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Can dose-dense chemotherapy improve outcome in patients with better-prognosis small-cell lung cancer?

GLOSSARY

DOSE INTENSITY
The amount of drug delivered per unit of time, expressed as mg/m^2/week

DOSE-DENSE THERAPY
Treatment where dose intensity is increased by shorter treatment interval rather than by dose escalation

KAPLAN–MEIER ANALYSIS
A conditional probability strategy used for estimation of survival in clinical trials with censored observations

NORTON–SIMON HYPOTHESIS
A mathematical model suggesting that more frequent dosing of chemotherapeutic agents minimizes tumor regrowth between doses; this theory forms the basis for dose-dense and sequential chemotherapy

GOMPERTZIAN PHENOMENON
Where the cell number increases with time, but the relative rate of increase falls exponentially until a 'plateau phase' of very slow actual growth is reached

Original article Lorigan P *et al.* (2005) Randomized phase III trial of dose-dense chemotherapy supported by whole-blood hematopoietic progenitors in better-prognosis small-cell lung cancer. *J Natl Cancer Inst* **97**: 666–674

SYNOPSIS

KEYWORDS dose-dense chemotherapy, small-cell lung cancer, survival

BACKGROUND

For patients with small-cell lung cancer (SCLC), response rates with combined chemotherapy and radiotherapy are high, but long-term survival is poor. The role of dose intensification in the treatment of SCLC is controversial. The main dose-limiting toxicity of ifosfamide, carboplatin and etoposide (ICE) chemotherapy is hematologic, so the authors used filgrastim and autologous whole-blood progenitor cells (WBPC) to allow an increase in the relative DOSE INTENSITY of this chemotherapy regimen.

OBJECTIVES

To compare ICE chemotherapy with a 4-week interval between cycles (standard therapy) with ICE chemotherapy with a 2-week interval between cycles supported by filgrastim and WBPC (DOSE-DENSE THERAPY).

DESIGN AND INTERVENTION

In this phase III trial, patients with pathologically confirmed SCLC with a prognostic score of 0 or 1 were randomized to receive six cycles of ICE chemotherapy (ifosfamide at 5 g/m^2 intravenously for 24 hours on day 1 with mesna at 5 g/m^2, carboplatin at 300 mg/m^2 intravenously on day 1, and etoposide at 180 mg/m^2 intravenously on days 1 and 2). For standard therapy, a 4-week interval was left between cycles, whereas dose-dense therapy cycles were given at 2-week intervals, with subcutaneously administered filgrastim (300 μg for patients weighing <70 kg and 5 μg/kg for patients weighing >70 kg, daily on days 4–14) and autotransfusion of autologous blood.

OUTCOME MEASURES

The primary outcome assessed was survival, estimated using KAPLAN–MEIER ANALYSIS. Response rate, relative dose intensity, time to disease progression and toxicity were studied as secondary endpoints.

RESULTS

Age, sex and performance status were balanced between the groups receiving dose-dense or standard chemotherapy (median age 58 years in both groups). All 318 patients were analyzed for survival on an intention-to-treat basis. Median follow-up was 14 months. Response rates, median time to progression, median survival and 1-year or 2-year survival did not differ significantly between the groups. Overall response to treatment was seen in 129 of 147 patients receiving dose-dense therapy (88%) versus 118 of 148 patients receiving standard therapy (80%) (a nonsignificant difference). Median overall survival was 14.4 months (95% CI 13.1–15.4 months) for dose-dense therapy versus 13.9 months for standard therapy (95% CI 12.1–15.7 months) and 2-year survival rates were 19% (95% CI 14–27%) and 22% (95% CI 16–29%) respectively, with neither difference reaching statistical significance. Median delivered dose intensity was 99% for standard therapy and 182% for dose-dense therapy. More hematologic toxicity was reported in the dose-dense arm than in the standard arm, but the number of cycles complicated by neutropenic sepsis was higher with standard therapy than with dose-dense therapy (15.3% versus 11.6% respectively; 95% CI –2% to 9.6%; $P = 0.03$).

CONCLUSION

Dose-dense ICE chemotherapy has been validated as a safe, acceptable regimen and might be applicable to other tumor types in which dose intensification might improve survival.

COMMENTARY

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Randomized trials using various dose intensities to treat SCLC have shown inconsistent survival results. Nevertheless, when the same drugs were delivered at the same dose per cycle, the same number of cycles, and the same planned cumulative doses using shorter treatment intervals supported by hematopoietic growth factor, a modest survival benefit was demonstrated in four randomized trials.[1] Dose intensity was 106–134% in these trials versus 100% for standard treatment, a moderate increase. Superior results using dose-intensified chemotherapy could therefore be anticipated in the treatment of SCLC.

Lorigan and colleagues have reported the first randomized trial in which the dose density of ICE chemotherapy was doubled, facilitated by filgrastim and WBPC—an attractive method for accomplishing dose densification effectively and safely[2] in patients with better-prognosis SCLC. Dose-dense chemotherapy using WBPC and filgrastim produced acceptable toxicities, a lower risk of infection and shorter treatment duration than standard chemotherapy.[2] Although more red-cell and platelet transfusions were needed to treat grade 3–4 anemia and thrombocytopenia resulting from dose-dense chemotherapy, 69% of the patients still completed six cycles of dose-dense chemotherapy. Dose-dense chemotherapy with a 2-week interval resulted in a greater relative dose intensity (up to 182%) than standard ICE chemotherapy with a 4-week interval, but could not prolong overall survival.

Why did dose-dense chemotherapy supported by WBPC fail to improve overall survival in this trial? First, this phase III trial was designed to clarify the efficacy of dose-dense chemotherapy with a focus on specific drugs only, and leaving thoracic radiation therapy out of consideration. More patients in the standard-treatment arm than in the dose-dense chemotherapy arm received thoracic radiotherapy, whereas more patients receiving dose-dense treatment achieved objective response than those receiving standard treatment. The use of thoracic radiotherapy, the most powerful treatment for local control in limited-stage SCLC, might have cancelled a dose-dense effect in this trial. Second, the advantage of dose densification is in its ability to improve cure rates. Based on the NORTON–SIMON HYPOTHESIS, an increased chemotherapy dose rate enhances cell kill in *ex vivo* and *in vivo* experiments.[3] The true benefit of dose-dense therapy comes from total tumor-cell kill, because even if repeated therapy induces multiple regressions, tumor-cell regrowth occurs because of GOMPERTZIAN PHENOMENA. Thus, the 2-year survival rate of around 20% is somewhat low to enable a comparison with the cure rates in patients with better-prognosis SCLC. Similarly, dose-dense chemotherapy as adjuvant treatment produces longer survival in primary breast cancer,[4] but not in breast cancer that has metastasized.

A preliminary report of a randomized phase II study with the same design as this study reported significantly better survival, but not time to progression, in the dose-dense treatment arm than in the standard treatment arm. The 2-year survival rate was 62% in the dose-dense treatment arm, but the study size was small and thoracic radiotherapy was not mentioned.[5] We will have to reserve final judgment on dose-dense chemotherapy supported by WBPC in the clinical practice of SCLC.

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Competing interests
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PRACTICE POINT
Dose-dense chemotherapy supported by whole-blood progenitor cells should not be routinely employed in the clinical practice to treat small-cell lung cancer