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Selected reports edited by Janet Fricker

Elderly pancreatic cancer patients benefit from chemotherapy

→ Journal of Geriatric Oncology

Chemotherapy is associated with improved overall survival in patients with metastatic pancreatic cancer aged over 80, a US retrospective analysis has found.

Metastatic pancreatic cancer is an incurable disease with a dismal prognosis. Survival ranges from three to six months for all patients, but drops to two to three months for untreated patients. Despite the incidence of pancreatic cancer peaking at between 70 and 79 years of age, patients aged 65 years or older have been under-represented in clinical trials, resulting in a lack of evidence-based data to make treatment decisions with regard to chemotherapy.

In the current study, Shanmuga Subbiah and colleagues, from Creighton University Medical Center (Omaha), identified patients aged 80 or older treated by the Veterans Health Administration between 1997 and 2007, whose data had been recorded in the VA Central Cancer Registry (VACCR). Altogether, 440 patients were identified who had information available with respect to age at diagnosis, race, sex, tobacco history, tumour location, tumour histology, grade and type of therapy received.

Of the patients identified, 83% (n=367) received no therapy, 12% (n=52) received chemotherapy alone, 2% (n=9) received radiotherapy alone, 1% (n=5) received chemoradiation therapy and 2% (n=7) underwent surgery.

Multivariate analysis demonstrated that median overall survival was 4.9 months for patients receiving chemotherapy versus 1.7 months for patients receiving no therapy (HR 0.41, P<0.0001). Survival at one year was 13% for patients receiving chemotherapy versus 3% for patients receiving no therapy (P<0.0001). Furthermore, current smoking was associated with decreased median overall survival compared to past or never smoking status (1.18 vs 1.63 and 1.57 months respectively, P=0.0087).

"Our results regarding the effectiveness of treatment vs no treatment in pancreatic cancer are encouraging and consistent with similar data in other malignancies but are not definitive. However, we recommend that very elderly patients with good performance status should be offered chemotherapy based on our analysis, and age by itself should not preclude these patients from receiving chemotherapy," write the authors. Treatment decisions, they add, should be based on physiologic rather than chronological age, with the factors that need to be evaluated including functional status, comorbidity and cognition.

Limitations of the study included its retrospective nature, the predominance of men in the study population (only 10 women were included in the analysis), and the lack of information regarding performance status and patients' quality of life. "This is very important in elderly patients since increasing survival by a few weeks at the cost of decrease in quality of life is not acceptable in this patient population," the authors write. Further randomised studies, they add, will be needed to confirm whether chemotherapy offers benefit in very elderly patients with advanced pancreatic cancer.

■ IT Aldossa, T Tashia, W Gonsalvesa et al. Role of chemotherapy in the very elderly patients with metastatic pancreatic cancer. A Veterans Affairs Cancer Registry analysis. *J Geriatr Oncol* 2 July 2011, 2:209–214

Goserelin does not protect ovarian function

→ Journal of Clinical Oncology

Giving goserelin to young women undergoing standard anthracycline-based chemotherapy for hormone-insensitive breast cancer shows no effect on preserving ovarian function, the ZORO study has found.

Currently 1.9% of breast cancers are diagnosed in women aged between 20 and 34 years, and 10.5% in women aged between 35

and 44 years. Although patients younger than 50 years achieve significant benefit from adjuvant systemic chemotherapy in terms of prolonged disease-free and overall survival, a significant number suffer from premature ovarian failure. Cytotoxic agents, especially anthracyclines and alkylating agents, are known to induce premature ovarian failure, most probably through causing apoptotic oocyte death in primordial follicles.

Observational studies and one recent single-institution randomised study have suggested that luteinising hormone-releasing hormone agonists (LHRHa) might offer protection against premature ovarian failure. No explanation has been offered for the benefit.

The German Breast Group ZOladex Rescue of Ovarian function (ZORO) study was designed to investigate the preventive effect of the LHRHa goserelin on chemotherapy-induced ovarian failure in young patients with hormone-insensitive breast cancer who are treated with neoadjuvant chemotherapy based on anthracycline/cyclophosphamide (with or without a taxane). Between March 2005 and December 2007, the study, led by Sibylle Loibl, recruited 60 patients from 16 centres, who were randomly assigned in a 1:1 ratio to receive chemotherapy with goserelin (n=30) or chemotherapy without goserelin (n=30). To be eligible, patients needed to be aged between 18 and 45 and to have requested preservation of ovarian function; they also needed to have had regular and spontaneous menstrual periods, and follicular stimulating hormone levels below 15 mIU/ml in the follicular phase of the menstrual cycle. Patients assigned to goserelin received their first injection of 3.6 mg at least two weeks before the start of chemotherapy and then every four weeks until the last chemotherapy cycle.

At six months, 70% of patients in the group taking goserelin had regular menses compared to 56.7% in the group without goserelin (P=0.284). After adjusting for age (patients in the goserelin group tended to be younger), 70.7% of patients in the goserelin group versus 65.9% in the group without goserelin menstruated (P=0.708). The median time to restoration of menstruation was 6.8 months in the goserelin group versus 6.1 months in the group without (P=0.304).

"The ZORO trial did not provide evidence that use of goserelin for ovarian suppression was associated with a large clinically and statistically significant protective effect on ovarian function in patients with hormone-insensitive breast cancer. The resumption rate of regular menstruation within 2 years after modern chemotherapy was highly independent of goserelin," write the authors, adding that other ongoing randomised trials may clarify the role of LHRHa in protecting ovarian function. "Until these results are available, the uncritical use of LHRHa for ovarian protection should be stopped, and patients should be enrolled onto clinical trials," the authors conclude. Other fertility preservation strategies such as oocyte or embryo freezing, they add, might be preferred.

■ B Gerber, G von Minckwitz, H Stehle et al. Effect of luteinizing hormone-releasing hormone agonist on ovarian function after modern adjuvant breast cancer chemotherapy: The GBG 37 ZORO study. *JCO* 10 June 2011, 29:2334–41

Low-dose CT screening reduces mortality in lung cancer

➜ NEJM

People at high risk from lung cancer randomly assigned to screening with low-dose computed tomography (CT) had fewer deaths from lung cancer than did those randomly assigned to screening with chest radiography, reports a study from the US National Cancer Institute. Researchers showed that three times as many clinically significant abnormalities were identified in the low-dose CT group compared with the radiography group, and furthermore mortality was decreased by one-fifth in the low-dose CT group.

Although effective mass screening of high-risk groups for lung cancer might potentially offer benefits, randomised screening trials with chest radiography with or without sputum cytological analysis have shown no reduction in lung cancer mortality. However, advances in multidetector CT have recently made high-resolution volumetric imaging possible in a single breath hold with acceptable levels of radiation exposure, thereby enabling lung-specific applications.

In the current study, the National Lung Screening Trial (NLST), funded by the American NCI, enrolled 53,454 people considered at high risk for lung cancer who were randomly assigned to undergo three annual screenings with either low-dose CT (n=26,722) or single-view posteroanterior chest radiography (n=26,732). To be eligible, participants needed to be aged between 55 and 74 years of age, and have a history of cigarette smoking of at least 30 years; former smokers were eligible providing they had quit less than 15 years prior to the study. Volunteers were invited to undergo three screening sessions at yearly intervals, with the first performed soon after randomisation.

Results show substantially higher rates of positive results for all three screening sessions in the low-dose CT group compared with the radiography group – 27.3% versus 9.2% for the first round; 27.9% versus 6.2% for the second round; and 16.8% versus 5.0 % for the third round. Altogether 247 deaths from lung cancer per 100,000 person-years occurred in the low-dose CT group compared with 309 deaths per 100,000 person-years in the radiography group, representing a relative reduction in mortality from lung cancer with low-dose CT screening of 20.0% (95%CI 6.8%–26.7%; P=0.004).

"The observation that low-dose CT screening can reduce the rate of death from lung cancer has generated many questions," write the authors. These include whether populations with risk profiles differing from those of the NLST participants would benefit; whether less frequent screening regimens would be equally effective; and for how long screening should be continued?"

The potentially harmful effects of low-dose CT, they add, include false-positives, detection of cancers that would never have

become symptomatic, and the association of low-dose CT with development of radiation-induced cancers.

In an accompanying commentary, Harold Sox, from Dartmouth Medical School (West Lebanon, New Hampshire, US), suggests that, with around seven million adults in the US meeting entry criteria for the study and an estimated 94 million current or former smokers, the introduction of a national screening programme for lung cancer would prove prohibitively expensive. "Policymakers should wait for cost-effectiveness analyses of the NLST data, further follow-up data to determine the amount of over diagnosis in the NLST, and, perhaps, identification of biologic markers of cancers that do not progress," he writes.

■ The National Lung Screening Trial research team. Reduced lung-cancer mortality with low-dose computed tomographic screening. *NEJM*, 4 August 2011, 365:395–409

■ H Sox. Better evidence about screening for lung cancer. *ibid* pp 455–457

Ipilimumab improves survival in melanoma

→ NEJM

Ipilimumab combined with dacarbazine improved survival in patients with previously untreated metastatic melanoma compared with dacarbazine alone, reports a phase III study, which was presented at ASCO and published simultaneously online in the *New England Journal of Medicine*.

Metastatic melanoma has a low survival rate, with only 10–20% of patients alive at two years. Ipilimumab, approved by the US regulatory body, the FDA, in March 2011, is a fully human IgG1 monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), known to be a negative regulator of T cells. An earlier phase III study, presented at ASCO in 2010, showed that ipilimumab improved survival in comparison with an experimental vaccine. The earlier study involved a different population of patients who had received prior therapies for metastatic melanoma.

In the current phase III study, Jedd Wolchok and colleagues, from the Memorial Sloan-Kettering Cancer Center, in New York, randomly assigned 502 patients with previously untreated metastatic melanoma in a 1:1 ratio to receive ipilimumab (10 mg/kg) plus dacarbazine (850 mg/m^2 body-surface), or dacarbazine (850 mg/m^2) plus placebo, given at weeks 1, 4, 7, and 10, followed by dacarbazine alone every three weeks through week 22 (n=252). Although dacarbazine has never been shown to improve survival in randomised controlled studies, it is the drug that is most frequently compared with new agents in trials of patients with melanoma.

Results showed that the median overall survival was 11.2 months in the group receiving ipilimumab plus dacarbazine versus 9.1 months in the group receiving dacarbazine plus placebo (HR 0.72; P<0.00). At one year, the estimated overall survival rate was 47.3% in the ipilimumab plus dacarbazine group versus 36.3% in the dacarbazine plus placebo group, at year two the results were 28.5% versus 17.9%, and at year three 20.8% versus 12.2%. Grade 3 or 4 adverse events occurred in 56.3% of patients treated with ipilimumab plus dacarbazine, as compared with 27.5% treated with dacarbazine plus placebo (P<0.001). No drug-related deaths or gastrointestinal perforations occurred in the ipilimumab–dacarbazine group.

"This trial showed that there was a significant improvement in overall survival among patients with previously untreated metastatic melanoma who received ipilimumab plus dacarbazine as compared with dacarbazine plus placebo," conclude the authors, adding that the present study showed notably higher rates of high-grade hepatic adverse events than previous studies of ipilimumab.

"The apparent shift in the rates of adverse events associated with ipilimumab may be due to its combination with dacarbazine, which is known to cause hepatotoxic effects when it is used as monotherapy," write the authors.

Key side-effects of ipilimumab, such as entercolitis and endocrinopathy, could be managed effectively according to established guidelines, including the administration of systemic glucocorticoids or other immunosuppressive agents.

■ C Robert, L Thomas, I Bondarenko et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *NEJM* 30 June 2011, 364:2517–26

Vemurafenib improves overall survival in melanoma

→ NEJM

Vemurafenib (PLX4032) improved both overall and progression-free survival in previously untreated melanoma patients with *BRAF* mutations in comparison to dacarbazine, according to the findings of a phase III study presented at ASCO 2011 and published simultaneously online in the *New England Journal of Medicine*.

Approximately 40–60% of cutaneous melanomas carry mutations in *BRAF* leading to activation of downstream signalling through MAPK pathways. Vemurafenib is a potent inhibitor of mutated *BRAF* that has been shown to have marked antitumour effects against melanoma cell lines with *BRAF* mutations, but not against cells with wild-type *BRAF*. Phase I and II clinical trials of vemurafenib have demonstrated response rates of more than 50% among patients with metastatic melanoma and *BRAF* mutations.

In the current study, Paul Chapman and colleagues, from the Memorial Sloan-Kettering Cancer Center in New York, randomised 675 patients with previously untreated *BRAF* mutations in a 1:1 ratio to receive either vemurafenib (at a dose of 960 mg twice daily orally) or dacarbazine (at a dose of 1000 mg/m^2 body surface area by intravenous infusion every three weeks). Patients with the required mutation had been identified from a total of 2107 patients undergoing initial screening at 104 centres in 12 countries.

Results show that, at six months, overall survival was 84% in the vemurafenib group versus 64% in the dacarbazine group (HR 0.37, 95%CI 0.26–0.55; *P*<0.0001). The final analysis for progression-free survival (evaluated in 549 patients) showed that vemurafenib was associated with a relative reduction in the risk of either death or disease progression of 74% compared with dacarbazine (*P*<0.001).

Survival benefits for the vemurafenib group were observed in each prespecified subgroup according to age, sex, ECOG performance status, tumour stage, lactate dehydrogenase levels and geographic regions. Common adverse events associated with vemurafenib were arthralgia, rash, fatigue, alopecia, photosensitivity, nausea, and diarrhoea. Altogether, 18% of patients treated with vemurafenib developed at least one squamous cell carcinoma, but the lesions could easily be excised and none required dose modifications of vemurafenib. Overall, 38% of the patients receiving vemurafenib required dose modifications due to adverse events.

"Our results show that single-agent vemurafenib improved the rates of response and of both progression-free and overall survival, as compared with dacarbazine, in patients with metastatic melanoma with the *BRAF* ...mutation," write the authors, adding that their findings provide a solid foundation for the development of future combination therapies.

The mechanism for induction of cutaneous neoplasia (which are far easier to treat than melanoma) is currently under investigation, write the authors, who speculate that it involves the activating effect of vemurafenib on preneoplastic cells.

In an accompanying commentary, Marc Ernstoff, from Dartmouth Medical School (Lebanon, New Hampshire), writes, "Although little is known about the use of targeted adjuvant agents in patients undergoing surgery, it is now reasonable to consider testing of adjuvant vemurafenib in patients with high-risk stage II or III melanoma with the BRAF V600E mutation on the basis of the findings in the BRIM-3 study."

■ PB Chapman, A Hauschild, C Robert, et al. Improved survival with vemurafenib in melanoma with *BRAF* V600E mutation. *NEJM* 30 June 2011, 364:2507–16

■ MS Ernstoff. Been there, not done that – melanoma in the age of molecular therapy. *ibid* pp 2547–48

CT-based simulation improves survival in non-small-cell lung cancer

➜ Journal of Clinical Oncology

The introduction of CT-based simulation improved survival in patients with stage III non-small-cell lung cancer (NSCLC) undergoing thoracic radiation therapy, a retrospective analysis of the US SEER data has found.

Thoracic radiation therapy is commonly used in the management of patients with stage III NSCLC to improve local control and survival. Technical studies have shown that introducing CT-based simulation helps improve local control by allowing for better anatomic definition of the targeted lesion and more precise calculation of dose to both tumour and normal tissues. Despite a good theoretical rationale, prospective data supporting CT simulation has been lacking.

In the current study Aileen Chen and colleagues, from the Dana Farber Cancer Institute (Boston, Massachusetts), analysed data from Medicare's SEER database to identify patients with stage III NSCLC who had received thoracic radiation therapy within six months of diagnosis, between 2000 and 2005. Investigators analysed the effectiveness of CT-based simulation versus conventional simulation with respect to overall survival.

Results showed that the proportion of patients treated with thoracic radiation therapy who had CT simulation increased from 2.4% in 1994 to 34.0% in 2000 and 77.6% in 2005. Overall, of the 5540 patients treated between 2000 and 2005, 60.1% received CT simulation. After controlling for demographic and clinical characteristics, CT simulation was associated with a lower risk of death (HR 0.77; 95%CI 0.73–0.82; *P*<0.01) compared with conventional simulation.

The investigators found regional variation in use of CT simulation. Patients from the northeast and midwest were more likely to receive CT simulation than those in the west or south, and CT simulation was more common in urban areas and among patients with higher incomes.

Furthermore, patients treated with chemotherapy were more likely to have CT simulation (65.2% vs 51.2%; adjusted odds ratio 1.67; 95%CI 1.48–1.88; *P*<0.01), but no significant association was found between surgery and use of CT simulation.

"We cannot be certain whether patients who had CT simulation had better outcomes because of the technique itself, or because CT simulation is a marker for higher TRT [thoracic radiation therapy] doses, more aggressive treatment, greater institutional resources, or differences in the attitudes and mindset of providers likely to adopt new technologies," write the authors, adding that in the absence of randomised data, the results indicate that the new technology is not associated with any unanticipated harms.

In an accompanying commentary, Andrea Bezjak, from the University of Toronto (Ontario, Canada), writes that the regional differences observed suggest that it was not the medical situation or the appropriateness of high-dose radiation that influenced selection of CT-based simulation, but availability of the technology in the centres where patients were treated. "This suggests a potential alternative hypothesis for the survival outcomes: it may be that whether or not a patient underwent CT based simulation was a marker for overall quality of care in the center in which the patient was treated," she writes.

■ AB Chen, BA Neville, DJ Sher et al. Survival outcomes after radiation therapy for stage III non-small-cell lung cancer after adoption of computed tomography-based simulation. *JCO* 10 June 2011, 29:2305–11

■ A Bezjak. Harnessing radiation technology to improve survival. *ibid* pp 2295–96