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p53 mutations as predictors for response to neoadjuvant chemotherapy

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Keywords

Chemotherapy, p53, predictor, response

Introduction

Neoadjuvant chemotherapy is being increasingly utilised in patients with advanced breast cancer. Considering that many patients will fail to respond and that chemotherapy has toxic side-effects, a method of predicting response to certain chemotherapy schedules would undoubtedly be of value. There is evidence that p53 status of the tumour may influence the response to certain types of chemotherapy. In particular, DNA-damaging agents such as the anthracyclines are considered to induce p53-dependent apoptosis; thus, theoretically, regimens including anthracyclines should be most effective in tumours with wt p53. Taxanes, which act through stabilising tubulin polymerisation, are thought to cause cell death in a p53-independant manner. Thus, response to taxane chemotherapy should not be affected by p53 status.

Aims

To assess the value of tumour p53 status in predicting the effect of two neoadjuvant chemotherapy schedules in patients with advanced breast cancer.

Comments

This paper adds to the growing literature concerning the role of p53 status in determining chemotherapy response. It suffers from the study including only a small number of patients and being retrospective. Definitive conclusions on the role that p53 plays in the response to different chemotherapy agents remain elusive. Although there is support for the hypothesis that DNA-damaging agents are more effective against tumours with wild-type (wt) p53 (as there will be effective p53-driven apoptosis), there is also *in vitro* evidence that wt p53 status can result in relative resistance to DNA-damaging agents, through p53-dependent cell cycle arrest and DNA repair following exposure to the agent. Complicating

matters more, it is rapidly becoming clear that although p53 is a key protein in cell cycle control, it does not work in isolation and there are many other important proteins interacting with it and influencing its behaviour in response to exposure to cytotoxic agents.

Methods

Eighty-two patients with advanced breast cancer were included in the study protocol, of whom 67 were available for retrospective analysis. Patients received either an anthracycline-based schedule (FEC [5-fluorouracil, epirubicin, and cyclophosphamide] given thrice weekly for 3-4 cycles; $n = 35$), or single agent taxane (paclitaxel 215-300mg/m^2 over 3 h thrice weekly for 3-4 cycles; $n = 32$). All patients then went onto surgical treatment. Tumour response was followed clinically and radiologically, and pathological response was also determined. Tumour biopsies were analysed for histological diagnosis, p53 immunohistochemistry (IHC), p53 gene analysis and apoptosis by IHC.

Results

Mutations were identified in 13 (19%) of the 67 patients and 27 (40%) had positive IHC staining. Only seven patients had both a mutation and positive IHC staining. FEC chemotherapy was administered to 35 patients, with 18 (51%) responding. Of these 18 patients, none had a p53 mutation and only one stained positive. Of the 17 nonresponders, seven had a p53 mutation ($P = 0.0029$), and 14 had positive IHC ($P < 0.0001$). Thus, patients with normal p53 status were highly likely to be responders to FEC chemotherapy, whilst those with abnormal p53 status were highly likely to be nonresponders ($P < 0.0001$). Presence of apoptosis was also related to p53 status with 17/18 responders being positive for apoptosis, and all nonresponders being negative. There were 32 patients treated with paclitaxel, with 15 patients (47%) responding. Of the 15 responders, five had p53 mutations and eight had positive IHC. Of the nonresponders, one had mutant p53 ($P = 0.07$) and four stained IHC positive ($P = 0.14$). Comparing patients with normal p53 status ($n = 17$) versus those with abnormal status ($n = 15$) showed that there was a relationship with response to paclitaxel, with abnormal p53 patients more likely to respond ($P = 0.012$). Response to paclitaxel was not related to the presence of apoptosis.

Discussion

Results showed that response to FEC can be predicted by a normal p53 status and that responders to FEC have higher rates of apoptosis. This supports the hypothesis that response to DNA-damaging agents such as cyclophosphamide and the anthracyclines is a p53-dependent process. However, response to paclitaxel appeared to be related to the absence of normal p53. Loss of p53 function, leading to loss of G1 arrest, may allow cells to more effectively enter mitosis (the phase where paclitaxel exerts its

antitumour-cell effects). Thus tumours with mutant p53 may be more responsive to taxane-containing regimens. Interestingly, there did not appear to be high levels of apoptosis in the tumours responding to paclitaxel and this may reflect the fact that, at the blood levels achieved by the doses used in this study, paclitaxel seems to have a mainly cytostatic rather than an apoptotic effect.

References

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