PublisherInfo		
PublisherName	:	BioMed Central
PublisherLocation	:	London
PublisherImprintName	:	BioMed Central

Exemestane as third and fourth line hormonal therapy for metastatic breast cancer

ArticleInfo		
ArticleID	:	3721
ArticleDOI	:	10.1186/bcr-2000-66684
ArticleCitationID	:	66684
ArticleSequenceNumber	:	87
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2000–6–23 OnlineDate : 2000–6–23
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	1305822

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Keywords

Endocrine therapy, metastatic breast cancer, postmenopausal

Introduction

Although the duration of response to hormone therapy in MBC can initially be substantial, most cancers become progressively less sensitive to hormonal manipulation and the chance of response declines with increasing lines of therapy. Nevertheless, most hormone therapies are very well tolerated and can delay the need for chemotherapy. Thus, if even a small proportion of patients can derive benefit from third and fourth line hormone therapies, the gain in quality of life can be meaningful.

Aims

To explore the efficacy and safety of exemestane 25 mg/day in a phase II single arm trial, given as third and fourth line hormone therapy to postmenopausal women with MBC while on a nonsteroidal aromatase inhibitor (aminoglutethimide [AG], anastrozole, letrozole, or vorozole [A/L/V]). To determine whether the level of suppression of plasma estradiol and estrone is greater with exemestane than with the prior aromatase inhibitor, and to test the efficacy of increasing the dose to 100 mg/day once the disease progresses on dosage at 25 mg/day.

Comments

Generally speaking, we tend to discount the value of therapies with response rates (RR) of less than 15-20%. This large single arm phase II trial elegantly demonstrates the value of clinical benefit (CB) as a measure of efficacy of hormone therapies in metastatic breast cancer (MBC). Although the objective RR to third and fourth line exemestane 25 mg/day after progression on nonsteroidal aromatase inhibitors was low (6.6%), the overall CB was 24%, with a median duration of 37 weeks among patients whose disease stabilised and 58 weeks among responders. Thus, patients for whom delaying or avoiding

chemotherapy is desirable and who have hormone receptor (HR)-positive or hormone-responsive low burden disease (particulary soft tissue) merit a trial of third or fourth line exemestane 25 mg/day. The low RR is mitigated by the meaningful disease stabilization and balanced by low toxicity and maintenance of quality of life.

Methods

Postmenopausal women who progressed after at least 8 weeks on a nonsteroidal aromatase inhibitor and who had HR-positive or HR-unknown hormone responsive disease, a performance status of 0-2 and no more than one type of treatment with chemotherapy for metastatic disease were eligible. Response was assessed using World Health Organisation criteria and was independently reviewed every 8 weeks. Quality of life was also assessed. Plasma E levels were compared prior to discontinuation of the nonsteroidal aromatase inhibitor and after 8 weeks of exemestane. If clinically appropriate, at the time of disease progression clinicianscould elect to continue treating the patient with exemestane at 100mg/ dayinstead of 25mg/day. RR and toxicity were assessed.

Results

Of 242 patients enrolled, 231 were off treatment at analysis (213 progressed, seven deaths, five refusals, four adverse events, one marker increase, one non-compliance), and 11 were still under treatment with a median follow-up of 37 weeks for the entire population. Exemestane was give as a third and fourth line therapy to 75% and 22% of patients respectively. Three patients had complete responses, 13 patients had partial responses and 42 had disease stabilization of at least 24 weeks (24.3% CB). Responses were seen in bone and visceral disease, but were most significant in patients with soft tissue disease: RR 25%, CB 50%. Fifty-eight patients were treated at 100 mg/day with a RR of 1.7%. There were insufficient deaths (88) to determine the median overall survival. Quality of life parameters were stable throughout treatment. Toxicity was modest with nausea, fatigue, and hot flushes being the most frequent side effects occurring in 7.5% to 10.8%. Three of the four adverse events which resulted in treatment discontinuation at 25 mg/day were not drug related and the fourth (grade 2 nausea) was reversible on discontinuation. Although exemestane further reduced plasma E levels compared to AG, the level of suppression was similar for exemestane and A/L/V. There was no difference in RR or CB for AG and A/L/V pretreated patients.

Discussion

This study demonstrates a very modest RR of third and fourth line exemestane 25 mg/day in postmenopausal women. The clinical benefit rate of 24.3% with a median duration of 37 weeks for

patients with disease stabilization and 58 weeks for responders is of value, especially considering the extremely good tolerability and quality of life stabilization. It is also particularly noteworthy given that all patients had progressed on nonsteroidal aromatase inhibitors, confirming a lack of cross resistance between this drug group and exemestane. A minority of patients may enjoy durable stabilization of both disease and quality of life with exemestane 25 mg/day as third or fourth line hormonal therapy for metastatic disease, providing an additional low toxicity therapeutic option for this group. The use of higher doses of exemestane at the time of progression does not appear to offer any benefit.

References

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