Controversies in the timing of chest radiotherapy

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Since the metaanalysis conducted by Pignon et al, chest radiotherapy is now a classical component in the treatment of limited small cell lung cancer. The next question is to define the optimal way of combining drugs and radiation including the drugs, the sequence and the characteristics of the radiation treatment (doses, volumes, fractionation and timing). So, the issue of timing is only one variable amongst different possibilities. This issue have been addressed by a series of randomised trials and metaanalysis.

Six randomised trials have addressed the question of the timing: 5 have used a concurrent chemo radiotherapy schedule while one used a sequential approach (Work). Trials are using a cisplatin based chemotherapy and a continuous irradiation (a split-course schedule was only used in the Work trial). The timing of chest RT varies from 42 to 169 days for the late group and during the first cycle of chemotherapy for the early group. Three trials are in favour of an early administration (Murray, Skarios, Jeremic) while 3 are in favour of a late chest RT (Spiro, Work, Perry). Except for Murray and Works trials, the late chest irradiation was delivered within 64 days and certainly not at the end of the chemotherapy programme. It is interesting to compare the results of Spiro and Murray trial with a very similar design but leading to different results: the Spiro trial favours the late chest RT while the Murray is in favour of an early administration. There are some differences in the treatment design: the timing of chest radiotherapy was respectively on day 22 and 105 for Murray trial and on day 1 and 64 for the Spiro trial. The radiation schedule was also slightly different: 40 Gy in 15 fractions over 3 weeks for Murray and 50 Gy in 25 fractions over 5 weeks for Spiro. Nevertheless, chemotherapy compliance was certainly the main difference between the two trials: in Spiro trial, the six cycles of chemotherapy were given to 69% of the patients in the early RT vs. 80% for the late group while in the Murray trial there was no major difference between the two arms with a chemotherapy compliance over 80%. In general, the compliance to chemotherapy was reduced in most trials in case of the early chest RT (Skarios, Work, Perry).

Different metaanalysis have been conducted including some of those trials and other trials not especially design to study the timing but were a difference in timing was observed between the two arms (An alternating schedule vs. a sequential for the Gregor trial and an early concurrent approach vs. a sequential for the Japanese trial). The definition of early varies from one metaanalysis to another (from within one month or before the 3 cycles of chemotherapy).

In those metaanalysis, there was a trend in favor of an early radiotherapy when the non-platinum chemotherapy trials were excluded. In Fried metaanalysis including 7 trials, an early RT means an RT delivered within 9 weeks or before the 3 cycles of chemotherapy. A benefit in favor of an early chest RT was seen only for platinum based chemotherapy and for hyper fractionated radiation schedule. In the Cochrane analysis, only a trend was observed in favor of a chest RT delivered within 30 days after the start of chemotherapy after excluding the Perry trial. If 5-year data are taking into account, then thoracic radiation delivered within 30 days after the start of radiation increases the survival from 13.8 to 20.2% but at the expense of more acute toxicity, esophagitis and leucopenia.

Furthermore, reviewing the data available from randomized trial, De Ruyscher and Vansteenkiste introduced the SER concept: this is the time elapsed between the start of any therapy and the end of the radiation: in an analysis including 5 trials (Takada, Jeremic, Murray, Work and Turrisi), a short SER time led to a clear survival benefit. This concept is based on the assumptions that the first cytotoxic insult may trigger an accelerated tumor repopulation and a more aggressive treatment is an important issue. It is interesting to notice that in Murray trial the radiation was an accelerated schedule 45 Gy in 3 weeks and in Turrisi trial the accelerated schedule (45 Gy in 3 weeks with 2 fractions a day) led to a clear survival advantage over the classical 45 Gy in 5 weeks.

In conclusion, there is certainly not a clear answer but the data may suggest a small advantage for a concurrent chemo radiotherapy approach and an early administration of chest radiotherapy. This implies to have an adequate patient selection including the extent of the tumor and the patient side effects, to avoid an excessive toxicity and to ensure a good compliance to the subsequent chemotherapy cycles. This raises another question: is the classical definition of limited disease the good one to help us to select the patient for an aggressive approach.

Selected References

De Ruyscher et al Time between the first day of chemotherapy and the last day of chest irradiation is the most important predictor of survival in limited-disease small-cell lung cancer. J.Clin.Oncol. 2006; 24: 1057
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Controversy in Small cell lung cancer : targeted therapy

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For three decades, trials of new chemotherapy regimens for small cell lung cancer (SCLC) have failed to substantially improve clinical outcomes. The promise of targeted therapy has yet to be realised for SCLC but there is cautious optimism that there will soon be a breakthrough for this disease.

Angiogenesis Inhibitors: To date the majority of agents evaluated in SCLC have been inhibitors of angiogenesis. Trials of interferons conducted during the early 1990’s were halted due to lack of significant benefit and toxicities that limited administration [1-4]. Trials of matrix metalloproteinase inhibitors also failed, and proved toxic due to musculoskeletal toxicity [5,6]. The first evidence that inhibition of angiogenesis may be a viable therapeutic strategy comes from the results of a randomised, phase III, placebo-controlled trial of maintenance thalidomide in patients with previously untreated extensive stage SCLC conducted by the French Intergroup [7]. The thalidomide treated group had a median survival of 11.7 months versus 8.7 months for the placebo group (HR: 0.48 [95% CI: 0.24-0.93]; p = 0.03). However toxic-