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After 65, Cancer has a Different Impact on Life Expectancy in Men and Women

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MORE THAN half of all malignancies in Western countries occur in persons aged 65 years or more [1], and, in the elderly, cancer is the second most common cause of death (after cardiovascular diseases), being responsible for about one quarter of all deaths in men and one fifth in women between 65 and 79 years of age [1]. In developed countries, cancer mortality rates have been steadily increasing during the last decades in those aged 65 years or more, in contrast with those among younger subgroups of the population [2]. Thus, malignancy substantially reduces life expectancy in the elderly. Because of the increasing proportion of the elderly in Western countries, urgent efforts need to be made to cope with cancer in this age group, in particular the implementation of specifically designed therapeutic strategies [3]. In this regard, a consensus meeting of the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute (NCI) held in Venice (October 1990) has recommended that the chance of entering protocols for prospective controlled randomised trials should be offered to elderly patients, since this is often accompanied by better care and outcome.

Since site-specific cancer mortality rates show substantial differences between the two sexes, we have estimated the probabilities of dying of selected cancers among Italian men and women aged between 65 and 79 years, using cancer mortality statistics from 1975 to 1977 and the corresponding life-table [4, 5].

As Table 1 shows, elderly men had an overall probability of dying of cancer that was nearly twice that registered among women of the same age. The major contribution to this higher risk in men comes from smoking-related malignancies, which accounted for more than 10% of the total probability of dying of cancer in men and less than 2% in women. The probabilities of dying of non-smoking-related cancers, although higher in men than women, did not show substantial differences.

In countries where the smoking habits of women in the last decades have tended to become similar to those of men, the different impact of smoking-related cancers on probability of death, in elderly men and women, is less striking. In the USA, women aged 65 or older have a higher probability of dying from lung cancer than breast cancer, while men of the same age have a 3-fold higher risk of dying from lung cancer than women (in contrast to a 7-fold risk in Italy). Since the beginning of the century, the constant and substantial increase in life expectancy at any age registered was equally distributed among men and women until 1930–1940 [6]. From 1950 onwards, however, women showed a higher life expectancy than men at all ages. At 65 years of age, a man has, presently, an average life expectancy of nearly 13 years, in contrast to 17 years for a woman.

Table 1. Probability of dying of selected cancers between 65 and 79 years of age, according to sex: Italy, 1975–77

	Men	Women	M/W ratio
Lip, oral cavity and pharynx	0.0081	0.0015	5.40
Trachea, bronchus and lung	0.0746	0.010	7.46
Oesophagus	0.0081	0.0018	4.50
Stomach	0.0479	0.0276	1.74
Intestines, chiefly colon and rectum	0.0331	0.0261	1.27
Bladder	0.0175	0.0033	5.30
Kidney	0.0040	0.0021	1.90
Non-Hodgkin lymphoma	0.0023	0.0016	1.44
Leukaemias	0.0084	0.0053	1.58
Prostate	0.0260	—	—
Breast	—	0.0218	—
Uterus	—	0.0146	—
All malignant tumours	0.2927	0.1666	1.76

It is of course difficult to estimate the quantitative impact of a single cause of death on life expectancy. Nevertheless, little doubt remains that smoking-related malignancies, for which therapy has little impact in reducing mortality (e.g. lung and oesophageal carcinoma), are largely responsible for the shorter life expectancy in elderly men as compared to women. On the other hand, the higher life expectancy in women may be also explained by the fact that therapy does have a positive impact in reducing mortality for breast, cervical and endometrial carcinomas.

In persons aged more than 65 years, a different strategic approach for the two sexes is needed, in order to give men the possibility of approaching women's lifespan and to prevent women regressing to the males' present unsatisfactory situation. The following points are worth considering. First, through specifically designed studies for elderly patients, further improvement can be expected for women with tumours for which therapy has a positive effect on survival such as breast, cervical, endometrial and ovarian carcinomas. Programmes of early diagnosis of cervical and breast carcinomas, specifically targeted to elderly women, could also increase further the survival of these individuals. If the smoking habit in women continues to increase, the difference in lifespan between the two sexes will probably be reduced in the next 20 years because of smoking-related neoplasia. Secondly, in the future, the main tool for decreasing cancer mortality in elderly men will be primary prevention of smoking-related neoplasia (e.g. lung carcinoma, head and neck and bladder carcinoma). In addition, specifically oriented therapeutic studies should be designed for older men with bladder and prostate carcinoma. Thirdly, a common strategy for the elderly of both sexes, through specifically designed protocols, should be adopted for chemosensitive tumours such as acute non-lymphoblastic leukaemia and malignant lymphomas. Effective surgical treatment will have to be expanded through medical education.

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Fotemustine with or without Dacarbazine for Brain Metastases of Malignant Melanoma

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FOTEMUSTINE (Laboratoires Servier, Belgium) is a new nitrosourea which is active against cerebral metastases of melanoma due to its ability to cross the blood–brain barrier, and also against visceral and non-visceral metastases. We present our experience using fotemustine, with or without dacarbazine, in patients with brain metastases of melanoma [1].

18 patients with histologically confirmed malignant melanoma and radiologically detected brain involvement were included, provided that consciousness and mentality were preserved.

Their age range was 19–75 years (median 45.5), Karnofsky performance status was higher or equal to 60% and life expectancy was at least 3 months.

The primary site was skin in 16 patients, rectum in 1 and eye in 1. Previous treatments for brain metastases included craniotomy followed by radiotherapy (30 Gy) in 4, and radiotherapy only (30 Gy) in 2 patients. Steroids were administered in all the patients, starting at least 8 days prior to the protocol. Previous systemic treatment was immunotherapy with or without dacarbazine in 7 patients.

Treatment protocols included three versions, according to the different phase II trials with fotemustine alone or fotemustine–dacarbazine combinations.

The first version consisted of a 7-week induction of fotemustine 100 mg/m^2 on days 1, 8 and 15, then 4 weeks' rest. If response or stabilisation was documented on evaluation, maintenance with fotemustine 100 mg/m^2 every 3 weeks was given until progression was observed. Follow-up intervals were of 6 weeks.

The second version consisted of a 7-week induction of fotemustine 100 mg/m^2 on days 1 and 8, and dacarbazine 500 mg/m^2 on days 15 and 16. If response or stabilisation was documented on evaluation on days 49 or 50, 6-week maintenance courses of fotemustine 100 mg/m^2 on day 1 and dacarbazine 500 mg/m^2 on days 2 and 3 were given, until failure was observed. Follow-up intervals were of 6 weeks.

The third version consisted of dacarbazine 400 mg/m^2, followed 4 hours later by fotemustine 100 mg/m^2. Maintenance courses were to be administered to the non-progressor patients, 28 days later, including dacarbazine 250 mg/m^2 followed 4 hours later by fotemustine 100 mg/m^2 on days 1 and 8.

The overall response rate (CR + PR) of brain metastases to these treatments was 22%, for a median duration of 4 months. 3 patients were treated according to the first version, of whom 1 achieved a CR for 3 months, and one SD for 1 month. 13 patients were treated according to the second protocol, of whom 3 achieved PR for a median duration of 4.5 months, 1 MR for 8 months and 1 SD for 4.5 months. 2 patients were treated with the third version, and no response was observed.

All the responders had a primary cutaneous melanoma. No response was found in meningeal spread. Median survival of brain responders was 7.5 months, and that of the non-responders was 3 months (not statistically significant).

Toxicity was generally mild. Grade I-II thrombocytopenia was observed in 46% and grade I-II nausea and vomiting in 61% of the patients. A transient increase in serum transaminase level was noted in 23% of patients.

The response rate achieved in the brain is attributed to the efficacy of fotemustine, since this drug is known to cross the blood–brain barrier [2] and dacarbazine to a much lesser extent; and spontaneous regression of metastatic melanoma occurs only rarely [3]. Dacarbazine failed to enhance the efficacy of fotemustine against cerebral metastases [4]. None of the patients in our series had been previously exposed to nitrosourea, but 83% of the patients who had been previously treated by immunotherapy and dacarbazine for systemic metastases failed to respond to fotemustine.

The first treatment version was also used by Jacquillat *et al.* who reported a response rate of 28% (CR 5%; PR 23%) in 39 patients with brain metastases [2].

The response rate achieved by the second treatment version was 23%. No comparable literature data are available.

The third version has been reported to yield an extracerebral response rate of 35%, but a cerebral response rate of 0% [5].

We conclude that treatment based on fotemustine was associated with clinical and radiological evidence of regression of brain metastases of malignant melanoma reflecting the intracerebral activity of the drug. Our results confirm other investigators' observations.

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