Annals of Oncology 10: 1007–1009, 1999.

Editorial

Little to learn from phase II trials in small-cell lung cancer

Small-cell lung cancer (SCLC) is the classic example of a chemosensitive solid tumor in which a dose-response relation has been demonstrated [1]. Despite high response rates with standard combination chemotherapy, overall survival remains poor [2]. With the aim to overcome drug resistance high dose chemotherapy has been extensively investigated for two decades. A multitude of small phase II trials revealed contradictory results. Most of these trials comprised small patient numbers with heterogeneous prognostic factors [3] and did not allow the detection of small, but valuable improvements. More recently intensification has been facilitated with the availability of hematopoetic growth factors and progenitor cell support, leading again to many phase I–II trials. Yet, another phase II trial is presented in this issue of *Annals of Oncology* by van de Velde et al. [4]. These investigators administered 4 alternating cycles of ifosfamide–epirubicin and carboplatin–etoposide to 35 patients with limited stage small-cell lung cancer. Concomitant but split course once daily radiotherapy was given for five days during each cycle of chemotherapy. At a median follow-up of almost 4 years they report an overall median survival of 25 months and an actuarial three-year survival of 36%. These results are impressive when compared to other standard or intensive regimens, but was this outcome due to intensive chemotherapy? The regimen they used with stem-cell support can also be administered with growth factors alone, as shown in their trial for the first cycle. Dose escalation was moderate and consisted mainly of doubling the dose of ifosfamide and carboplatin, while maintaining standard doses of etoposide and epirubicin. Based solely on the chemotherapy, this regimen cannot be considered intensive. The expected conclusions from this type of phase II trials are feasibility and the claim for a future randomized trial, which only rarely follows. At this years ASCO meeting again two such trials were reported [5, 6], at a time when randomized trials have already been completed [7–13] or are ongoing. Some definite conclusions can be drawn from the two largest and most recent trials [12, 13]. Stewart et al. randomized 300 patients to either standard or intensified V-ICE (vincristine, ifosfamide, carboplatin, etoposide) [12]. Chemotherapy was administered for six cycles every four weeks in the standard arm, and every three weeks in the intensified arm (increase in dose intensity of 25%). Although the complete remission rates were comparable, the median survival was 16 months in the high-dose arm and only 12.5 months in the standard arm. At two years this translated into almost twice as many patients being alive (33% vs. 18%). An even larger trial conducted by the MRC with over 400 patients was reported in abstract form showing an improved survival already at one year [13]. In all these studies the increase in dose intensity was only moderate reaching 33% at the most. This is far from the 300%–500%, what should be obtained according to *in vitro* modeling [14]. This intensity can be obtained in the clinic as demonstrated in a multicenter trial [15]. Sixty-nine patients were treated with three cycles of a high-dose ICE-regimen (ifosfamide, carboplatin, etoposide) with peripheral stem-cell support and a relative dose-intensity of 290% was achieved compared to the standard ICE-regimen. This intensive regimen is currently compared to six cycles of standard ICE in a randomized international multicenter trial by the European Group for Blood and Marrow Transplantation. The primary endpoint in this trial is long-term survival and thus possibly cure at three years.

Accelerating the radiation therapy is another way to increase treatment intensity. Indeed, a recently reported large randomized trial in selected patients with limited disease (exclusion of N_3 and pleural effusion) showed significantly higher two- and five-year survival rates after hyperfractionated twice daily radiotherapy (2 × 1.5 Gy, 45 Gy) *versus* the same total dose delivered once daily (1.8 Gy) [16]. Radiation therapy was given over a period of three weeks in the experimental arm, and over five weeks in the standard arm. All patients received concomitant chemotherapy and radiation was begun together with the first cycle of chemotherapy. Median survival was 23 vs. 19 months, and at 5 years the actuarial survival was 26% for patients receiving twice daily vs. 16% only for patients with once daily radiotherapy. There is now the need to develop a concept of treatment intensification in SCLC not only focused on chemotherapy, but on an overall strategy of intensive concomitant chemoradiotherapy with optimal delivery of all modalities. The study by van de Velde et al. was an attempt in that direction [4]. Unfortunately neither the chemotherapy nor the radiation therapy were sufficiently intensive as documented by the very low rate of mucosal toxicity.

Recurrence in the brain remains a major site of treatment failure. The randomized NCIC trial suggested that the failure in the brain be closely related to the early control of the primary disease [17]. In patients receiving late concomitant chemoradiotherapy brain metastases could be detected on CT scan prior to PCI twice as frequently than in patients treated with early radiation. Accordingly, the risk of developing brain metastases during the course of disease was 28% and 18% for patients treated with late and early radiation, respectively. This suggests that CNS recurrence can be reduced by

more early intensive treatment at the primary site at least in patients with limited stage. High-dose chemotherapy may in part overcome the blood–brain barrier. Several new and active drugs have become available for the treatment of SCLC. In particular topotecan may be of interest for the treatment of occult CNS disease. Topotecan has a good penetration into the CSF and can also be given intrathecally [18, 19]. This drug should be integrated into current standard and intensive regimens.

For the future, innovative treatments remain to be explored. Indeed, despite improvements and impressive complete response rates, a majority of patients continue to die of their disease. Too few patients are cured by present therapies and strategies against minimal residual disease should be studied. Neither maintenance chemotherapy [20, 21], nor adjuvant interferons [22, 23] seemed to lower the recurrence rate. Immunotherapy using anti-idiotype antibody BEC2, mimicking the ganglioside GD3 present on the majority of the tumor cells, combined with BCG, increased dramatically the relapse-free survival of a small number of patients with limited disease responding to chemotherapy [24]. After a median follow-up of 47 months, only one of seven patients with limited stage disease relapsed. Obviously confirmation is needed in a large randomized trial currently conducted by the EORTC. Other approaches are undergoing phase III trials, like the adjuvant use of the matrix metalloproteinase inhibitor marimastat, or BAY 12-9566, a new anti-angiogenesis compound. Vascular endothelial growth factor (VEGF) has an important role in tumor angiogenesis and VEGF has been associated with poor response to treatment and short survival [25]. Agents blocking VEGF are in clinical development. Modulation of radiation and drug resistance by interfering with apoptotic mechanisms may be another avenue to be explored. Antisense oligodeoxynucleotide targeted against c-*myc* or *bcl*-2 have been shown to reduce the viability, to facilitate apoptosis and to increase the sensitivity to chemotherapy [26, 27]. Such a treatment has already been tested in lymphoma [28] and remains to be evaluated in SCLC. The use of antibodies against autocrine growth factors or cell surface antigens, linked to a toxin, has already been tested in the clinic with some efficacy in relapsed SCLC [29].

Even if currently available treatment options for patients with SCLC remain unsatisfactory, only continuous and rigorous research will lead to improvement. Clinical research has to be conducted in an orderly and timely fashion with a rapid transition from toxicity and feasibility trials to well controlled clinical investigation. Too much time, energy, money and ultimately patients are lost in small, inconclusive phase II studies, when progress will come only from well designed, and sufficiently powered randomized trials.

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