Eur J Cancer, Vol. 28A, No. 6/7, pp. 1009–1010, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00

Comments and Critique

Sequential Cisplatin – doxorubicin, Early Debulking in Advanced Ovarian Cancer

SINCE THE simultaneously introduced concepts of cytoreductive surgery and cisplatin-based combination chemotherapy, many studies have been published about the effects of these treatment modalities and their combination [1–2]. Although there is no doubt about the response of ovarian cancer to this type of chemotherapy, the role of cytoreductive surgery remains unclear. The major prognostic factor of a histologically proven complete response is reported to be a diameter of residual tumour masses less than ± 1 cm at the start of chemotherapy [3–4]. This does not necessarily imply that the better prognosis is a function of the procedure itself. This is only true if the surgically reduced tumour volume can be more effectively killed by chemotherapy before resistance has developed. But one may hypothesise that the curability of ovarian cancer does not depend on tumour size itself but on chemosensitivity. In that case only patients with very chemosensitive tumours will be cured independent of the outcome of the operation. The biological question in ovarian cancer can therefore be formulated as follows: Does the better prognosis of patients with successful initial cytoreductive surgery relate to the procedure itself or does it reflect other, favourable tumour characteristics? This question can only be answered in a prospective randomised study in which cytoreductive surgery is randomised against the standard operative procedure (total abdominal hysterectomy + bilateral oophorectomy + omentectomy) [5]. For the same reason the role of secondary cytoreductive surgery or intervention surgery during or after first-line chemotherapy remains controversial.

In the Dutch multicentre CHAP-5/CP study, an attempt at optimal cytoreductive surgery was performed during first-line chemotherapy in 47 patients. In all these cases a clinically detectable tumour was present before the operation. In 63% of the patients the residual disease was smaller than 1 cm; however this reduction in tumour load did not lead to longer survival compared with patients in whom the attempt was unsuccessful. In fact, survival was worse compared with those who achieved the optimal status at the initial laparotomy [2].

The study of de Gramont and colleagues (ref) reports on 40 patients with advanced ovarian cancer. They were treated with immediate cytoreductive surgery followed by 6 courses of a sequential regimen of cisplatin and doxorubicin. In those patients who had residual disease over 2 cm, early cytoreductive surgery was performed after 3 courses of chemotherapy, followed by another 6 courses of the same chemotherapy. 26 patients who had a negative second-look laparotomy or residual disease under 2 cm received intraperitoneal cisplatin 200 mg/m^2. In a study where so many different therapies were employed it is difficult to get a clear view of the influence of each individual modality. Besides, other well-known prognostic factors, such as grade and the presence of ascites, have to be taken into account, as well as the influence of retreatment.

Unfortunately, the authors did not perform an analysis of prognostic factors. For this reason it is impossible to state that the survival of these patients is the result of treatment alone since patient selection might have influenced the outcome. In general the survival analysis does not present figures different from other, larger studies. For example Neijt *et al.* reported a 5 year survival of 61% in patients with no visible tumour before the start of chemotherapy, 41% of those with tumour residual under 1 cm and 25% of those with tumour diameter 1–5 cm [6]. The progression-free survival of 16% at 5 years as reported by de Gramont *et al.* suggests that the good overall survival (32% at 5 years) is a result of the treatment of recurrence or of favourable prognostic factors, but not of the initial treatment used. The paragraph on intraperitoneal treatment gives an illustration of the treatment regimen the author and co-workers employed in those patients with small disease after first-line treatment. Indeed, small, residual disease is a major problem in ovarian cancer treatment. Up to the present time no treatment modalities have proved to be of much benefit; indeed they have not demonstrated a survival benefit in patients clinically free of disease after first-line treatment. For this reason the performance of second look laparotomy followed by intraperitoneal chemotherapy must be considered in the context of an experimental design [5]. In de Gramont's paper, however, the details of this part of the study are scanty and again the treatment is not compared with other prognostic factors so the data on this subject are illustrative but not conclusive. Advanced ovarian cancer still is a chronic and lethal disease for the majority of our patients. As a consequence our efforts must not be based solely on attempts to achieve a cure but also on care. In this respect it would have been refreshing if the authors had addressed the issue of quality of life in the 32% who survived the first 5 years, as well as in the 68% who died before that time.

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Received 4 Nov. 1991; accepted 9 Dec. 1991.

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Eur J Cancer, Vol. 28A, No. 6/7, pp. 1010–1012, 1992.
Printed in Great Britain

0964–1947/92 $5.00 + 0.00
Pergamon Press Ltd

Low-dose Radiation Carcinogenesis

THE PRINCIPLE that radiation causes cancer, life shortening and an array of other pathological disorders, is well accepted [1, 2], yet the quantification of sequelae at the lower endpoint of the dose–response curve is still controversial [3]. Since the presence of a significant effect at very low doses would have strong financial implications, social and economic flavours blur the assessment of available information. Let us not forget that in contrast with high dose irradiation, delivery of low-dose radiation (LDR) is mostly in our hands, while health policy is a compounded balance of risks and resources.

The controversy focuses on the inconsistency of and ensuing discrepancy in risk estimates, between results coming from studies based on populations actually exposed to low doses [4–11], and extrapolations derived from high-dose studies. The latter include primarily studies of A-bomb survivors in Hiroshima or Nagasaki and individuals exposed to therapeutic irradiation [12–15], where, with a few exceptions [16, 17], no increased risk has been detected at levels below 0.1 Gy. The former comprise populations exposed to fallout, those residing in the vicinity of nuclear reactors, patients affected by scattered radiation following X-ray therapy, workers in the nuclear industry and children exposed *in utero*.

Unfortunately, the interpretation of the direct LDR findings is confounded by inadequate dosimetry, small sample sizes, lack of adequate controls, simultaneous exposure to extraneous carcinogenic factors, and possibly by erroneous measurements as well.

One major problem is that doses used in the computation of risk estimates are usually based on group exposure rather than on the individual subject. For instance, tilting of an irradiated child's head, or a neglect on the part of a technician to turn off the X-ray machine, result in a much higher exposure level than estimated retrospectively. Dosimeters inadequately used by technical personnel will have a similar effect, as would an occasional higher discharge from a nuclear reactor [18, 19]. Another constraint is that in order to demonstrate a true effect at a low dose, exceedingly large population samples are needed. Consequently, the literature is weighted by low-dose studies, where an excess risk was found, while studies showing negative findings are discriminated against, and yield a "publication bias" [20]. However, perhaps the strongest factor of uncertainty, in this context, stems from the virtual impossibility to distinguish between a genuine radiation effect, and the contribution of other established carcinogens, to which the subjects could have been simultaneously exposed, e.g. chemicals in the workplace of nuclear industry employees.

The issue of LDR carcinogenesis has reached impetus with the slowly accumulating data on excess leukaemia near nuclear installations in the UK. Roman *et al.* [8] demonstrated a significantly increased incidence of leukaemia among children younger than 5 years of age in and around the West Berkshire area, which was limited to less than 10 km from the nuclear establishment. Likewise, Gardner and colleagues [9, 21] found an increased risk for leukaemia in children born to mothers in the Seascale parish but not in those born elsewhere but attending school there. More recent and highly publicised findings by Gardner *et al.* [10, 22], relate to an apparent early paternal exposure. Yet, that particular comparison was based essentially on only 4 cases of leukaemia (out of 46), and 3 control children (out of approximately 300), whose fathers had been exposed to over 10 mSv in the 6 months preceding conception, and to over 100 mSv in total, and confounded by maternal age and proximity of residence to the nuclear plant. Furthermore, home exposure to dust, or contaminated paternal clothing, could have contributed to the observed effect. Gardner and coworkers' findings were supported, to a certain extent, by McKinley *et al.* [23], but in their study the fathers were also more significantly exposed to wood dust and chemicals. A whole array of studies, in other British locations [24–27] and elsewhere [28–31], failed to confirm an excess cancer risk near nuclear installations, suggesting that other factors (e.g. higher discharge, chemical carcinogens, contaminated dust, etc.) played a much stronger role in the reported leukaemogenesis than ionising radiation. Data based on civil or military populations exposed in the course of experimental nuclear testings [5, 6, 11, 32, 33] in the Southwestern US and the Pacific Ocean, are also hard to construe.

The simultaneous exposure to a multitude of chemical substances and "the healthy worker effect" constitute two principal obstacles for a definitive assessment of the effect of LDR on nuclear industry employees. The most illustrative controversy in this respect is probably the study of Hanford employees [7, 34–36], where the only genuine finding may be an excess of multiple myeloma, in persons who have had a cumulative exposure above 0.15 Gy. Studies of British Atomic Energy employees [37, 38], showed a significantly increased mortality

Received and accepted 28 Nov. 1991