Quimio-radioterapia sequencial no carcinoma pulmonar não de pequenas células: estudo retrospectivo de 100 doentes

Sequential chemo-radiation in non-small cell lung cancer: a retrospective study of 100 patients

RESUMO
A combinação da quimioterapia e da radio-terapia revelou-se a terapêutica corrente no carcinoma pulmonar não de pequenas células irresecável, após a aplicação da radioterapia isolada, durante vários anos, ter revelado sobrevidas

ABSTRACT
Combined chemotherapy and radiotherapy has shown to be the correct treatment of unresectable non-small cell lung cancer, after many years of poor survival figures with standard radiotherapy alone. It has also been demonstrated

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INTRODUCTION

Non-small cell lung cancer (NSCLC), accounts for about 80% of all lung cancers and surgery is the curative treatment\(^3\), with 5 year survival rates of 55%, 30% and 18% in stages I, II and III, respectively\(^13\). Unfortunately, surgery is only possible in 15% to 25% of cases, due to loco-regional invasion or disseminated disease at the diagnosis, or medically inoperable patients or surgery refusal\(^3,8,41\). In locally advanced tumours, those with small and ipsilateral mediastinal lymph nodes — minimal N2 — are a therapeutic challenge, because they may benefit with neo-adjuvant treatment\(^2,4,5,8,11,12,16,17,21,23,28,29,35,39\). Randomized studies published in 1994 have confirmed that benefit\(^25,26\) and the studies from Memorial Sloan-Kettering Cancer Center\(^22\) and from Southwest Oncology Group\(^1\) have demonstrated resection rates of 65% and 73%, respectively, after chemotherapy (CT) and radiotherapy (RT). All other stage IIIA and all stage IIIB cases are classically considered unresectable\(^18,24\) and, since many years, RT alone has been the standard therapy\(^19\). Although the results were extremely disappointing, with median survival less than one year and 5 year survival rates of 0% to 9%\(^6,10,15,17,32\), it was the only chance of cure for a very small number of patients.

From the end of 80 decade and beginning of 90 decade, some authors have shown that the ideal approach in unresectable NSCLC is combining CT and RT, in patients with good performance status and minimal weight loss\(^2,4,5,8,11,12,16,17,21,23,28,29,35,39\). In most series, this combination demonstrated a survival gain of 2 to 4 months and two times more survivors at 2 and 3 years with CT schedules containing cisplatin\(^18\), if combined with RT, when compared with RT alone\(^20\). The randomized study from CALGB, published in 1990\(^11\) and up-dated in 1996\(^12\) with 155 patients presents a median survival gain from 9.7 months to 13.8 months and a 3 year survival from 11% to 23%. Other randomized study from Institut Gustave Roussy\(^21\), with 353 patients, shows a median survival gain from 10 months to
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12 months and a 3 year survival from 5% to 11%. Both an Italian group and a Spanish group, with 66 and 45 patients, respectively, have shown encouraging results with combined CT-RT. However, timing of both modalities is still controversial, taking in consideration the final endpoint of a longer survival without increasing the toxicity. With the purpose of clearing this point, some publications have tried to demonstrate the superiority of concurrent CT-RT, with encouraging results.\textsuperscript{7,9,14,31,36,37,38,40}

**MATERIAL AND METHODS**

From January 1992 until December 1998, one hundred patients with stage III NSCLC and Karnofsky index ≥ 70, have been treated with 3 or 4 cycles of CT followed by RT with 60 Gy/6 weeks. Median age is 64.5 years (range 38-77 years), 90 patients are male and 10 are female. According to histologic type, 46% are squamous cell carcinomas. 34% adenocarcinomas. 3% mixed adenosquamous tumours, 1% large cell carcinoma and 16% unclassified NSCLC. According to stage, 24% are in stage IIIA and 76% in stage IIIB. In 23% of the patients, CT schedule includes mitomycin, vindesine and cisplatin (MVP), in 58% vindesine is changed to ifosfamide (MIP), in 14% vinorelbine is included in the schedule combined with ifosfamide and cisplatin (NIP) and in 5% gemcitabine is associated to cisplatin (GP). Complete CT schedule is presented in Table I. 60% of the patients have been submitted to 3 CT courses and 40% to 4

<table>
<thead>
<tr>
<th>TABLE I</th>
<th>CT schedule</th>
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| MVP     | Mitomycin 8 mg/m\(^2\)  
Vindesine 3 mg/m\(^2\)  
Cisplatin 80 mg/m\(^2\)  | each 28 days |
| MIP     | Mitomycin 6 mg/m\(^2\)  
Ifosfamide 3 mg/m\(^2\)  
Cisplatin 80 mg/m\(^2\)  | each 21 days |
| NIP     | Vinorelbine 30 mg/m\(^2\)  
Ifosfamide 3 mg/m\(^2\)  
Cisplatin 80 mg/m\(^2\)  | each 21 days |
| GP      | Gemcitabine 1000 mg/m\(^2\)  
Cisplatin 100 mg/m\(^2\)  | each 28 days |

<table>
<thead>
<tr>
<th>TABLE II</th>
<th>Patients and treatment features</th>
</tr>
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<tbody>
<tr>
<td>SEX</td>
<td>N(^o) = %</td>
</tr>
<tr>
<td>Male</td>
<td>90</td>
</tr>
<tr>
<td>Female</td>
<td>10</td>
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<tr>
<td>HISTOLOGY</td>
<td></td>
</tr>
<tr>
<td>Squamous cell</td>
<td>46</td>
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<tr>
<td>Adenocarcinoma</td>
<td>34</td>
</tr>
<tr>
<td>Mixed Tumours</td>
<td>3</td>
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<tr>
<td>Unclassified NSCLC</td>
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<tr>
<td>Large cell</td>
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<td>STAGE</td>
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<td>IIIA</td>
<td>24</td>
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<td>IIIB</td>
<td>76</td>
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<tr>
<td>CT SCHEDULE</td>
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</tr>
<tr>
<td>MVP</td>
<td>23</td>
</tr>
<tr>
<td>MIP</td>
<td>58</td>
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<tr>
<td>NIP</td>
<td>14</td>
</tr>
<tr>
<td>GP</td>
<td>5</td>
</tr>
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<tr>
<td>4</td>
<td>40</td>
</tr>
<tr>
<td>RT DOSE</td>
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</tr>
<tr>
<td>60 Gy</td>
<td>92</td>
</tr>
<tr>
<td>&lt;60 Gy</td>
<td>8</td>
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courses. Concerning RT, 8% of the patients did not complete 60Gy, due to disease progression or poor general condition. The patients and treatments features are summarized in Table II.

Kaplan-Meier method has been used for survival curves and log rank for significance tests.

RESULTS

Median survival is 17 months. There is not any statistically significant difference according to histology: 17 months in squamous cell carcinomas and 14 months in adenocarcinomas, with \( p = 0.6 \) (Fig. 1); there is not any statistical difference too between stages: 23 months in stage IIIA and 16 months in stage IIIB, with \( p = 0.16 \) (Fig.2); also according to CT schedule and number of courses, there is not any difference: 18 months with MVP 17 months with MIP, 15 months with NIP and 10 months with GP, with \( p = 0.79 \) (Fig. 3), 16 months with 3 courses and 17 months with 4 courses with \( p = 0.88 \) (Fig. 4); despite the very small number of patients treated with < 60 Gy, there is almost statistically significant difference between RT dosis: 17 months with 60 Gy and 9 months with < 60 Gy, with \( p = 0.069 \) (Fig. 5).

Overall survival at 1, 2 and 3 years and survival probability at 5 years is 69.2%, 36%, 23.3% and 11.6%, respectively (Fig. 6). Median time to local progression is 15 months. Local progression-free survival at 1, 2 and 3 years is 65.9%, 28.7% and 26.7%, respectively (Fig. 7).

Median time to distant progression is 17 months. Distant progression-free survival at 1,2 and 3 years is 58.8%, 38.2% and 34.2%, respectively (Fig. 8). The most frequent first site of dissemination is brain in 37% of the cases, followed by bone (33.3%), lung (16.6%) and liver (13%).

Five patients developed second neoplastic diseases: thyroid, pancreas, prostate, myelodisplasia and rectum.
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Fig. 3 — Survival curve according to CT schedule

Fig. 4 — Survival curve according to number of CT courses

Fig. 5 — Survival curve according to RT dosis

Fig. 6 — Overall survival
Today, combination of CT and RT is the standard treatment of unresectable NSCLC. Concerning CT, it has been demonstrated that cisplatin is the reference to combine with other drugs. The sequential approach of CT and RT has been largely performed, showing an improvement of survival compared with RT alone.
Our series of 100 patients has 76% of cases with stage IIIB and a slight predominance of squamous cell carcinomas. CT consisted of 3 or 4 courses and two of the so-called new drugs — vinorelbine and gemcitabine — were introduced in our schedule in 1996 and 1997, respectively, leading to a smaller number of patients treated with those drugs. However, at this time, there is not any difference in survival results according to the CT scheme. Histologic type did not show either any prognostic relevance. The statistic difference between RT dosis, almost significant, probably means that 60 Gy might be the minimal dosis required in NSCLC, which perhaps means that dosis has prognostic value, as it is suggested in a recent recursive partitioning analysis.

The results of our series are quite similar to those published in literature with combined CT-RT in NSCLC (Table III) with 2- and 5-year survival rates of 36% and 11.6%, respectively. Nevertheless, better results could be achieved with improvements in both therapeutic modalities. Concerning CT a wider utilization of the new drugs seems to obtain promising results with more responses and longer survival, and this fact is more attractive if RT is given concomitantly, in spite of more toxicity, mainly esophageal. What concerns RT, a sequential approach of CT-RT, in which part of RT was given with accelerated fractionation, obtained a 3-year survival rate of 26%, bringing to discussion the benefit of altered fractionation schemes. On the other hand, 3-dimensional planning and conformal RT have launched the debate about the optimal field size (is uninvolved elective areas irradiation needed?) and consequent escalation dosis, in order to reach better local control.

REFERENCES

