	MTD of pemetrexed was 500 mg/m^2 and MTD of PLD was 40 mg/m^2
Chambers[24]	2012	Stage III OC	15	Escalating dose IP pemetrexed + cisplatin + paclitaxel, 21-day cycle	MTD of pemetrexed was 500 mg/m^2

*Given intravenously unless otherwise noted. Vitamin B12 and folate supplementation given unless otherwise noted. IP, intraperitoneal; MTD, maximum tolerated dose; OC, ovarian cancer; PLD, pegylated liposomal doxorubicin.

Table 2. Phase II studies.

Author	Year	Study population	Study size	Treatment*	Outcome
Miller[25]	2009	Platinum resistant recurrent OC	51	Pemetrexed 900 mg/m^2, 21-day cycle	The overall response rate of pemetrexed in this population was 21%. One patient had a complete response. The toxicity profile was mild
Vergote[26]	2009	Platinum resistant recurrent OC	98 (47 given 500 mg/m^2; 51 given 900 mg/m^2)	Pemetrexed 500 mg/m^2 or 900 mg/m^2, 21-day cycle	The response rate was 9.3% for those given 500 mg/m^2 and 10.4% for patients given 900 mg/m^2. The higher dose did not significantly improve response. Therapy was better tolerated at 500 mg/m^2
Sehouli[27]	2012	Platinum sensitive recurrent OC	61	Pemetrexed 500 mg/m^2 + carboplatin AUC 6, 21-day cycle	Overall response rate for this study was 32.8%, with one patient experiencing a complete response. This combination demonstrated little serious toxicity
Matulonis[28]	2008	Platinum sensitive recurrent OC	45	Pemetrexed 500 mg/m^2 + carboplatin AUC 6, 21-day cycle	The response rate for this pair was 51.1%, with no complete responses. It exhibited an acceptable toxicity profile
Hagemann[31]	2013	Platinum resistant and platinum sensitive recurrent OC	34	Pemetrexed 500 mg/m^2 + bevacizumab 15 mg/kg, 21-day cycle	The overall response rate was 41%, with no complete responses. One patient with platinum-sensitive disease developed acute myeloid leukemia, possibly related to therapy

*Given intravenously. All studies used vitamin supplementation. OC, ovarian cancer; RR, response rate; CR, complete response.

Optimal dose and toxicity

The optimal dosing of pemetrexed was first explored in trials focusing on non-small cell lung cancer. This was found to be 500 mg/m^2, as higher doses were accompanied by more severe side effects, usually gastrointestinal upset and myelosuppression.[15,16] Further research demonstrated that elevated pretreatment levels of homocysteine and methylmalonic acid place a patient at higher risk for severe pemetrexed toxicity. Pretreatment with vitamin B12 and folic acid reduced severe neutropenia and myelosuppression.[17,18] Vitamin supplementation has not been shown to adversely impact pemetrexed activity,[19] and as such it is now standard when administering pemetrexed.

Phase I trials

Initial studies determining the maximal tolerated dose (MTD) of pemetrexed, in combination with other cytotoxic therapies, in the setting of ovarian cancer have been conducted. Misset et al. administered pemetrexed and oxaliplatin every 21 days to 36 patients (5 of whom had a gynecologic malignancy), in a dose-escalation regimen starting at pemetrexed 300 mg/m^2 and oxaliplatin 85 mg/m^2. There were no dose limiting toxicities (DLTs) observed at dosages up to pemetrexed 500 mg/m^2 plus oxaliplatin 120 mg/m^2.[20] A study including 24 patients with recurrent ovarian cancer treated with pemetrexed in a dose escalation protocol starting at 300 mg/m^2 plus gemcitabine 1,500 mg/m^2 with Vitamin B12 and folic acid supplementation demonstrated the MTD was 600 mg/m^2.[21] The most common toxicities were hematologic, including neutropenia. A study by Sehouli and colleagues sought to determine the MTD of pemetrexed, this time in combination with carboplatin, in a similar dose escalation schema in 20 platinum-sensitive ovarian cancer patients.[22] Over 100 cycles were administered, with one DLT at pemetrexed 600 mg/m^2 + carboplatin AUC 6, and no serious adverse events observed. In a subsequent study of 29 patients, a majority of whom had recurrent ovarian, fallopian tube, or peritoneal cancer, pemetrexed 500 mg/m^2 and pegylated liposomal doxorubicin (PLD) 40 mg/m^2 administered every 28 days, with vitamin B_{12} and folic acid supplementation, was tolerated with a similar toxicity profile (*e.g.* neutropenia, thrombocytopenia, anemia).[23] In a novel approach by investigators at the University of Arizona, pemetrexed was administered intraperitoneally (IP) in a dose escalation fashion with intraperitoneal cisplatin and paclitaxel.[24] Fifteen patients were enrolled and treated. Of the three treated with 1000 mg/m^2 pemetrexed, two patients experienced DLTs (one pancytopenia who eventually recovered, one death from opportunistic infection). The median progression-free survival was 30.1 months. Patients receiving 500 mg/m^2 pemetrexed in combination with standard doses of IP cisplatin and paclitaxel showed a favorable toxicity profile. The MTD dose was suggested to be 500 mg/m^2, however further investigation of IP pemetrexed was deemed warranted.

Phase II trials - single therapy

Two trials have explored single agent pemetrexed as treatment for recurrent ovarian cancer.[25,26] In these trials, the primary outcome assessed was response rate.

Miller and colleagues administered intravenous pemetrexed to 48 patients at a dose of 900 mg/m^2 as single therapy every 21 days until disease progression or unacceptable adverse events. More than 250 cycles were given. The overall response rate was 21%, with one patient experiencing a complete response. The most common grade 3 and 4 toxicities were hematologic. They reported no treatment related deaths. Vergote *et al.* compared high (900 mg/m^2) and low (500 mg/m^2) dose intravenous pemetrexed in recurrent ovarian cancer. Ninety-eight patients were evaluable for toxicity, with 47 receiving low dose and 51 receiving high dose therapy. The response rate (9.3% for low dose; 10.4% for high dose) and median progression-free survival (PFS) (11.9 months; 10.3 months) were comparable. However, treatment with high dose therapy demonstrated more serious drug related adverse events, including two deaths possibly related to treatment complications. Given the above, the study's authors recommended low dose therapy (500 mg/m^2) as standard treatment.

Phase II trials - combination therapy

Multiple phase two trials have been conducted with pemetrexed as combination therapy in patients with recurrent ovarian

Table 3. Reviews.

Author	Year	Conclusion	Comments
Tomao[4]	2009	Continued exploration of pemetrexed and other cytotoxic agents/targeted therapies is warranted in recurrent OC	
Morotti[33]	2012	Pemetrexed appears to have similar clinical activity in ovarian cancer compared to current therapies. Further pharmacogenomic and clinical trial data are warranted to better define the role of pemetrexed in recurrent OC.	
Miller[34]	2013	Pemetrexed shows activity in ovarian and cervical cancers with tolerable side effect profile, warrants further study	Included patient series of 13 patients who received pemetrexed for recurrent OC. Treatments were well
Egloff[35]	2014	Pemetrexed demonstrates efficacy in both recurrent and primary OC, warrants further investigation.	tolerated with a median OS of 4.8 months. No dose/schedule available on cohort.
Smith[36]	2004	Preliminary findings in ovarian cancer also indicate activity of pemetrexed in this setting. Ongoing and planned studies will help to establish the optimal uses and role of pemetrexed in gynecologic cancers.	

OC, ovarian cancer.

Table 4. Expert commentary.

Author	Year	Study design	Conclusion
Ledermann[32]	2009	Expert commentary	Pemetrexed is active in a variety of cancers and warrants further investigation

cancer. Two such trials compared intravenous pemetrexed in combination with carboplatin, both in platinum-sensitive disease.[27,28] This combination has been shown to be effective in the setting of advanced breast cancer and non-small cell lung cancer.[29,30]

Matulonis *et al.* administered carboplatin AUC 5 and pemetrexed 500 mg/m^2 every 21 days to 44 patients for a total of 235 cycles. Response rate was 51.1%, with no complete responses. Median PFS was 7.57 months. Thirteen patients required dose reduction for toxicity. Eight patients were prescribed myeloid growth factor support. No other serious adverse events were reported. Carboplatin AUC 6 and pemetrexed 500 mg/m^2 given every 21 days were studied by Sehouli and colleagues. Sixty-six patients were treated, and 61 were evaluable. Twenty patients (32.8%) experienced a response, with one of those patients experiencing a complete response. The median PFS was 9.4 months. One patient died due to multiple organ failure, possibly related to chemotherapy. The authors independently conclude that this combination should be used in randomized testing against other therapies for recurrent epithelial ovarian cancer given its acceptable side effect profile and response rates comparable to standard therapies.

Another trial by Hageman studied dual therapy with pemetrexed 500 mg/m^2 and bevacizumab 15 mg/kg in 34 patients with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer.[31] Therapy was given every 21 days. Women with both platinum sensitive and platinum resistant disease were included. Response rate for the entire population was 41%, with zero complete responses. Median PFS was 7.9 months, and median overall survival (OS) was 25.7 months. Two patients eventually developed hematologic malignancies. One patient developed acute myeloid leukemia (AML) and recovered after therapy and stem cell transplant. The other patient developed myelodysplastic syndrome.

Reviews and editorials

In 2009, an editorial was published in the European Journal of Cancer highlighting the need for further research on pemetrexed as therapy in ovarian cancer.[32] As of this writing, five reviews have been published on this topic, most recently in 2014.[4,33-36] Each review separately highlights both the clinical efficacy and tolerable side effect profile of pemetrexed. The studies conclude that while the current literature presents pemetrexed as a promising therapy for recurrent ovarian cancer with a favorable side effect profile, the lack of phase III trials comparing its clinical activity to current accepted treatments prohibits its use in these patients.

Future directions

With the limited efficacy of a nondiscriminatory approach to treatment with pemetrexed there may be a role for a directed approach based on mutational analysis, as has been tested in other tumor types. Thymidylate synthase (TS), an enzyme inhibited by pemetrexed, has been studied most extensively. In a phase II trial of pemetrexed treatment for advanced breast cancer by Gomez *et al*., the correlation between TS levels in surgical specimens and clinical response was evaluated.[37] Patients with lower tumor TS levels at baseline were more likely to respond to pemetrexed than those with higher levels. Subsequent studies in other tumor types, including non-small cell lung cancer and mesothelioma, have demonstrated a similar relationship.[38-43] Other tumor-expressed markers such as miR-25, miR-145, miR-210, thyroid transcription factor 1, and serum leptin have been studied as potential predictors of pemetrexed response.[42,44,45] In their Phase II trial of pemetrexed in platinum resistant ovarian cancer, Vergote *et al.* showed low levels of both reduced folate carrier (RFC) and excision repair cross-complementation group 1 (ERCC1) were associated with improved outcomes.[26] While these results are intriguing, additional investigations are needed to verify these markers in the clinical setting. We are not aware of any other studies evaluating the correlation between an ovarian cancer expression profile and pemetrexed response.

Currently, one phase II clinical trial (NCT01001910) studying pemetrexed and carboplatin in the setting of recurrent ovarian cancer is completed and awaiting final results.[46] Two trials are recruiting as of this writing: a phase I trial using bosutinib in combination with pemetrexed in patients with selected metastatic solid tumors (NCT03023319) and a phase I study of methoxyamine in combination with cisplatin and pemetrexed in patients with advanced non-small cell lung cancer, mesothelioma, thymoma, and ovarian cancer (NCT02535312).[47,48]

Discussion

Pemetrexed enters the cell through a folate receptor system, folate receptor alpha (FRα), which has been shown to be overexpressed in multiple solid cancer lines, including ovarian. Moreover, its expression correlates with the severity of the disease.[12,49] It disrupts folate-dependent metabolic processes essential for nucleic acid synthesis. Thus, it acts with greatest effect on rapidly growing cells. Unlike other antifolate agents, pemetrexed exerts effects on multiple enzymes. It is an antimetabolite that inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), glycinamide ribonucleotide formyltransferase (GARFT), and 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICARFT).[50,51] It is similar to methotrexate in its activity against DHFR and it is similar to 5-fluorouracil in its activity against TS. GARFT and AICARFT are two enzymes in the pathway of purine synthesis not currently targeted by antineoplastic agents.[52,53]

The efficacy of pemetrexed in other solid tumors has been previously described. Pemetrexed and cisplatin have become standard therapy for patients with nonresectable malignant pleural mesothelioma (MPM) based on a phase III trial by Vogelzang comparing combination pemetrexed/cisplatin with single agent cisplatin.[19] The combination cohort showed a better response rate (41.3% *vs* 16.7% in control, P<0.0001). It also demonstrated significantly improved median survival time (12.1 *vs* 9.3 months, P=0.020) and longer median time to progression (5.7 months *vs* 3.9 months, P=0.001). Encouraged by these results, pemetrexed has been studied in the setting of other solid tumor types, including epithelial ovarian cancer. Response rates in phase II trials are comparable to the current standards utilized in both platinum-sensitive and platinum-resistant recurrent disease with a favorable side effect profile (Table 2). Despite these promising early trials, its efficacy in recurrent ovarian cancer requires further study.

While most patients initially respond to first-line therapy for ovarian cancer, most will experience a recurrence. Many agents are currently used for treatment of these recurrences. However, most offer a low response rate. These treatments are rarely curative and offer a median survival of only two years.[4] Pemetrexed is a newer cytotoxic agent that has drawn interest given its activity in several different solid tumor types. Its biochemical pathways are well-documented. It offers a favorable toxicity profile and it has response rates comparable to other agents used in first-line combination in GOG 182,[54] suggesting it can be used as a leading therapy in this setting. It has been most extensively studied at a dose of 500 mg/m^2 administered every 21 days with vitamin supplementation.

This review highlighted the possible utility of biomarkers. Their potential role to assess the effectiveness of pemetrexed in

recurrent ovarian cancer is intriguing, especially given recent increased interest in pharmacogenomics. Despite the promise of ERCC1 and RFC as predictors of response to pemetrexed in recurrent ovarian cancer, additional research is paramount to validate their routine use. Furthermore, although thymidylate synthase has been studied extensively as a biomarker in non-small cell lung cancer, this analysis has not begun in ovarian cancer. The field of biomarkers to predict response is an emerging one. Preliminary data warrant further study of these biomarkers for pemetrexed in various tumor types.

Conclusions

The purpose of this review was to address the knowledge gaps in the current published literature regarding the efficacy of pemetrexed, alone and in combination, as a treatment option for women with recurrent ovarian cancer. We also hoped to highlight the need for phase III trials comparing this medication to current standard therapy. It is evident given the clinical efficacy and favorable toxicity profile of pemetrexed that further studies comparing it to current therapies for recurrent ovarian cancer are warranted. Response rates for platinum-resistant ovarian cancer have been historically poor. Targeted, novel agents are needed. Pemetrexed has shown responses in a typically chemoresistant population that warrant continued investigation. No published studies have directly compared pemetrexed to other treatments, and no studies are currently listed as recruiting to investigate this purpose. The likelihood of phase III clinical trials will be dependent on the outcomes of the pending phase I and phase II clinical trials. Future determination of its role awaits further investigation.

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