E10. High-dose chemotherapy in breast cancer – a critical review

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The introduction of a novel drug or treatment strategy in oncology is often associated with an initial phase of excitement and broad application, which is later followed by disappointment. High-dose chemotherapy has followed this pattern to an unprecedented extreme: widely accepted in the 1990s, it has now essentially been abandoned. Nevertheless, there are indications that high-dose chemotherapy, particularly with alkylating agents, may be effective in a subgroup of breast cancers. In a sense, high-dose alkylating therapy could be considered 'targeted therapy'.

Twenty years ago, the rationale for the testing of high-dose chemotherapy in clinical studies was excellent. High-dose alkylating agents had been shown to have steep log-linear dose–effect relationships, both *in vitro* and *in vivo*. The technique of autologous peripheral blood progenitor cell transplantation (PBPC) was becoming routine in many centres and phase II studies had shown high complete remission rates. A sizeable proportion of highly selected patients achieved long-term survival despite a diagnosis of stage IV disease. An uncontrolled study in the adjuvant setting suggested that high-dose chemotherapy achieved a disease-free survival in high-risk patients that far exceeded expectations based on historical controls [1]. In 1998, the first report of a randomised study of high-dose chemotherapy in the adjuvant setting was published [2]. This small study was negative and it was quickly followed by several others that failed to show a survival advantage. One year later, a clearly positive study was presented by Bezwoda at the American Society of Clinical Oncology (ASCO) meeting. When this was subsequently shown to be the result of scientific fraud [3], the medical oncology community lost most of its remaining interest.

In the past few years, 14 randomised trials have been reported, which studied high-dose chemotherapy in a total of 5627 patients with high-risk breast cancer. A further 7 randomised studies were published, reporting on a total of 423 stage IV breast cancer patients. The interpretation of these studies is difficult. Almost all show a better relapse-free survival in the high-dose arm, but all but one lack evidence for improved overall survival. All studies are underpowered, most of them severely so. A large number of widely varying high-dose regimens has been employed and most of the studies are non-symmetrical: high-dose chemotherapy is only one of two or more differences between the treatment arms. At least two meta-analyses of these studies are now in progress, but it is doubtful that these will have the statistical power to determine whether or not high-dose therapy is worthy of further pursuit.

The largest randomised study in high-risk breast cancer is that of the Dutch study group [4]. This study in 885 patients showed a non-significant relapse-free survival advantage for the high-dose arm. Subgroup analyses confirmed the finding from earlier studies that HER2/neu-positive tumours do not benefit from high-dose therapy. HER2/neu-negative tumours, however, respond quite favourably: these 621 patients had a substantial relapse-free and overall survival benefit from high-dose therapy. This finding and several other observations raise the question of whether high-dose therapy may be active in some of the biological subgroups of breast cancer but not in others.

Many high-dose chemotherapy regimens are based on classical bi-functional alkylating agents (such as cyclophosphamide or thiotepa) and/or include a platinating agent such as cisplatin or carboplatin. These anticancer drugs induce inter- and intra-strand DNA cross-links. This type of DNA damage can only be reliably repaired through a single DNA-repair process: homologous recombination. Alternative repair mechanisms, such as non-homologous end-joining or single-strand annealing, are non-conservative and potentially mutagenic (for a review see [5]). We now know that hereditary breast cancers characterised by the absence of a functional *BRCA1* or *BRCA2* gene are unable to employ this type of DNA repair. In addition, defects in the Fanconi anaemia pathway or amplification of a gene called *EMSY* (both abnormalities occur as somatic mutations in sporadic breast tumours) also leads to failure of homologous recombination. Tumour cells exhibiting this defect become highly sensitive to bi-functional alkylating agents. Since the homologous recombination defect is present only in the tumour cells and not in the other cells of the organism, alkylating agents may represent a targeted approach for this subgroup of tumours. Targeting this DNA-repair defect could also be achieved by employing inhibitors of the enzyme poly(ADP-ribose)polymerase (PARP) [6]. Inhibition of this enzyme, which is involved in base excision repair, leads to the persistence of DNA lesions

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that would otherwise be dealt with by homologous recombination. It has been estimated that about 30% of sporadic breast cancers and probably an even larger proportion of the so-called triple-negative breast cancers harbour the homologous recombination defect.

It could well be that therapy with bi-functional alkylating agents will receive a second chance in the treatment of breast cancer. Alkylating agents have relatively few side-effects other than nausea and bone-marrow suppression, and the supportive care to manage both has improved dramatically. There may be no need to increase the dose as high as was customary in the high-dose trials. Importantly, practical tests are now required to detect homologous recombination defects and hypersensitivity to alkylators in clinical tumour samples.

References

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