Experimental Studies and Preliminary Clinical Trial of Vinorelbine-loaded Polymeric Bioresorbable Implants for the Local Treatment of Solid Tumors

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The properties of natural or synthetic polymers are such that the choice of a product as an effective drug delivery system is critical, as has been discussed by many authors (15–19). Indeed, efficient local treatment of cancer by drug-containing polymeric implants requires both safe matrix components and an active antitumor drug. The chosen drug must also be compatible with the polymer. Among the numerous polymers available, PLA-GA is one of the best studied, and its biocompatible and biodegradable properties have been well documented (20–21). Several studies have used this copolymer to produce nonloaded or drug-loaded microspheres (22–24). According to the physicochemical properties of the entrapped drug, the release can be controlled by varying the ratio between lactide and glycolide units in the copolymer, as was verified in a previous study with the anticancer drug cisplatin (9). Thus PLA-GA copolymers are good candidates for further investigation as implants in cancer treatment.

In our previous work (9), which was limited to the study of the in vitro and in vivo release characteristics of two PLA implants, i.e., PLA 37.5 GA 25 and PLA 75, cisplatin was chosen because of its X-ray opacity, which greatly facilitated the evaluation of the in vivo behavior of implants. Cisplatin was not selected for further development, because the molecule could be hydrolyzed in the aqueous medium diffusing in the polymeric matrix (25). Indeed, it would then be possible that the diffusing species differ from the initial ones. Therefore, we chose a more stable anticancer agent, namely Vinorelbine, a new Vinca alkaloid anticancer drug (26–28), which has physicochemical properties which might be associated with interesting release characteristics. Vinorelbine is presently used in treatments of non-small cell lung cancer and advanced breast cancer by systemic chemotherapy (29–33) and is under clinical trial for other cancer localization (34).

Thus, the present study was designed in order to evaluate thoroughly the potential usefulness in cancer treatment of a sustained-release system based on a poly(lactide-co-glycolide) copolymer, namely PLA 37.5 GA 25 (21), loaded with Vinorelbine. Accordingly, it includes the preparation of the device, its in vitro and in vivo characteristics of release, its experimental antitumoral activity in P388-bearing mice, its toxicity in dogs, and, finally, a preliminary clinical trial.

MATERIALS AND METHODS

Polymeric Matrix

The PLA 37.5 GA 25 (21) sample was obtained by ring-opening polymerization of a monomer feed composed of a 75% D,L-lactide/25% glycolide (w/w) mixture. The polymerization was carried out in bulk for 96 h at 140°C using Zn powder as the initiator. After recovering, the crude copolymer was purified twice by dissolution in acetone.
and precipitated by methanol. The resulting purified copolymer was characterized by size exclusion chromatography in dioxane and showed a monomodal size exclusion chromatagram with a maximum at \( M, 120,000 \) with respect to polystyrene standards. Molecular weight polydispersity was 1.5, and the glass transition temperature was 44°C.

**Preparation of Vinorelbine-containing Implants**

The PLA 37.5 GA 25 copolymer (\( M, 120,000 \)) was dissolved at room temperature in a mixed solvent composed of chloroform and \( n \)-hexane (80:20, v/v). When the medium was homogeneous, Vinorelbine ditartrate (Pierre Fabre Médicament, Boulogne, France) was added, and the resulting mixture was stirred vigorously for 30 min. Hexane was then added dropwise to the suspension until the copolymer-Vinorelbine combination was completely precipitated. The paste mass thus obtained was kneaded in order to eliminate most of the entrapped solvent. Residual solvent was finally evaporated in a vacuum drier for one night at 50°C. The resulting solid matrix was extruded through a 1.2-mm heated die (70–80°C) in order to make cylindrical rods. The polymer-drug combination never remained more than 1 or 2 min in the heated apparatus. Rods were allowed to cool to room temperature, and implants (designated as type E) were cut from the rods according to the desired drug dose. They were finally stored in a light-protected sterilized environment.

In preliminary studies, cylindrical rods were handmade (since the heated die was not yet available). These devices were designated as type H implants.

**HPLC Determination of Drug Load and Stability**

Vinorelbine-containing implants were dissolved in 2 ml of dichloromethane. Vindoline (Pierre Fabre Médicament) was added in known amounts to serve as an internal standard. The HPLC apparatus consisted of a constant flow-rate pump (6000A; Waters) a Lichrospher 100-RP-8 (5 \( \mu \)m) column (Merck), and an UV detector (Uvicord; LKB) (\( \lambda = 254 \) nm). The mobile phase was an admixture of 100 mM KCl in diluted HCl (pH 2.5), methanol and tetrahydrofuran (69:19:12, v/v/v), at a flow rate of 1.0 ml/min. The resulting solution was filtered and the filtrate was injected into the HPLC with forceps through an incision made at 1 cm from the axilla. Incisions were closed with nonresorbable sutures. The day of the implantation was designated as day 0.

**Implantation of the Polymeric Devices.** By using the incision previously made to insert the tumor fragment, implants were placed either in contact with the tumoral tissue in the case of small tumors (early treatment) or in a slot inside the tumor mass for larger tumors.

**Quantification of Effect.** Results were reported as T/C%. Antitumor efficacy was evaluated until day 45. Tumor areas were calculated using the program of the two largest perpendicular dimensions on the surface of the tumor mass. Histological examination of tumoral tissues was also performed in some cases.

**Intrinsic toxicity of nonloaded polymeric implants (types H and E)** was evaluated both by survival time of implanted mice and by their daily weight evolution.

**Toxicity Studies in Dogs**

Type E Vinorelbine-containing implants (5 mm long, 1 mm diameter) were inserted under general anesthesia (nitrous oxide, pentothal 38 mg/kg, ethrane, oxygen) in different organs and tissues of healthy mongrel dogs (25–50 kg): liver, pancreas, kidney, spleen, muscle, bone, perivascular tissues, and skin. Each implant was kept in position using wire which also facilitated subsequent identification. Toxicity was evaluated both by observation of clinical symptoms and by measurements of several blood parameters: urea, creatinine, bilirubin, alkaline phosphatase, and WBC counts. Local toxicity was determined by macroscopic and histological examination of tissues and organs after death or sacrifice of the animals.

**Clinical Trial**

The patient group consisted of 9 consecutive patients with carcinoma of the head and neck. The median age was 56 years (range, 42–62 years). The criteria for entry into this study were histologically confirmed carcinoma, life expectancy greater than 2 months, performance status between 0 and 3 (WHO classification), and absence of severe hematological or renal impairment. Finally, all patients selected for this treatment had been previously scheduled for surgical excision of their tumor. Written informed consent was obtained from all patients, and the study had been approved by our Ethical Committee.

Of the patients previously treated with systemic chemotherapy, none sustained biological toxicities \( \geq 2 \) (WHO classification). Five patients had received previous radiotherapy in the region to be implanted; two patients had received no previous treatment.

Two weeks before surgery, implantation of the polymeric device (type E implants containing 20% Vinorelbine) was performed using a needle with an introducer to insert the implant (1.2 mm diameter) into the tumor mass. The length of the implant was adjusted to the tumor size in order to preserve a 4–5 mm margin at each extremity of the tumor mass. Table 1 summarizes the localization for each patient of the tumor mass to be implanted, its volume at the time of implantation, and the depth of the implant site relative to the skin level.

Surgical excision was performed 14 days after implantation of the device. The implant was recovered from the tumor mass to measure the amount of residual Vinorelbine, while the tumor was submitted for histological examination.
Preparation and Release Properties of Vinorelbine-containing PLA 37.5 GA 25 implants used during the clinical trial on patients with head and neck cancer.

### Table 1

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Implant localization</th>
<th>Tumor size (cm)</th>
<th>Implant depth (mm)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right jugular lymph node</td>
<td>7 x 5</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Submental lymph node</td>
<td>6 x 7</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Right jugular lymph node</td>
<td>2 x 2</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>Left submandibular lymph node</td>
<td>3 x 3</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td>Left jugular lymph node</td>
<td>4 x 3</td>
<td>15</td>
</tr>
<tr>
<td>6</td>
<td>Right jugular lymph node</td>
<td>3 x 3</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>Right upper posterior neck lymph node</td>
<td>1.5 x 1.5</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>Right mandibular lymph node</td>
<td>4 x 3</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>Right spinal lymph node</td>
<td>2 x 2</td>
<td>5</td>
</tr>
</tbody>
</table>

* Depth of implant localization relative to the cutaneous plane.

### Table 2

<table>
<thead>
<tr>
<th>Distance between implant and tissue sample</th>
<th>Radioactivity measurements (dpm/mg tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>Day 1</td>
</tr>
<tr>
<td></td>
<td>760</td>
</tr>
<tr>
<td>2 mm</td>
<td>42</td>
</tr>
<tr>
<td>5 mm</td>
<td>13</td>
</tr>
<tr>
<td>7 mm</td>
<td>21</td>
</tr>
</tbody>
</table>

Pathological Examinations

All specimens were fixed in 10% buffered formalin. All conspicuous injuries were measured, described, and cut off. The specimens were processed in the routine manner. Paraffin sections from each block, 5 μm in thickness, were stained with hematoxylin.

### RESULTS

Preparation and Release Properties of Vinorelbine-containing Implants

**Preparation.** For both type H and type E implants, three different Vinorelbine loads were tested, starting from solutions containing 1%, 5%, and 20% drug with respect to the polymer (w/w). Preparation resulted in hard cylinders at room temperature, with quantitative incorporation of the drug load in the polymeric matrix [19.6 ± 0.5% (SD) for a 20% load]. HPLC experiments revealed no apparent degradation of the drug due to the preparation methods. Studies of stability with time indicated no apparent loss of drug or polymer degradation until at least 2 months of storage in a light-protected dessicator. On the contrary, implants stored in a humid atmosphere became soft and increased in volume. Higher drug loads could be achieved, but the resulting devices appeared to be unsuitable, because they exhibited important loss of mechanical properties.

**In Vitro Profile of Release.** In physiological sodium chloride solution at 37°C, 50% of the total amount of Vinorelbine was released within 6 days, and 75% was released within 12–15 days for implants containing 20% (w/w) Vinorelbine. No significant difference in release was detected between type H and type E implants. In both cases, a slight increase in implant volume was observed within the first days of incubation. After 30 days of incubation, the weight loss of the implants corresponded approximately to the initial amount of incorporated drug.

**In Vivo Profile of Release.** Release of Vinorelbine was also measured in vivo in rats. Type H implants containing 5% Vinorelbine and small amounts of [³H]Vinorelbine as a tracer were introduced into muscle. The median weight of the implants was 2.6 mg. Fig. 1 shows the percentage of residual radioactivity in the implant measured at different times after administration. Experiments show that half of the implant content was released between 10 and 20 days after administration. Extrapolating these results led us to expect a complete drug delivery in 6 or 8 weeks.

Table 2 gives radioactivity measurements from tissue samples located near the implants, at three different time intervals. Despite the spreading of data points, tissue concentration appeared to strongly depend on the distance between the implant and the sample site. At 7 mm from the implant, the radioactivity was negligible. The drug concentration in tissues located close to the implants increased from day 1 to day 10. However, no significant accumulation of drug occurred with time in the tissue surrounding the implant.

Antitumoral Efficacy on the P388 Murine Solid Leukemic Model in Mice

**Validation of the Model.** All nontreated control mice (n = 55) developed a s.c. solid tumor when inoculated with a freshly excised tumoral fragment. Table 3 shows tumoral evolution in the absence of any treatment, characterized by a median survival time of 12.5 days (range, 11.0–14.0 days). Statistical comparison of weights between subgroups of nontreated mice with different survival times indicates that neither initial animal weight nor initial amount of inoculated tumor influences survival, at least within the considered weight ranges. In the absence of any treatment, the median value of the apparent tumor area, measured at death, was 1.9 cm² (range, 0.8–3.5 cm²). Histological examination of nontreated animals at death revealed the presence of multiple metastatic cells in all the organs studied (liver, spleen, kidney, etc.). Table 3 also summarizes the results of different standard schedules of i.v. treatments with injectable 5-fluorouracil or injectable Vinorelbine taken as references for later experiments with implants. Vinorelbine antitumoral efficacy was comparable to that of 5-fluorouracil when administered i.v. soon after tumor inoculation (T/C% = 152% with 24 mg/kg administered on day 1; T/C% = 148% with the same dose administered on day 5). But Vinorelbine had no effect on survival time when administered

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Table 3 Description of tumor evolution in the P388 solid murine leukemia model

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival time (days)</th>
<th>T/C (%)</th>
<th>Tumor surface at death (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nontreated control</td>
<td>12.5 (11.0-14.0)</td>
<td>1.9</td>
<td>(0.8-3.5)</td>
</tr>
<tr>
<td>i.v. 5-fluorouracil²</td>
<td>19.0 (19.0-20.0)</td>
<td>152</td>
<td>ND</td>
</tr>
<tr>
<td>60 mg/kg/d, D6-10-14</td>
<td>(n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60 mg/kg/d, D1-5-9</td>
<td>19.5 (19.0-22.0)</td>
<td>156</td>
<td>ND</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>i.v. Vinorelbine²</td>
<td>19.0 (17.0-21.0)</td>
<td>152</td>
<td>1.1 (1.0-2.4)</td>
</tr>
<tr>
<td>24 mg/kg, D1</td>
<td>(n = 6)</td>
<td></td>
<td>(n = 6)</td>
</tr>
<tr>
<td>24 mg/kg, D5</td>
<td>18.5 (17.0-24.0)</td>
<td>148</td>
<td>2.0 (0.3-2.3)</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td>(n = 6)</td>
</tr>
<tr>
<td>24 mg/kg, D10</td>
<td>12.0 (11.0-13.0)</td>
<td>96</td>
<td>1.8 (1.4-2.7)</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td>(n = 6)</td>
</tr>
<tr>
<td>12 mg/kg, D6-10-14</td>
<td>20.5 (17.0-24.0)</td>
<td>164</td>
<td>ND</td>
</tr>
<tr>
<td>(n = 12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 mg/kg, D1-5-9</td>
<td>23.5 (9.0-29.0)</td>
<td>188</td>
<td>ND</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data points are the median and extrema values.

Table 4 Effect of Vinorelbine-containing PLA 37.5 GA 25 implants on P388 solid murine leukemia model

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Survival time (days)</th>
<th>T/C (%)</th>
<th>Tumor surface at death (cm²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonloaded implants</td>
<td>13.0 (11.0-16.0)</td>
<td>104</td>
<td>1.9 (1.2-3.6)</td>
</tr>
<tr>
<td>(n = 24)</td>
<td></td>
<td></td>
<td>(n = 18)</td>
</tr>
<tr>
<td>1% loaded implants</td>
<td>17.0 (15.0-18.0)</td>
<td>136</td>
<td>ND</td>
</tr>
<tr>
<td>Implantation on D1</td>
<td>(n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5% loaded implants</td>
<td>&gt;45.0 (17.0-&gt;45.0)</td>
<td>&gt;360</td>
<td>ND</td>
</tr>
<tr>
<td>Implantation on D1</td>
<td>(n = 6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20% loaded implants</td>
<td>&gt;45.0 (16.0-&gt;45.0)</td>
<td>&gt;360</td>
<td>0.0 (0.0-1.2)</td>
</tr>
<tr>
<td>Implantation on D1</td>
<td>(n = 24)</td>
<td></td>
<td>(n = 6)</td>
</tr>
<tr>
<td>Implantation on D6</td>
<td>15.5 (13.0-20.0)</td>
<td>124</td>
<td>0.5 (0.0-0.6)</td>
</tr>
<tr>
<td>(n = 12)</td>
<td></td>
<td></td>
<td>(n = 6)</td>
</tr>
<tr>
<td>Implantation on D10</td>
<td>13.0 (12.0-16.0)</td>
<td>104</td>
<td>2.8 (1.4-3.8)</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* See Table 3 for explanations.

later (T/C% = 96% after administration on day 10). Multiple injections of Vinorelbine allowed administration of larger cumulative doses and resulted in a slight increase in the survival time (T/C% = 188% with injections of 12 mg/kg/day on days 1, 5, and 9).

Toxicity of Nonloaded Implants. Both unloaded type H and type E implants had no effect on the survival time of P388 leukemic mice (Table 4, T/C% = 104%) or on the apparent tumor area (median, 1.9 cm², range, 1.2-3.6 cm²). In addition, histological examination led to results comparable to those found for nontreated mice. No other apparent toxicity could be assigned to the polymer matrix itself.

Antitumor Efficacy of Vinorelbine-containing Implants on P388 Leukemia. A significant increase in survival time was caused by all the Vinorelbine-containing implants when implantation was performed within the first period of the tumor evolution (Table 4). One % loaded implants were the least active (T/C% = 136%). When implanted on day 1, 5% and 20% loaded implants resulted in T/C% values >360 in each case and cured more than half of the mice. The numbers of long-term survivors were 4 of 6 and 18 of 24, respectively. Type H and type E implants behaved similarly, so that the results have been grouped in Table 4 for the sake of clarity. The antitumoral effect of these implants is also demonstrated on Fig. 2, with reference to a nontreated tumor.
Toxicity in Dogs

6, dogs 3 and 4), even when administered in major organs. Histological examination of the organs showed massive necrosis and viable tumor, composed of dystrophic squamous carcinomatous cells. The cytoplasm and nuclei of these cells were enlarged, and some giant tumoral cells were observed. Mitosis figures were less numerous. A peripheral ring of viable tumor was observed in all cases. In some cases, the necrotic zone had reached the surrounding normal tissue, damaging the peripheral healthy cells.

Clinical Response. While patient 2 demonstrated a significant decrease in tumor size at the time of surgical intervention, all other patients had an increase in the tumor volume, associated with a change in the consistency of the tumor mass, which appeared as a fluctuating mass. Macroscopic examination of the tumors after surgical excision revealed the existence of a circular necrotic area centered on the implant. This necrotic area had a diameter ranging from 0.5 to 3.5 cm (Table 7) and consisted of both coagulation and liquefaction types of necrosis, as determined by histological examination of the excised tumors (Fig. 3). There was frequently a transitional zone between necrosis and viable tumor, composed of dystrophic squamous carcinomatous cells. The cytoplasm and nuclei of these cells were enlarged, and some giant tumoral cells were observed. Mitosis figures were less numerous. A peripheral ring of viable tumor was observed in all cases. In some cases, the necrotic zone had reached the surrounding normal tissue, damaging the peripheral healthy cells.

Characteristics of Removed Implants. The implants recovered from the tumor mass after surgical intervention exhibited an increase in volume, with a diameter of about 1.5 mm, but were not dramatically altered with regard to their external aspect. Measurements of residual Vinorelbine in the implants indicated that total drug release after 2 weeks ranged from 45 to 76% of the total amount administered (Table 7).

DISCUSSION

The PLA 37.5 GA 25 copolymer selected to serve as the matrix in the investigated sustained release system is a member of the family of biocompatible and bioresorbable aliphatic polyesters derived from lactic and glycolic acids. The selection was made on the basis of its specific physical, thermal, and biological properties in order to achieve the best compromise with prerequisites of the application. PLA 37.5 GA 25 is a glassy and thus rigid polymer at room temperature, since its glass transition temperature is in the 40–45°C range. However, it is a viscous polymer.
Fig. 3. Histological examination of the antitumoral effect of Vinorelbine-loaded PLA 37.5 GA 25 implants on human head and neck tumors. Examination was performed on samples taken at the time of tumor exeresis (14 days after implant administration) and stained with hematoxylin and eosin. A, macroscopic photograph of a tumor sample, performed just after exeresis. The excised tumor was cut into two parts relative to the implantation site. B, same tumor sample. The implant cavity is surrounded by a circular necrotic area. Peripheral viable tumor is visible on the right (arrow). H&E, ×6. C, same tumor sample. Left to right, implant cavity necrosis, fibrotic and dystrophic zone, and viable tumor. H&E, ×25. D and E, the last two areas at higher magnitude. D, Left, necrosis with cellular remains; right, transitional zone with altered, dystrophic squamous carcinomatous cells with cytoplasmic and nuclear enlargement. H&E, ×250. E, viable squamous cell carcinoma. Solid clusters of moderately differentiated nonkeratinizing squamous cell carcinoma are well preserved. H&E, ×250.
liquid at low temperatures. This property allows easy and drug-
respecting processing. As Vinorelbine is not soluble in the
polymer, the glass transition temperature of the drug/matrix
mixture is unchanged, and thus the drug delivery needle-like
system is also rigid at room temperature and can be easily
implanted in the solid tumor masses. Furthermore, PLA 37.5
GA 25 is known to degrade rather rapidly. Generally, no solid
residue is detectable after 6–8 weeks (21). Another advantage
is that the system softens at body temperature, which is close
to the glass transition. This allows fast absorption of water, a
factor which is significant for the release of the drug.

The combination of Vinorelbine with the PLA 37.5 GA 25
copolymer, obtained by mixing a solution of the polymer with
the solid drug, results in easily produced and reproducible
monolithic systems with an averaged dispersion of the solid
drug particles in the polymeric matrix. The load of drug can be
set by the relative proportion of polymer and drug in the initial
solution. The maximum loading that allows practical use is
20% (w/w), since higher contents of drug lead to some decreases
in mechanical properties of the devices. The solid drug-contain-
ing polymeric matrix can be shaped in cylindrical implants
either manually (type H) or by using an extrusion mold (type
E), without significant modification in the Vinorelbine release
properties. Both types of implants release one-half of their drug
content within about 6 days in vitro.

In vivo release in rat muscle is slower than in in vitro exper-
iments, as demonstrated in Fig. 1, which depicts results obtained
from titrated Vinorelbine in type H implants. In this case, one-
half of the drug content is released within about 14 days. The
distribution of Vinorelbine in tissues around the implant indi-
cates an increase of tissue exposure to the drug, rather than an
effect of peak concentration. This is evidenced by results in
Table 2 which show no drug accumulation in the surrounding
tissues, although almost all the initial drug load has been
released from the implant. Vinorelbine probably diffuses con-
tinuously from the implant to the whole body, but the slow
release rate avoids any enhancement of local drug
decentration.

Insertion of nonloaded implants adjacent to s.c. tumors (solid
P388 murine leukemia) in mice does not influence the survival
time (Table 4), the tumor development, or the evolution of
animal weight (data not shown). This confirms the absence of
acute toxicity due to the polymeric matrix itself. In contrast,
Vinorelbine-containing implants reveal potential beneficial ef-
fects both on the survival time and on the local evolution of the
solid tumor (Table 4). These effects are dose dependent, as
revealed by T/C% values for 1% loaded implants (136%) and
5% or 20% loaded implants (>360%) administered on day 1.

The delay between tumor implantation and treatment plays a
decisive role on efficacy, since 20% loaded implants adminis-
tered late in the course of treatment (day 6) are unable to cure
mice (T/C% = 124%), in contrast to those given on day 1.
However, it is of value to note that the tumor size at death in
the case of a 20% implant administered on day 6 is significantly
smaller than in the case of nontreated mice. This feature is
probably related to the well-known metastatic behavior of the
P388 model. Thus, the death of animals treated by implants is
actually due to metastatic dissemination rather than to local
growth of the tumor. When the implant is introduced into the
tumor on day 6, the tumor volume does regress; however, the
animals still die of metastatic disease. In contrast, when admin-
istered on day 1, the implant is able to kill all tumor cells before
dissemination begins.

Improvement of the effect of the local treatment beginning
on day 6 is obtained by additional i.v. Vinorelbine only when
i.v. administration follows or is performed at the same time as
implant administration. In this case, both reduction of tumor
mass and delay in dissemination are observed (Table 5). When
i.v. administration precedes treatment by implant, lethal tox-
icity is observed and mice die before nontreated animals. This
can be explained by the toxic effect of i.v. Vinorelbine which
diminishes the ability of animals to survive surgical
implantation.

Results in mice more accurately define the potential interest
of treatment with drug-loaded implants. They could be used in
the treatment of small tumors without any local extension or
distant metastases or as adjuvant therapy to decrease large
tumor masses.

Additional studies on implant toxicity have revealed a lethal
toxicity when highly loaded Vinorelbine implants are adminis-
tered in the vital organs of healthy dogs (Table 6). Conversely,
s.c. administration does not result in severe toxicity. As a result
of these observations, clinical trials should not be attempted on
tumors located within vital organs.

The best way to evaluate the short-term effects of Vinorel-
bine-loaded implants in humans, without any therapeutic dis-
advantage for patients, is to administer the polymeric devices
before a planned surgical excision. With this in mind, a clinical
trial was designed for patients with carcinoma of the head and
neck. This tumor site is well suited to such a clinical trial, since
it does not involve any vital organs and since it allows easy
access for implant positioning.

The clinical trial revealed the feasibility of this new method
in cases where the delivery system can be easily inserted into
the tumor. (The only failure was in a patient with a very fibrotic
neck secondary to radiotherapy.) No toxicity was observed,
except for local inflammatory reactions which were treated by
nonsteroidal antiinflammatory agents. Following tumor exci-
sion, macroscopic examination of implants revealed an increase
in volume (from 1.2 to 1.5 mm in diameter), comparable to
that observed during in vitro studies in physiological solution.
This phenomenon is typical of such polymeric matrices and
corresponds to a swelling process caused by water. Likewise,
the total amount of released Vinorelbine after 2 weeks of
implantation (45 to 76%; Table 7) is of the same order in
humans as that obtained in vitro (70% within 15 days). These
results confirm that in vitro release studies of such polymeric
devices are of value in predicting in vivo behavior.

Histological examination of freshly excised tumors revealed
the existence of a necrotic area around the implant (range of
extent, 0.5–3.5 cm; Table 7), showing clearly a cytotoxic effect
of Vinorelbine. Also, a relationship between the percentage of
drug released and the diameter of the necrotic area might exist,
as suggested by the Spearman rank correlation coefficient,
which is near the limit of significance (P = 0.08).

Thus, Vinorelbine-loaded implants can induce a marked an-
titumoral effect, leading to massive necrosis around their im-
plantation site, without serious systemic side effects. Neverth-
less, three major characteristics of this treatment should be
underlined. First, necrosis appears rapidly in the early days
after implantation of the polymeric device, as shown by local
inflammation. Second, the necrotic areas are always limited to
a spherical zone around the implant. Thus, precise positioning
of the implant results in a controlled effect. However, it also
implies that several devices must be implanted in the case of
large tumors. The third point concerns the apparent nonspeci-
ficity of Vinorelbine action. Indeed, normal tissues surrounding the tumor are also adversely affected by the treatment in cases where implants are located at the periphery of the tumor mass. This phenomenon may be explained by very high local drug concentrations, which are toxic to normal tissues. Consequently, very careful positioning of the implant is required, especially in the case of small tumors.

In conclusion, this study demonstrates a cytotoxic effect of Vinorelbine-loaded polymeric matrices based on poly(lactide-co-glycolide) implants which are directly inserted into a tumor mass. Studies focusing on their long-term effects and use of implantable drugs with different mechanisms of action should help pave the way for a new therapeutic modality in the treatment of cancer.

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REFERENCES

Experimental Studies and Preliminary Clinical Trial of Vinorelbine-loaded Polymeric Bioresorbable Implants for the Local Treatment of Solid Tumors

Charles Fournier, Bernard Hecquet, Philippe Bouffard, et al.

Cancer Res 1991;51:5384-5391.

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