In 1977, I wrote a review article on small cell lung cancer (SCLC) for Cancer Treatment Reports (a journal that was subsequently merged with the Journal of National Cancer Institute) in which I quoted Shakespeare, “Diseases desperate grown by desperate appliance are relieved or not at all,” (Shakespeare: Hamlet IV.3.9) to epitomize the state of the art in SCLC therapy (1). The bad news is that 30 years later, we are still reading about the “desperate” use of escalating doses of the same toxic drugs. In addition, we are still using underpowered small randomized trials that have difficulties in accruing patients, in part because enthusiasm is low. Novel research strategies and funding for them are poor. The good news is that the recent study by Leyvraz et al. (2) is likely to put the final nail in the coffin of high-dose cytotoxic chemotherapy for SCLC, that the incidence of SCLC is falling in developed countries, and that understanding the biology of SCLC will lead to better and less desperate therapies.

Cytotoxic chemotherapy improves the prognosis of SCLC patients, but 2-year and 5-year survival rates remain extremely low (3,4). In vitro studies indicating that exposure to higher doses of alkylating agents could increase cytotoxicity led to trials of high-dose chemotherapy supported by autologous bone marrow cells or peripheral blood bone marrow cells. Early single-arm studies with this strategy reported promising results in highly selected subjects (5,6). Subsequent small randomized trials reported more conflicting results (7,8). The phase III randomized study reported in this issue (2) was designed to determine whether a dose-intensified three-drug combination of ifosfamide, carboplatin, and etoposide (ICE) would provide superior survival compared with standard-dose ICE. The primary study endpoint was 3-year overall survival assessed by the log-rank test, which did not favor the high-dose therapy. The secondary endpoints of disease-free survival and response also were not different between the groups. In fact, progression-free survival after the second year favored the standard-dose group. If there was to be a benefit from high-dose therapy, it would be expected to be characterized by an improvement in progression-free survival, especially after 2 years. There is no evidence that such a benefit occurred. Not surprisingly, there was a marked, clinically relevant, and statistically significant increase in toxicity associated with the high-dose therapy. All patients in the high-dose arm had grade 4 leukopenia and thrombocytopenia; 31% had grade 3/4 infections, and 8% had toxic deaths. Patients on the high-dose arm had more prolonged hospitalizations as well.

The authors’ conclusions state the following: “The approach explored in the present trial succeeded in raising the peak dose, total dose, and dose intensity of ICE by threefold but has clearly been ineffective and highly toxic. In addition, this regimen is costly. As a result, this strategy should be abandoned.” Enthusiasm for this conclusion might be tempered by the small sample size and slow accrual in this study, but the data from this study combined with those from other studies should put an end to the era of high-dose “desperate” therapies.

The declining incidence of SCLC and the lack of progress seem to have dampened the enthusiasm of funding agencies and industry for exploring novel therapies. This is indeed unfortunate because SCLC remains a common cancer in both the developed and developing world. SCLCs have a large number of potential therapeutic targets, including G-protein–coupled neuropeptide receptors (eg, bradykinin, bombesin) (9,10), tyrosine kinase growth factor receptors (eg, IGFR-1R, FGF, axl, met, kit) (11–14), myc, FHIT, Fus-1, p53, and other oncogenes and tumor suppressor genes (15–17). The tumor microenvironment and angiogenesis are also important targets for lung cancer therapy (14,18–20). For the sake of our lung cancer patients, we should strive to obtain funding to move these opportunities to the clinic as rapidly as possible.

References


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See “Note” following “References.”

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**Note**

This editorial is dedicated to the memory of my good friend and colleague, Daniel C. Ihde, MD.