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ORIGINAL PAPER

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Evidence that a "treatment-free interval of less than 6 months" does not equate with clinically defined platinum resistance in ovarian cancer or primary peritoneal carcinoma

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Abstract The standard definition of platinum-resistant ovarian cancer or primary peritoneal carcinoma commonly includes patients whose disease initially responded to a platinum-based combination regimen, but recurred less than 6 months after the completion of primary therapy. Recent experience with several patients with these malignancies treated in the Gynecologic Cancer Program of the Cleveland Clinic Foundation, whose disease recurred within this period but who subsequently responded to platinum therapy, calls into question the validity and clinical relevance of this commonly employed definition, both for the conduct of phase 2 trials of new agents in ovarian cancer and primary peritoneal carcinoma, and for the standard management of women in this clinical setting.

Key words Ovarian cancer · Platinum resistance · Peritoneal carcinoma · Treatment-free interval

Introduction

The importance of the platinum agents (cisplatin and carboplatin) in the management of ovarian cancer is well established (Cannistra 1993). It is also known that patients who initially respond to a platinum-based chemotherapy regimen can achieve objective tumor regressions in response to the same or similar chemotherapy programs if the disease subsequently recurs (Gershenson et al. 1989; Gore et al. 1990; Markman et al. 1991b, 1997; Hoskins et al. 1991). This biological feature of ovarian cancer and primary peritoneal carcinoma is quite relevant in standard patient management, as it can significantly influence the choice of therapy employed in the second-line, or salvage setting.

Clinical investigators involved in chemotherapeutic drug development in ovarian cancer have long recognized the importance of examining new agents in individuals whose tumors have been shown to be resistant to initial (i.e., platinum-based) chemotherapy (McGuire et al. 1989; Markman 1991a; Thigpen et al. 1994). Drugs that demonstrate a substantial level of activity in this specific clinical setting are of particular interest, as tumor regression would strongly suggest the lack of complete cross-resistance between the new agent and the front-line platinum-based chemotherapy program (Markman and Hoskins 1992).

To evaluate the level of activity of investigative agents appropriately in platinum-resistant ovarian cancer and primary peritoneal carcinoma, it is important that the definition of this clinical state be well-conceived. This must be done to insure that patient entry into trials examining this question is limited to individuals whose disease has been unequivocally demonstrated to be clinically refractory to this class of cytotoxic agent.

In the absence of a clear definition to select the patient population to be treated, it will remain unknown whether any of the response observed to the new drug might have been achieved simply by delivering a platinum drug (cisplatin or carboplatin) instead of the investigative agent.

Therefore, how should "platinum-refractory ovarian cancer" be defined? Individual patients whose cancers actually demonstrate growth during treatment or where there is no objective evidence of tumor regression following four to six cycles of therapy can appropriately be considered to have clinically defined platinum-resistant disease.

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However, phase 2 trials in platinum-refractory ovarian cancer have commonly included patients whose cancers actually initially responded to therapy, but "recurred within 6 months of the completion of chemotherapy" (Thigpen et al. 1994).

Does this broader definition of platinum resistance appropriately separate those individuals whose cancers are clinically resistant to this class of drugs, from those who remain potentially sensitive? Recent experience with three patients cared for in the Gynecologic Cancer Program of the Cleveland Clinic Foundation calls into question the validity and clinical relevance of this common definition and suggests the need carefully and critically to reexamine this important clinical trial design issue.

Case reports

Case 1

L.P. is a 62-year-old woman with extensive primary peritoneal carcinoma, originally diagnosed in July 1996. Following initiation of a carboplatin and paclitaxel regimen, the patient experienced considerable improvement in symptoms, with a decline in the CA-125 level from 2400 to 22 at the time of her sixth and final treatment in November 1996. Unfortunately, by March 1997 (4 months off therapy) the CA-125 has increased to 640, with the development of recurrent symptoms (abdominal bloating, pelvic pain). Carboplatin and paclitaxel were reinstituted with the disappearance of symptoms and a decline in the antigen level to 53 at the time of her fourth course of the "salvage" treatment regimen. The patient remains on this treatment regimen (4+ month response to "second-line" chemotherapy).

Case 2

H.C. is a 71-year-old woman with primary peritoneal carcinoma. Following suboptimal debulking performed in May 1996, the patient was treated with carboplatin and paclitaxel, with a decline in her CA-125 from 1070 to 12 after six treatment courses (last therapy October 1996). However, by January 1997 (3 months off therapy), the patient developed symptomatic ascites and abdominal cramping, and the CA-125 had increased to above 1000. Treatment with carboplatin and paclitaxel was reinitiated. Symptoms improved, and the CA-125 declined to 62 after the fourth course of therapy. Unfortunately, by June 1997, the CA-125 began to increase again (5-month response to second-line therapy), and alternative therapy was initiated.

Case 3

Y.H. is a 67-year-old woman with advanced ovarian cancer who had chemotherapy with carboplatin and paclitaxel initiated in October 1995. The CA-125 antigen level declined from 788 to 72 following the completion of six courses of therapy (last dose of carboplatin January 1996). Owing to the persistently elevated CA-125, single-agent paclitaxel was delivered until May 1996, when all chemotherapy was discontinued. Tamoxifen was initiated at this time. Unfortunately, by August 1996 the CA-125 had increased to 1390, and symptomatic ascites as well as pelvic pressure developed. Pelvic examination revealed nodularity in the culde-sac. A carboplatin/paclitaxel regimen was re-instituted (3 months after discontinuation of chemotherapy, 7 months after the last course of front-line carboplatin), with a major reduction in ascites, disappearance of pain and the pelvic nodules, and a decline in the CA-125 antigen level to 166 by the fifth course of treatment. This response to second-line therapy persisted for 5 months, at which time an alternative treatment program was initiated because of progression of symptoms and a rising CA-125.

Discussion

Within a period of less than 1 year, our group has cared for three women with ovarian cancer or primary carcinoma of the peritoneum who achieved objective and subjective evidence of a response to a second-line platinum-based chemotherapy regimen after having disease recurrence less than 6 months after the completion of their initial treatment program.

As a result, two of these individuals would have been considered to be platinum-resistant, by many standard entry criteria for phase 2 trials of investigative second-line chemotherapy in advanced ovarian cancer. The third patient might also have been considered in this category on the basis of the fact that her disease recurred less than 6 months following the completion of the initial chemotherapy regimen, although actually 7 months after her last dose of a platinum agent.

If these patients had been entered into a "platinum-resistant" trial, and had responded to the new chemotherapeutic agent, this response would have been characterized as having developed in an individual resistant to platinum. Such a conclusion, while supported by the definition of the trial, would have been incorrect, on the basis of the demonstrated sensitivity to platinum when this drug was actually tried in the patients.

Of greater importance, the misleading data might have led investigators to conclude the presence of a certain level of noncross-resistance between the new agent and the platinum compounds, which did not actually exist. Selection of patients for entry into trials with a more appropriately characterized definition of platinum-resistant disease will provide an important level of assurance that the degree of activity observed to the new agent actually represents tumor regression by a mechanism of action at least partially different from that of the platinum compounds.

The inappropriate labeling of an individual as being platinum-resistant also has important implications for standard patient management. If an individual has achieved a response to initial chemotherapy of only limited duration (e.g., less than 6 months), the chances for achieving a major and sustained response to any currently available therapy are extremely limited. Thus, the most realistic objective of second-line therapy in such patients should be an attempt to maximize the quality of remaining life, rather than its duration.

If a patient has exhibited evidence of significant tumor cell kill with initial chemotherapy and has tolerated that treatment program well, it is difficult to understand the rationale for trying a "new regimen" at this point rather than attempting to determine whether the malignancy persists in maintaining some level of sensitivity

to the prior chemotherapy. On the basis of the level of symptomatic response to even a single course of therapy, it will be possible to know if the tumor is now truly resistant. If the patient exhibits improvement, therapy can be continued, depending on the toxicity observed and duration of response.

While it might be argued that a new agent has a greater opportunity to bring about tumor regression and symptomatic improvement, data from controlled clinical trials do not exist to support this conclusion. In addition, instituting a new regimen at this point leads to the potential for greater toxicity, compared to a drug program with which the patient has had prior experience.

When it has been demonstrated that the patient is resistant to platinum-based chemotherapy, a decision can be made as to whether or not it is appropriate to initiate a second-line regimen in this individual. However, in making this decision, the overall goals for such therapy, noted above, must be kept in mind.

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