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

Tailored versus high-dose chemotherapy as adjuvant breast cancer treatment

ArticleInfo		
ArticleID	:	3754
ArticleDOI	:	10.1186/bcr-2000-66717
ArticleCitationID	:	66717
ArticleSequenceNumber	:	26
ArticleCategory	:	Paper Report
ArticleFirstPage	:	1
ArticleLastPage	:	4
ArticleHistory	:	RegistrationDate : 2000–10–31 OnlineDate : 2000–10–31
ArticleCopyright	:	Current Science Ltd2000
ArticleGrants	:	
ArticleContext	:	1305833

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Keywords

Adjuvant, breast cancer, high-dose chemotherapy, tailored

Introduction

Efforts to improve the efficacy of adjuvant chemotherapy in patients with high risk EBC include the use of increased doses, both within the conventional dose range and at high doses, where the associated haematological toxicity necessitates bone marrow support. Whether adjuvant HDC impacts upon survival remains controversial, with recent publications generally not supporting superiority over standard therapies. Patients receiving standard chemotherapy all receive the same mg/m^2 dose, but it has been shown that drug distribution varies greatly among individual patients. Thus, some patients may be overdosed while others may be under-dosed. The authors developed an individualised FEC regimen in an attempt to improve outcomes in these patients. The treatment was tailored to achieve haematologic equitoxicity between patients, using this as a surrogate marker for equieffective doses.

Aims

To compare TFEC regimen with conventional therapy followed by consolidation with HDC with stem cell support.

Comments

This interesting study found that tailored fluorouracil, epirubicin and cylcophosphamide (TFEC), which aims to avoid under-dosing, resulted in a significantly improved relapse free survival (RFS) and equivalent overall survival when compared to high dose chemotherapy (HDC), with lesser associated toxicity. The major drawback with TFEC was the increased risk of acute myeloid leukaemia (AML) or myelodysplastic syndrome (MDS). Thus, the authors conclude that TFEC is an attractive option for patients with high-risk early breast cancer (EBC) but one that needs further refinement to reduce the rate

of secondary haematological malignancies. This study has been cited as further evidence that HDC in EBC offers no advantage over standard therapies. However, it can be criticised in that it does not contain a standard therapy arm. It has a fluorouracil, epirubicin and cyclophosphamide FEC arm, with many patients receiving above average doses (especially of anthracycline), and an HDC arm. Thus, this study tested two experimental arms. In so doing, it did not really answer whether HDC is better than standard chemotherapy in this setting. Another caveat is that a longer follow up is needed to see possible late benefits/toxicities. The high rate of secondary haematological malignancies was also seen in the Canadian adjuvant study that administered high doses of epirubicin. It remains unanswered whether such high doses of anthracycline are required. This provocative study may lead to changes in the determination of standard chemotherapy doses during the course of a patient's treatment.

Methods

Patients <60 years of age with high-risk primary BC were randomised after surgery to receive either nine cycles of TFEC (3-weekly) to haematological equitoxicity with granulocyte colony-stimulating factor (G-CSF) support, or three cycles of standard 3-weekly FEC followed by HDC with cyclophosphamide, thiotepa, and carboplatin, with bone-marrow or peripheral-blood stem-cell support. There were six defined dose levels in the TFEC schedule. All patients received the same dose for cycle 1 and then were either dose-escalated, -unchanged or -decreased depending upon haematologic parameters. Following chemotherapy, patients in both groups received radiation and tamoxifen for 5 years. The primary outcome measure was RFS, and analysis was by intention to treat.

Results

Between 1994-98, 525 patients were divided into two treatment groups, TFEC (n = 251) and HDC (n = 274). In the TFEC group, 244 patients received at least six cycles of treatment (214 received all nine). In the HDC group, 266 patients received at least three cycles of FEC and 264 received HDC. At a median follow-up of 34?3 months, there were 81 BC relapses in the TFEC group *versus* 113 in the HDC group (P = 0.04). The 3 year RFS rates were estimated at 72% and 63%, respectively. In the TFEC group, 60 patients died, compared with 82 in the HDC group and the calculated 3 year overall survival rates were 83% and 77%, respectively (P = 0.12). Seven patients in the TFEC group died of AML or MDS. The estimated Kaplan-Meier risk at 3.2 years was 4.55%. Patients who received HDC experienced more grade 3 and 4 toxicities, including anorexia, diarrhoea, infections, nausea, and stomatitis (P<0.0001). Seven patients in the TFEC group and five in the HDC group were treated for cardiac symptoms.

Discussion

Tailored FEC with G-CSF support resulted in a significantly improved RFS and fewer grade 3 and 4 toxicities compared with marrow-supported HDC as adjuvant therapy for women with high-risk EBC. However, the TFEC regimen was associated with an increased risk of AML and MDS. It is too early to determine if there is a difference in overall survival, although the calculated 3 year survival was not statistically significant. Subanalysis of the tailored arm showed that RFS rates were virtually identical among different FEC doses.

References

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