The role of surgery in patients with advanced gynaecological cancers participating in phase I clinical trials

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Summary

Objective: While gynaecological cancer patients who participate in Phase I clinical trials are not routinely considered for elective surgery because of a short life expectancy, this should not be overlooked in carefully selected responding patients. *Methods/Results:* We describe two cases of patients with different gynaecological cancers, who received treatment within separate phase I trials, and who then proceeded to surgical resection of their cancers, resulting in complete remission. *Conclusion:* Surgery, when feasible, should be taken into consideration as a potential management option, even when patients are receiving treatment within a phase I trial.

Key words: Phase I trial; Gynaecological cancers; Surgery.

Introduction

Phase I clinical trials are designed primarily to assess the tolerability and toxicity profile of an investigational medicinal product [1]. Patients who are referred for experimental therapies as part of a phase I trial have locally advanced or metastatic solid tumours and have generally exhausted all standard treatment options.

Clinicians managing patients in early clinical trials have to balance modest anti-tumour gains with the risk of drug-related toxicities. Surgery is usually only considered in patients with advanced or recurrent disease, where the benefits outweigh the risks and is generally carried out as a palliative procedure. For certain patients (including those with breast and colorectal cancers), several studies suggest that surgical approaches for carefully selected patients may be positively associated with increased long-term survival [2, 3]. Despite this, patients who participate in phase I trials are often deemed to have modest life expectancies and are not routinely considered eligible for elective surgery.

In this report, we highlight the importance of considering surgical interventions for patients undergoing experimental therapy within phase I trials, especially those who have had an anti-tumour response to such treatments. We describe two cases of patients with metastatic disease, who had surgery undertaken in this context.

Case Reports

Case 1

A 73-year-old female was diagnosed in January 2002 with FIGO Stage IIIC poorly differentiated serous ovarian adenocarcinoma. In addition, the patient was found to have an associated germline BRCA2 mutation. Her previous anti-cancer management included optimal surgical debulking followed by adjuvant carboplatin and paclitaxel chemotherapy completed in July 2002 with a complete Response Evaluation Criteria In Solid Tumors (RECIST) response. The patient had three recurrences of her cancer over the next five years, but her disease responded to treatment with single agent carboplatin on each occasion. During the third relapse, the carboplatin chemotherapy had to be discontinued prematurely due to a severe allergic reaction.

In October 2007, the patient was found to have RECIST progressive disease, with multiple liver metastases, which were not surgically resectable, as well as the development of ascites and CA125 tumour marker progression by Gynecologic Cancer InterGroup (GCIG) criteria. She subsequently commenced treatment with the poly (ADP-ribose) polymerase (PARP) inhibitor, olaparib (AZD2281; AstraZeneca) within a phase I trial (clinicaltrials.gov, NCT00516373). After 48 weeks of treatment with olaparib, her computed tomography (CT) scan showed a RECIST complete response and a CA125 response by GCIG criteria. Olaparib treatment was continued and the patient remained in complete cancer remission. Following two years and four months of treatment, an enlarged portocaval lymph node was noted on a surveillance CT scan (Figure 1). As this was the only site of relapse, she was referred for surgical resection of the enlarged node, which was undertaken in March 2010 (Figure 2). No other sites of disease were seen at surgery. Histopathology of the resected node confirmed metastatic high-grade serous papillary adenocarcinoma of ovarian origin. Treatment with olaparib was restarted four weeks after surgery and as of October 2010, the patient was still in RECIST complete remission.

Case 2

The second patient, a 37-year-old female, was diagnosed in December 2007 with Stage 1B moderately differentiated squamous cell carcinoma (SCC) of the cervix with involvement of her common iliac lymph nodes. Surgery was undertaken, prior to adjuvant chemo-radiotherapy with weekly cisplatin and brachytherapy. A CT scan in June 2008 confirmed RECIST progressive disease within the pelvis, but also revealed multiple lung metastases, making surgery inappropriate. In July 2008, the patient commenced treatment with an irreversible dual EGFR and HER2 inhibitor, afatinib (BIBW 2992; Boehringer Ingelheim) administered in combination with paclitaxel and bevacizumab within a phase I trial. A restaging CT scan after

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24 weeks confirmed a RECIST partial response (PR) with a decrease in size of pulmonary and pelvic disease. The patient continued treatment with a maintained PR for a further 80 weeks (paclitaxel was discontinued after 40 weeks, but therapy was continued with the two other agents). At that stage, a repeat CT scan showed increases in metastatic lesions at the right lung base (Figure 3) and on the pelvic sidewall. She was referred for consideration of surgery, and this was undertaken as a two-stage procedure involving thoracic and pelvic surgery. A pulmonary metastasectomy was carried out (Figure 4), followed by surgical resection of her pelvic wall disease a month later, with no residual disease left, histological clear margins (R_0) and no postoperative complications. Trial therapy was not restarted and eight months later in October 2010, the patient remained well and in complete cancer remission.

Discussion

In general, patients with gynaecological cancers who participate in phase I trials have a poor overall survival. A retrospective review carried out at our phase I unit, which included 142 patients treated between 2003 and 2008, showed an overall median survival of 11 months [4]. Patients may occasionally respond to treatments within phase I trials and in some cases, even merit consideration for surgery, despite this not being appropriate prior to trial entry.

These two cases illustrate this point in patients with gynaecological cancer in different ways. In ovarian cancer, surgery for liver metastases may be of benefit in a selected number of cases [5], but – as in Case 1 – the presence of multiple liver metastases generally rules out a surgical option. On the other hand, surgery for recurrent extrahepatic disease, when limited in extent, can be beneficial [6] and this was confirmed in Case 1. In cervical cancer, total exenterative surgery for pelvic recurrence in selected cases, despite the inevitable morbidity of surgery, may be of benefit [7], but the presence of disease spread beyond the pelvis, such as multiple lung metastases, as in Case 2, contraindicates this approach. On the other hand, surgery for limited pulmonary metastases from cervical cancer at the appropriate time may be of benefit in selected cases [8], and this was also demonstrated in Case 2.

Favourable prognostic factors for improved survival in patients with gynaecological cancers following surgical resection for metastases include a) a good performance status, b) long disease-free interval, c) absence of other systemic disease and d) surgical complete resection [9]. Based on these criteria, our two patients were excellent candidates for surgery as they both had an Eastern Cooperative Oncology Group (ECOG) performance status of 1, absence of other systemic disease, and surgery was performed with clear histological margins (R_0) in both cases. Furthermore, the patient with ovarian carcinoma was also considered to have a long disease-free interval as her first disease relapse appeared more than one year after the last cycle of her initial chemotherapy.

The literature data concerning surgery in metastatic ovarian and cervical cancer clearly illustrate that survival may potentially be extended by optimal surgery in patients with metastatic disease [10]. Both our patients received optimal surgery and both remained in remission in October 2010 after the surgical resection. The prolonged survival seen in both of these patients would not have been anticipated with conventional treatment but is based on the treatments which they received within their phase I trial plus their surgery.

The phase I treatments included olaparib, which in patients with ovarian cancer and *BRCA1* and *BRCA2* mutations has shown very promising results in early clinical trials [11, 12], afatinib which has shown efficacy in non small cell lung cancer harbouring EGFR activating mutations [13], bevacizumab which in persistent or recurrent cervical cancer as a second or third line treatment has been shown to be well tolerated and active [14] and weekly paclitaxel in cervical cancer, which has also shown promising results [15].

In summary, we wish to emphasise that surgery, when feasible, should be taken into consideration as a potential management option even in patients with metastatic gynaecological cancers, who are receiving treatment within a phase I trial. As novel treatments for gynaecological cancer continue to produce promising results, more cases of this type may be anticipated in the future.

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