Eur J Cancer, Vol. 29A, No. 9, pp. 1225–1226, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Comments and Critique

Salvage Intraperitoneal Chemotherapy for Ovarian Cancer: A Possible Role for Mitoxantrone?

OVER THE past decade, intraperitoneal chemotherapy has evolved from a pharmacokinetic concept into a realistic treatment option for a subset of patients with advanced ovarian cancer [1]. Recent evaluations have begun to more critically define groups of patients who should not be treated with this therapeutic strategy. For example, two reports have noted a very low objective response rate (< 10%) to salvage intraperitoneal cisplatin-based therapy when patients had failed to exhibit at least a partial response to initial systemically delivered cisplatin or carboplatin, even though the largest tumour diameter measured < 0.5–1 cm [2, 3]. In contrast, patients with similar maximum tumour diameters who had previously exhibited a response to cisplatin or carboplatin, achieved greater than a 35% surgically documented complete response rate [2].

For patients with small volume residual ovarian cancer (largest residual mass < 0.5–1 cm) following initial systemic chemotherapy, who have failed to respond to systemic cisplatin or carboplatin, is there an intraperitoneal regimen which could be considered a reasonable therapeutic strategy? Mitoxantrone, a dihydroxyquinone derivative of anthracene, has been shown in the human clonogenic assay to have an extremely steep dose–response effect against human ovarian cancer [4]. A major pharmacokinetic advantage (> 1000-fold) for exposure of the peritoneal cavity compared to the systemic compartment following intraperitoneal delivery of mitoxantrone has been demonstrated [5, 6]. Several previously published phase 2 trials have documented that intraperitoneal mitoxantrone can result in surgically defined complete responses when used in the salvage setting in patients with ovarian cancer [7, 8]. Of particular interest, responses were observed in patients who had failed to respond to systemic or intraperitoneal cisplatin, supporting the *in vitro* observations noted above [7, 8].

Added to this interesting data concerning a potential role for intraperitoneal mitoxantrone in the treatment of ovarian cancer, we now add the report of Nicoletto *et al.*, in this issue of *The European Journal of Cancer* (pp. 1242–1248). In this study, 36 previously treated patients with advanced ovarian cancer were treated with intraperitoneal mitoxantrone. Patients were evaluated for response to this therapeutic program by laparoscopy with biopsy. Overall, 11 patients were reported to have achieved either a complete or partial response. Unfortunately, while we are told that patients had previously received systemic cisplatin, the authors have not reported their response rate based on the prior response to the initial chemotherapy programme. Thus, we cannot use this report to support the hypothesis that intraperitoneal mitoxantrone is effective in patients with small volume residual disease which has been documented to be platinum-resistant. In agreement with other reports, responses were *not* observed in patients whose largest residual tumour mass was > 2 cm in maximum diameter.

Two additional points regarding this paper are worthy of mention. First, the authors conclude that an intraperitoneal mitoxantrone dose of 28 mg/m^2 is generally well tolerated. This experience and recommendation is in sharp contrast to the previously reported work from the Memorial Sloan-Kettering Cancer Center in New York City [7]. This group noted that intraperitoneal doses of mitoxantrone of 20 or 30 mg/m^2 resulted in both considerable abdominal pain and in an unacceptably high incidence of bowel dysfunction [7]. Whether these differing experiences reflect a problem of small patient numbers, a fundamental difference in the patients treated, or the use by the Padova group of intraperitoneal bupivacaine hydrochloride when pain developed, is uncertain. However, on the basis of the Memorial Sloan-Kettering Cancer Center experience, caution is advised if intraperitoneal doses of mitoxantrone of greater than 10–15 mg/m^2 are to be employed.

Finally, the method of evaluation of efficacy used in this study must be addressed. While laparoscopy has certainly been demonstrated to be an effective method of evaluating the abdominal cavity in patients with abdominal cancer, the development of adhesions following intraperitoneal mitoxantrone [7, 8], as demonstrated in previously reported trials, raises the important issue of the clinical utility of laparoscopic evaluation in attempting to define a complete response in this setting. To the authors credit, they specifically address this point, but state that adhesion formation was not a problem in their surgical evaluation of the clinical activity of this treatment program. Again, this interpretation of the degree of adhesion formation is different from that previously reported by the Memorial group [7, 8]. Thus, the overall efficacy results of this trial must be viewed in the context of other reported experience.

Despite these concerns, this current report, added to other studies in the oncologic literature, provides strong support for a possible role for intraperitoneal mitoxantrone in a subgroup of patients with ovarian cancer who are to be considered for a salvage treatment programme. Future trials exploring the intraperitoneal delivery of mitoxantrone should attempt to optimise drug dose and schedule, as well as more critically define the patient population most likely to benefit from this therapeutic approach.

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Received Mar. 1993; accepted 9 Mar. 1993.

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Eur J Cancer, Vol. 29A, No. 9, pp. 1226–1227, 1993.
Printed in Great Britain

0964–1947/93 $6.00 + 0.00

Mechanisms of Carcinogenesis and Molecular Epidemiology

CARCINOGENESIS IN humans (and animals) is a long process involving multiple changes in genotype and phenotype. The complexity of this process is suggested by several sources of data. The exponential increase in cancer incidence with age can be interpreted as a result of multiple rate-limiting steps in the carcinogenic process, although the number of steps and the biological nature of each step cannot be inferred from the age-incidence pattern alone [1, 2]. Now classical experiments showed that the various steps in the carcinogenic process may occur as a result of the action of different chemical compounds, and that certain exposures may act specifically on cells which have already undergone one or several changes [3]. In colorectal cancer, many of the different steps in the carcinogenic process have been characterised at the molecular level [4]. Each step in the development of cancer may take years to complete and, accordingly, the occurrence of cancer is an event of extremely low probability per cell generation.

Cancer is characterised by unlimited proliferation of cells which fail to respond to physiological control mechanisms, thus destroying surrounding normal tissue, spreading to distant organs and, ultimately, killing the host. The nature of the individual steps in carcinogenesis and the mechanisms that trigger them off are understood only incompletely. New insights into the phenotypic changes required to produce a given cancer are provided by molecular studies of the genetic basis of cancer. Cancer-causing agents or their metabolites may interact with cellular macromolecules to form altered gene products, and the alterations in gene expression may, in some cases, lead to continuous cell proliferation and development of cancer (for references, see [5]).

Research generated during recent years has produced data which suggest that the cascade of molecular events, including chromosomal abnormalities, mutations in cellular oncogenes and tumour suppressor genes, and disturbances in signal transduction and the control of gene expression [6, 7] all play an important role. Disturbances in any of these components could, in theory, lead to uncontrolled cell proliferation and ultimately cancer.

The mechanisms of action of many human carcinogens include both genetic and epigenetic processes [8]. Mechanisms may be understood at many different levels, e.g. for genotoxic carcinogens: metabolism, DNA damage, DNA repair, mutational events, amino acid changes in a proto-oncogene or tumour suppressor gene, changes in the function of the protein, the effect of the altered protein on cellular function or the stage in the carcinogenic process at which the change may be effective [5]. A carcinogenic agent can thus have a multitude of actions which are not mutually exclusive.

In this issue of *The European Journal of Cancer*, Vineis and Brandt-Rauf (pp. 1344–1347) discuss how rapidly evolving knowledge in the molecular biology of the process of carcinogenesis could be integrated into epidemiological studies of human cancer. Epidemiology is the study of the occurrence and distribution of disease in populations, and the identification and quantification of associations between exposures and occurrence of disease. The use of biological measurements in epidemiological studies is an attractive option for the assessment of exposure or for the definition of the outcome under investigation.

For example, specification of the outcome by the presence or absence of a particular mutation in the cancerous cells may yield a higher statistical power for detection of an association, and an improved precision of a quantitative assessment of the relationship between exposure and disease than an analysis of the all-inclusive and often heterogeneous disease entity. The improved specificity may reveal previously obscured 'diluted' or 'averaged' effects. With the emergence of molecular techniques, one may go back to previously conducted case–control studies, apply the molecular techniques to stored samples of biological material from the cases and re-examine the data with separate analysis of each genetically defined subtype of disease.

As an example of the use of biological markers as a means of

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Received and accepted 26 Jan. 1993.