Cisplatin and gemcitabine in non-small-cell lung cancer

G. Cartei, C. Sacco, A. Sibau, N. Pella, A. Iop & G. Tabaro
Operative Unit of Medical Oncology and Cancer Prevention Center, Azienda Nazionale Ospedaliera di Alta Specializzazione, Udine, Italy

Summary

The nucleoside analogue, gemcitabine, has shown activity as a single agent in the treatment of metastatic non-small-cell lung cancer (NSCLC), producing consistent response rates of 20% and above. Because of its unique mechanism of action and its non-overlapping toxicity with other active agents, gemcitabine is an attractive candidate for trials in combination with other cytotoxic agents. In preclinical models, the cisplatin–gemcitabine combination suggested synergy between the two drugs. In phase I–II studies, response rates are as high as 54% when gemcitabine is combined with cisplatin, both in stage III and IV NSCLC. The gemcitabine-containing regimens showed a favourable safety-efficacy profile and compared well with standard regimens used in NSCLC. These preliminary results must be validated by large randomised trials comparing gemcitabine-containing regimens with NSCLC reference chemotherapy regimens.

Key words: gemcitabine, gemcitabine–cisplatin, non-small-cell lung cancer

Introduction

Chemotherapy of advanced non-small-cell lung cancer (NSCLC) was and is based on the assumption that 'something should be done' for the patient, but chemotherapy combinations were ineffective or pejorative [1] before platin was introduced in the NSCLC therapy. Combination chemotherapies based on this metal salt (i.e., the so-called second generation regimens) have been shown to give benefit with a reduction in the risk of death of 27%, and an increase in the survival rate of 10% at one year, i.e., a 1.5 month gain in the median survival-time [1]. Such a figure is obviously minimal, but a clear demonstration that the NSCLC is not a chemo-resistant tumor was reached by several authors [1], including our group [2].

The most largely used drugs are platin, vindesine, etoposide, vinblastine, vinorelbine, ifosfamide and mitomycin C as capable of a single agent response rate (RR) between 10%-20%. From 10 single-agent trials conducted from 1976–1989 in 479 patients, the overall major objective rate given by platin was 21% [3]. However, these drugs were investigated several years ago and results might be lower when the computerised tomography (CT) is used in measuring the RR. A study of ours indicates that the mitomycin percentage RR in advanced NSCLC is as low as 2.7% in 72 patients for which the CT was the chosen diagnostic procedure [4]. Platin gives no more than 9% RR (100 mg/m² every 28 days) [5] to 12% RR (120 mg/m² every 21 days) [6] in policentric studies which measured the response by means of CT.

The various platin combination chemotherapies achieved a variable RR, generally within the 20% to 40% range. In 623 patients platin (P), mitomycin, and vindesine or vinblastine combinations gave 43%-60% RR, but the survival was not really increased [7, 8]. These studies seemed to disconnect the hopefully expected positive relationship between the RR and the survival length. Recently, the combination of P and vinorelbine was recommended as a standard regimen [9].

More recent drugs like irinotecan, gemcitabine and taxanes, i.e., paclitaxel and docetaxel, also in chemotherapy combination (third generation regimens) are entering the clinical use, even before exhaustive phase III studies have been performed. Such a hurry is due to the general impression that combinations of older drugs are giving results good mainly for statisticians.

Gemcitabine

The difluorodeoxycytidine gemcitabine (G), a nucleoside analogue, competes with its physiologic counterpart for incorporation into nucleic acid. It is structurally related to cytosine arabinoside (ara-C) and they act as pyrimidine antimetabolites. G differs from deoxycytidine because of geminal fluorine atoms on the 2'-carbon (gem-citabine). The effectiveness of ara-C against solid tumors has declined almost to a non-use, but the ara-C tumor cell synchronisation preceding P in NSCLC therapy may be remembered [10]. The combination we devised for the advanced NSCLC was subcutaneous ara-C 50 mg/m² every eight hours for four to five days and i.v. P 100 mg/m² given eight hours after the last ara-C injection, every three weeks. It was based on the finding that ara-C exposure preceding P is a synergistic,
nuria have been observed [15, 16]. There is no evidence of benefit from 800-2400 mg/m². After higher doses a reversible increase in hepatic transaminases and proteinuria has been observed [15, 16]. There is no evidence of cumulative hepatic or renal toxicity and mild flu-like symptoms were observed in a small proportion of patients [17].

G displayed activity in vitro and in vivo against several murine solid tumors, tumor xenografts nodes LX-1 lung, MX-1 breast, CX-1 and GC3 colon [12], pancreas and ovarian carcinomas [18]. The activity spectrum of G includes non-small- and small-cell lung cancer, ovarian, breast, pancreatic, bladder, renal, uterine, cervix and head and neck cancer [18].

The most favourable therapeutic index has been obtained with a weekly schedule of the drug, for three weeks followed by a week rest. And this is also the case for NSCLC in which a response rate around 20% is obtainable with the single drug and a dose of 1000 mg/m² or more is required [19-21].

### Gemcitabine and platin

The profile toxicity of G and its therapeutic activity make the drug a good candidate for a combination regimen with P. This is especially true because P causes PNS and kidney toxicity, whilst G does not.

The major cytotoxic target of P is DNA. It correlates with the total P binding to DNA, to the interstrand cross-linking and to the formation of intrastrand bidentate adducts (about 90% of the P-induced lesions). These lesions inhibit the DNA replication as a marked distortion of conformation. Experiences on these topics have been reviewed by Reed et al. [22]. When the damage of DNA caused by P is repaired, resistance to P occurs [23].

Precinical studies have shown synergistic and additive tumor cell toxicity by G and P and that G has the potential to inhibit the repair of P induced DNA damage [24, 25]. As an inhibitor of DNA synthesis, G is more active in the S phase of the cell cycle; as ara-C, the cytotoxicity of G should be dependent on the rate of DNA synthesis. Thus the timing of the second dose of G may have a critical impact on the drug effectiveness also in relation to the P association.

G may inhibit the DNA repair by some of the aforementioned mechanisms, as elegantly hypothesized also by Plunkett et al. [26] and Abratt et al. [27]. When the damage of DNA caused by P is removed by nucleotide excision repair enzymes, the DNA polymerases synthesize new DNA, the opposite DNA strand acting as a

---

**Table 1. Timing of possible myelotoxicity of next gemcitabine (G) doses after the priming G (day 1) or G + platin (P) (day 1 or 2).**

<table>
<thead>
<tr>
<th>Priming therapy</th>
<th>Possible myelotoxicity at day</th>
</tr>
</thead>
<tbody>
<tr>
<td>G day 1</td>
<td>G + P (day 1 or 2)</td>
</tr>
<tr>
<td>+ -</td>
<td>+ + -</td>
</tr>
<tr>
<td>+ +</td>
<td>+ + + (unlikely third G dose [40])</td>
</tr>
</tbody>
</table>

The possible best timing of G and P (on a three-week cycle base) is G day 1 and G + P day 8.

The experience was the base for our recent GP combination (see later).

The better activity of G against solid tumors is based on several differences with ara-C: greater lipophilicity, greater cellular entry, higher intracellular level of triphosphate and more prolonged intracellular duration of the 'active' metabolite.

G is activated by deoxycytidine kinase to G-mono-, di- and tri-phosphate (GMP, GDP, GTP). The GMP incorporation into DNA causes the chain termination of DNA synthesis. The GTP is subsequently excited from DNA by DNA exonucleases at a rate which allows a certain amount of the drug to accumulate into the intracellular compartment.

Moreover, G is capable of inhibiting ribonuclease reductase, and the deoxynucleotides for DNA synthesis [12].

**In vitro** the G activity is reversed by deoxycytidine. Also, cells lacking deoxycytidine kinase are not sensitive to G. The GTP is an inhibitor of deoxycytidine deaminase, and then the drug has a self-potentiation, leading to a GTP accumulation which is 20-fold greater than ara-C triphosphate in Chinese hamster ovary cells. This greater accumulation may be related also to a more rapid entry into cells of G than ara-C, also perhaps to the G greater lipophilicity.

In cells that have accumulated enough GTP (>100 M cellular concentration) the inhibition of DNA synthesis is correlated to the residence time of GTP. In these conditions the terminal elimination time of GTP is prolonged. Then, the prolonged retention of GTP is at the same time a drug self-potentiation and an occurrence useful to the potential cellular toxicity. After GTP is attached into the growing strand DNA, the DNA polymerase incorporates one more nucleotide, the G-nucleotide residing in the penultimate position of the chain. This unique pattern of nucleotide incorporation is thought to mask the G-nucleotide from the exonuclease activity, with a consequent reduction and/or delay of removal of the mismatched base pairs. Also, incorporation of G into RNA has been reported [13].

The lipophilicity of G may have clinical relevance for the drug penetration in certain tissues, and studies are awaited to evaluate this possibility.

**Studies in mice, rats and dogs** indicated bone marrow depression as the major toxicity of G [14]. No evidence of neurotoxicity was observed. Phase I studies indicated that the weekly administration of G has a favourable toxicity profile and antitumor activity. Previously treated or minimally treated patients with good PS can receive benefit from 800-2400 mg/m². After higher doses a reversible increase in hepatic transaminases and proteinuria have been observed [15, 16]. There is no evidence of cumulative hepatic or renal toxicity and mild flu-like symptoms were observed in a small proportion of patients [17].

G displayed activity in vitro and in vivo against several murine solid tumors, tumor xenografts nodes LX-1 lung, MX-1 breast, CX-1 and GC3 colon [12], pancreas and ovarian carcinomas [18]. The activity spectrum of G includes non-small- and small-cell lung cancer, ovarian, breast, pancreatic, bladder, renal, uterine, cervix and head and neck cancer [18].

The most favourable therapeutic index has been obtained with a weekly schedule of the drug, for three weeks followed by a week rest. And this is also the case for NSCLC in which a response rate around 20% is obtainable with the single drug and a dose of 1000 mg/m² or more is required [19-21].

G displayed activity in vitro and in vivo against several murine solid tumors, tumor xenografts nodes LX-1 lung, MX-1 breast, CX-1 and GC3 colon [12], pancreas and ovarian carcinomas [18]. The activity spectrum of G includes non-small- and small-cell lung cancer, ovarian, breast, pancreatic, bladder, renal, uterine, cervix and head and neck cancer [18].

The most favourable therapeutic index has been obtained with a weekly schedule of the drug, for three weeks followed by a week rest. And this is also the case for NSCLC in which a response rate around 20% is obtainable with the single drug and a dose of 1000 mg/m² or more is required [19-21].

The possible best timing of G and P (on a three-week cycle base) is G day 1 and G + P day 8.

**Gemcitabine and platin**

The profile toxicity of G and its therapeutic activity make the drug a good candidate for a combination regimen with P. This is especially true because P causes PNS and kidney toxicity, whilst G does not.

The major cytotoxic target of P is DNA. It correlates with the total P binding to DNA, to the interstrand cross-linking and to the formation of intrastrand bidentate adducts (about 90% of the P-induced lesions). These lesions inhibit the DNA replication as a marked distortion of conformation. Experiences on these topics have been reviewed by Reed et al. [22]. When the damage of DNA caused by P is repaired, resistance to P occurs [23].

Precinical studies have shown synergistic and additive tumor cell toxicity by G and P and that G has the potential to inhibit the repair of P induced DNA damage [24, 25]. As an inhibitor of DNA synthesis, G is more active in the S phase of the cell cycle; as ara-C, the cytotoxicity of G should be dependent on the rate of DNA synthesis. Thus the timing of the second dose of G may have a critical impact on the drug effectiveness also in relation to the P association.

G may inhibit the DNA repair by some of the aforementioned mechanisms, as elegantly hypothesized also by Plunkett et al. [26] and Abratt et al. [27]. When the damage of DNA caused by P is removed by nucleotide excision repair enzymes, the DNA polymerases synthesize new DNA, the opposite DNA strand acting as a
Table 2. Summary of clinical trials using gemcitabine and platin (dose in mg/m²).

<table>
<thead>
<tr>
<th>Author, year [reference]</th>
<th>Schedule</th>
<th>Number of patients</th>
<th>Remission rate (%) (95% CI)</th>
<th>MDR weeks</th>
<th>MS weeks</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steward, 1996 [32]</td>
<td>G 1000 P 100</td>
<td>1, 8, 15 1, q28 1, 8, 15 2, q28</td>
<td>60</td>
<td>42 (NR)</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Crino, 1997 [33]</td>
<td>G 1000 P 100</td>
<td>1, 8, 15 2, q28 1, 8, 15 15, q28</td>
<td>48</td>
<td>54 (40-68) 52 (37-66) 25 (12-41)</td>
<td>45.5</td>
<td>61.5</td>
</tr>
<tr>
<td>Abratt, 1997 [27]</td>
<td>G 1000 P 100</td>
<td>1, 8, 15 15, q28 1, 8, 15, q28</td>
<td>53</td>
<td>52 (37-66) 45 (29-56)</td>
<td>34</td>
<td>52</td>
</tr>
<tr>
<td>Shepherd, 1997 [34]</td>
<td>G 1500 P 30</td>
<td>1, 8, 15 1, 8, 15, q28 1, 8, 15, q28</td>
<td>40</td>
<td>25 (12-41) 45 (29-56)</td>
<td>19</td>
<td>NR</td>
</tr>
<tr>
<td>Isla, 1997 [35]</td>
<td>G 1000 P 100</td>
<td>1, 8, 15 2, q28 1, 8, 15, q28</td>
<td>48</td>
<td>45 (29-56) 47.5 (31-63)</td>
<td>24.4</td>
<td>32</td>
</tr>
<tr>
<td>Anton, 1997 [36]</td>
<td>G 1200 P 100</td>
<td>1, 8, 15 15, q28 1, 8, 15</td>
<td>40</td>
<td>42 (29-57) 47.5 (31-63)</td>
<td>26</td>
<td>41</td>
</tr>
<tr>
<td>Gonzales-Baron, 1997 [37]</td>
<td>G 1200 P 100</td>
<td>1, 8, 15 1, q28</td>
<td>51</td>
<td>37 (NR)</td>
<td>NR</td>
<td>60</td>
</tr>
<tr>
<td>Einhorn, 1997 [38]</td>
<td>G 1000 P 100</td>
<td>1, 8, 15 1, q28</td>
<td>27</td>
<td>37 (NR)</td>
<td>NR</td>
<td>33.6</td>
</tr>
<tr>
<td>Lopez-Cabrerizo, 1997 [39]</td>
<td>G 1250 P 100</td>
<td>1, 8, 15 1, q21 1, 8, 15 15, q28</td>
<td>65</td>
<td>49 (NR)</td>
<td>NR</td>
<td>8.3 months</td>
</tr>
<tr>
<td>Crino, 1998 [40]</td>
<td>G 1000 P 100</td>
<td>1, 8, 15 2, q28</td>
<td>154</td>
<td>40 (NR)</td>
<td>NR</td>
<td>35</td>
</tr>
<tr>
<td>Rinaldi, 1998 [41]</td>
<td>G 1000 P 100 or 70</td>
<td>1, 8, 15 1, q28 1, 8, 15 2, q28</td>
<td>55</td>
<td>44 (NR) b</td>
<td>b</td>
<td>1</td>
</tr>
<tr>
<td>Sandler, 1998 [5]</td>
<td>G 1000 P 100</td>
<td>1, 8, 15 1, q28</td>
<td>~150</td>
<td>31 (NR) 75.5 (NR)</td>
<td>NR</td>
<td>8.7 months</td>
</tr>
<tr>
<td>van Zandwijk, 1998 [42]</td>
<td>G 1000 P 100</td>
<td>1, 8, 15 2, q28</td>
<td>44 a 75.5 (NR) 57 (46-68)</td>
<td>24</td>
<td>NR</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: MDR - median duration of response; MS - median survival; NR - not reported.

* Induction regimen only IIIA patients; b too early; c many censored patient; d figure at 31 December 1997.

If this strand is altered because of the presence of the G nucleotide, it cannot act as a guide to rebuild a correct DNA sequence. Also, some G depressive effects (limited? relevant?) occur on the deoxyribonucleotide and ribonucleotide pools [13] which are essential for the P damaged DNA repair [28]. Consistent with this observation, the degree of P and G synergism should be greater in cells that show a more effective DNA repair ability [28, 29]. The potentially reparable damage induced by P may become a DNA damage grave enough to induce cell apoptosis.

The P and G in vitro synergism is drug-schedule dependent. Briefly the synergism is observed in P-resistant and not in G-resistant cell-lines. The sequential administration of G and P, which would allow for some G being already incorporated into the DNA strand could reduce the effectiveness repair of the subsequent DNA damage caused by P [30]. However, definitive in vitro evidence on the best sequence of administration does not exist. The rationale for using in G first and P second clinics is more theoretic than demonstrated, because a randomised comparison with P first and G second is lacking. Further on the GP scheduling may flow from the way we are used to construct polichemotherapy regimens according to well established pharmacology lines [31]. It is generally accepted that an S-phase-specific agent is administered in fractionated schedules to eradicate proliferating cells, and then the residual non proliferating cells (or, to the contrary, the recruited cells into any phase of the cycle) may be vulnerable to this cycle-specific agent [31]. This is probably true in the treatment of acute leukaemia, and when ara-C was used before P, as we also did in patients with NSCLC (see above). Several phase I—II studies have indicated that a good therapeutic index is reached with the administration of P once a week. When we administer G not very frequently but only on this weekly base, the aforementioned rationale may fade. No study is available in patients with NSCLC on the metabolism and cycling activity of the tumor cells one week after one or two or more G weekly courses. In the end, the association timing of P and G is empirical.
In September 1996 we devised our regimen, having in mind a therapy cycle based on two administrations of drug which for patients is simpler than three. According to the currently accepted weekly schedule, the second half of the drug combination should be on day 8. After one administration of G a relevant myelotoxicity is unlikely and the second administration of G plus P can be delivered with a good dose intensity saving. Consequently we administered the second G dose on day 8, just preceding the onset of leukopenia and thrombocytopenia, as is usual in clinics. A third G dose (day 15) was placed on day 8 instead of 1 as a therapy cycle based on two administrations of G-P which for patients is simpler than three. According to the currently accepted weekly schedule, the second half of the drug combination should be on day 8. After one administration of G a relevant myelotoxicity is unlikely and the second administration of G plus P can be delivered with a good dose intensity saving. Consequently we administered the second G dose on day 8, just preceding the onset of leukopenia and thrombocytopenia, as is usual in clinics. A third G dose (day 15) was placed on day 8 instead of 1 not only because of the theoretical rationale mentioned above but also because of a lesser risk of a myelotoxicity which could have hastened the day 8 chemotherapy (Table 1).

Among myelotoxicities, thrombocytopenia could hopefully be reduced by this schema.

### Gemcitabine and platinum: Clinical use

Several phase I–II studies were designed in the last three years to evaluate the activity and safety of G in combination with P. The clinical results of most principal trials in chemonaive patients are summarised in Table 2. In all studies G was given i.v. over 30 minutes once weekly, mostly for three consecutive weeks, followed by a week rest-period. P was administered once on day 1, or day 2, or day 8, or day 15, and in one study on a weekly three-week basis. Among patients mainly with advanced disease the objective response ranged between 29% and 57% with a possible average response rate of 46%. In our intention-to-treat study on 104 consecutive patients the RR was 50% (43). Several studies are ongoing and figures may change somewhat. Most responses reported in such studies were validated by an external review board. The proportion of patients with stage IIIA, IIIB and IV is different among the reported studies, so it is possible that differences in RR are not due strictly to the treatment schedule but may reflect difference in patient populations and in prognostic variables. The median duration of response varied around 30 weeks and duration of survival ranged from 33 to 61 weeks still reflecting the variability among different reports.

A not negligible result is the symptomatic benefit and improvement of quality of life documented in the majority of G–P treated patients: pain reduction with decrease in analgesic use or marked relief of dyspnea, cough and hemoptysis were observed. The haematological toxicity was the limiting side-effect: the reported WHO grade 3 and 4 neutropenia occurred between 16% and 58% of patients. Similar values are reported on thrombocytopenia: grade 3–4 was recorded from 16% to 76% of patients (Table 3).

Non-haematological toxicity was usually not impressive and generally manageable. As expected, nausea and vomiting due to P occurred but they were usually well controlled by the routine use of antiserotoninergic drugs plus corticosteroids. The renal toxicity of these G and P associations seems comparable with other P-containing regimens with deteriorating creatinine and blood urea values over multiple cycles. Mild hepatic toxicity was more notable as a laboratory observation than a clinical problem. Other side effects were statistically insignificant.

In conclusion, in 895 patients (Table 1) mainly with IIIB and IV stage of disease the combination regimen with G and P has shown a favourable efficacy-safety compared with second generation regimens used in NSCLC. These results have now to be compared in a randomized fashion with the standard regimens. The Spanish Lung Group reported preliminary data which favour the GP containing chemotherapy, and similar preliminary conclusions come from others [44–47]. In patients with stage IIIA disease a presurgical induction therapy with G and P is currently giving a 75% RR [42]. Additional studies in which dose and administration schedules of the two drugs may be optimized are required. It is not clear if the best schedule is G followed by P or vice versa. Several studies are ongoing and the question is if the improvement in RR will result in a longer overall survival.

Final analyses of several experiences already published in Abstracts are awaited, also to quantitate the CR rate which is still small (Table 1) as well as the remission duration.

### Table 3. Hematological toxicity (in percentage) WHO grade 3–4 and use of G-CSF.

<table>
<thead>
<tr>
<th>Author, year [reference]</th>
<th>Anemia</th>
<th>Thrombocytopenia</th>
<th>Leucopenia</th>
<th>Neutropenia</th>
<th>Number of blood transfusion</th>
<th>G-CSF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crino, 1997 [33]</td>
<td>25</td>
<td>52</td>
<td>NR</td>
<td>36</td>
<td>16</td>
<td>NR</td>
</tr>
<tr>
<td>Abratt, 1997 [27]</td>
<td>13</td>
<td>21</td>
<td>29</td>
<td>58</td>
<td>34</td>
<td>NR</td>
</tr>
<tr>
<td>Shepherd, 1997 [34]</td>
<td>28</td>
<td>53</td>
<td>55</td>
<td>56</td>
<td>54</td>
<td>NR</td>
</tr>
<tr>
<td>Isla, 1997 [35]</td>
<td>6</td>
<td>38</td>
<td>NR</td>
<td>16</td>
<td>12</td>
<td>NR</td>
</tr>
<tr>
<td>Anton, 1997 [36]</td>
<td>NR</td>
<td>16</td>
<td>NR</td>
<td>56</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Gonzales-Baron, 1997 [37]</td>
<td>NR</td>
<td>23</td>
<td>NR</td>
<td>29</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Einhorn, 1997 [38]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Crino, 1998 [40]</td>
<td>28</td>
<td>NR</td>
<td>48</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Rinaldi, 1998 [41]</td>
<td>26</td>
<td>76</td>
<td>53</td>
<td>58</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>van Sande, 1998 [42]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Cartei, 1998 [43]</td>
<td>20</td>
<td>10</td>
<td>NR</td>
<td>28</td>
<td>16</td>
<td>NR</td>
</tr>
</tbody>
</table>

Abbreviation: NR – not reported.
Acknowledgements

This work, by EOLO Group (Eastern Oncology Lung Organization, Udine, Italy) on behalf of GOCNE (Gruppo Oncologico Clinico Cooperativo del Nord-Est, Aviano-PN, Italy) was partly supported by AOI (Associazione Oncologica Italina – Udine, Italy). Dr G. Tabaro is recipient of a fellowship from Associazione Nazionale Volontari Lotta contro i Tumori (Sez. Udine, Italy).

References


14. Eli-Lilly, data on file Eli-Lilly Co, Indianapolis, IN.


Correspondence to:
Prof. G. Cartei
Operative Unit of Medical Oncology
and Cancer Prevention Center
Azienda Nazionale Ospedaliera di Alta Specializzazione
Udine
Italy