Interferons in the therapy of solid tumors.
Part III. Interferon and various solid malignancies

ABSTRACT

Interferons exert a consistent therapeutic effect in a proportion of patients with renal cell carcinoma and melanoma. In other solid malignancies, this therapeutic approach is investigated at more limited extent; therefore, it is still in experimental area. In this review, we analyzed the clinical trials that used the IFN as monotherapy or, more frequently, as combined biochemotherapeutic regimen. This therapeutic strategy was not justified in colon cancer. Similarly, IFNs did not make a major progress in the treatment of lung cancer regardless the tumor type. Very limited activity was seen also in advanced breast cancer. In most other solid tumors, clinical experience is insufficient and only anecdotal benefits were reported. This is equally true for premalignant lesions, the possibilities of IFN-therapy of which are largely overlooked. In the future, some approaches such as combination of IFN and hormonotherapy in breast cancer, and with retinoic acid in squamous cell carcinomas, deserve further investigation. The optimization of IFN regimens in solid malignancies is the aim of current efforts. Better understanding of biological mechanisms of specific tumor sensitivity, and also the mechanisms of resistance of sensitive tumor types to IFN, will probably lead to the defining features of tumor responsiveness.

Key words: Colon cancer; Lung cancer; Breast cancer; Immunotherapy

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INSTITUTE FOR ONCOLOGY AND RADIOLoGY OF SERBIA, BELGRADE, YUGOSLAVIA

INTRODUCTION

Although at the first glance the results of interferon (IFN) therapy of solid tumors might seem discouraging, some metastatic tumors such as renal cell carcinoma (RCC) (1) and malignant melanoma (MM) (2) undergo regression in a fraction of treated patients. Apart from these tumors, IFNs were tried in a wide range of other solid malignancies. In the therapy of common solid tumors such as colon and lung cancers, the use of IFN is still experimental. In this review we summarize the results of clinical studies that used IFN, alone or in combination with other oncological treatment modalities, in the therapy of various cancers.

Colorectal cancer

There is, presently, no satisfactory standard treatment for advanced colorectal carcinoma (CC). Most commonly used chemotherapeutic agent, 5-fluorouracil (5-FU), definitely has some, but only modest activity, giving the response rates of 10-15% and no consistent effect on survival. Because of that, the developments of new therapeutic strategies are ongoing, with the aim to improve the response rate, time to progression and survival. Many of them include IFN, which was stimulated by preclinical data and encouraging results obtained in RCC and MM patients.

IFN as a single agent therapy

Several clinical trials used IFNα monotherapy in advanced colorectal cancer; a response rate of only 2% was obtained, regardless dose or schedule (3). Therefore, such a therapy seems to have no activity and virtually no clinical effects. Few studies with IFNβ (4) or IFNγ (5) also showed very limited activity. These disappointing results were the reason for abandonment of the IFN single-agent therapy of advanced CC.

The very poor responsiveness of this gastrointestinal malignancy to IFN treatment may be ascribed, at least in part, to the presence of both specific and non-specific IFN inactivators/inhibitors in sera of the patients (6,7); the nature of these factors is still unclear.

IFN and chemotherapy drug combinations

IFN and 5-FU combination. Preclinical data suggesting that IFNα and 5-FU have a synergistic cytotoxic effect upon cultured colon carcinoma cells (8), stimulated an increasing number of clinical investigations to evaluate the therapeutic potential of this combination. This was also supported by the observation that IFN-chemotherapy combination may reduce the IFN-inhibitors/inactivators in cancer patients (9). The results of 25 selected trials are presented in Table 1 (10-32). In various treatment schedules, 5-FU was used at doses ranging from 225-750mg/m² (usually 750mg/m²), and IFNα at doses of 0,5 - 20MU/day. The overall response (OR) rates varied very much (3-70%), giving an average OR of 27%. These divergent therapeutic results may be accounted, at least in part, to the small number of patients in some trials, and inclusion of patients refractory to 5-FU monotherapy. It is evident that the initial impressive response rate (63%) obtained in the Wadler’s report (11) has failed to be reproduced; the only exception is the recent study of Kimm et al. (28), the relevance of which is hampered by the small number of patients. However, the overall response rate of about 30%, although modest, is still higher than that of the each agent
monotherapy. In terms of survival, the results of several randomized trials gave no indication that the IFNα-5-FU combination had any advantage over the 5-FU monotherapy.

It should be noted that the constant evidence from most clinical trials was the increased systemic toxicity of 5-FU by IFNα, requiring the reduction of IFN dose in some patients (33).

Therefore, although these two drugs' synergism was reported in several preclinical studies, the results of trials analyzed in this review did not justify this therapeutic strategy. The enhanced toxicity, no survival benefit, along with cost consideration, compromise the beneficial effect on the OR rate.

Similarly to IFNα, IFNβ also potentiates the antitumor activity of 5-FU against human colon cancer cells in vitro and in vivo (34). Based on these findings, three recent clinical studies used IFNβ for the 5-FU biomodulation (Table 1).

The mean OR rate of 27% is similar to that of IFNα+5-FU combination. It seems that IFNβ does not increase the toxicity of 5-FU (30,32), and that this combination is less toxic than that of IFNα+5-FU. A significant increase of survival was reported in one study (32), suggesting that this combination might deserve further investigation.

**IFNα+5-FU+LV combination**

Another strategy aiming to enhance cytotoxicity of 5-FU is focused on the use of triple drug combination - 5-FU, leucovorin (LV) and IFNα. The potential advantage might be double modulation of 5-FU by LV and IFN, the drugs with different mechanisms of action. The results of 15 clinical trials with 908 patients are presented in Table 2 (35-43). The average OR of 29% was obtained with different doses and schedules of these drugs' administration (range 10-54%). The response rate and survival duration were not significantly better than that obtained with 5-FU alone or combined with either LV or IFN. In addition, virtually all trials have demonstrated a significantly higher rate of adverse events, and decreased quality of life. This is because such regimens cannot presently be recommended for routine use outside clinical investigation (43).

There exist little data for IFN and antineoplastic drugs other than 5-FU and LV for patients with advanced colorectal cancer (44,45); they provided no evidence of any therapeutic advantage over the 5-FU regimens.

**IFNα-5-FU combination and other biotherapeutics**

Further attempts to improve response rate and survival of advanced CC patients introduced IFNγ or interleukin-2 (IL-2) to the combination of 5-FU and IFNα (with or without LV). The rationale for such combinations was the preclinical data suggesting synergy between these biological agents, which was confirmed in clinical studies in RCC and MM patients (1,2). Few trials (46-49) using different scheduling and doses of these biochemotherapeutics, showed that these multiagent combinations failed to improve clinical benefit of 5-FU monotherapy, and were accompanied by severe toxicity that required the treatment interruptions or dose reductions.

As in RCC and MM (1,2), it is not possible to define the responders to IFN combination therapies. The predictors of response are still lacking. It is unlikely that ras mutations (such as c-Ki-ras 2, which occurs early in the pathogenesis of CC and is found in about 40% of patients) will have significant prognostic value for either response to therapy or survival (50). Similarly, the immunostimulation obtained by IFN treatment did not predict improved clinical outcome (51).

In conclusion, after the initial hopes, the combination of IFNα with 5-FU and other biochemotherapeutics does not seem to fulfill the original expectations. It is not sufficiently effective, it is toxic, and it is costly. Further research efforts are required and new treatment strategies are needed if progress is to be

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### Table 1. Response of advanced colorectal cancer patients to the IFNα+5-FU combinations.

<table>
<thead>
<tr>
<th>Study</th>
<th>Evaluate patients</th>
<th>CR</th>
<th>PR</th>
<th>OR (%)</th>
<th>Mean survival (months)</th>
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<td>0</td>
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<tr>
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### Table 2. Response of advanced colorectal cancer patients to the IFNα+5-FU+LV combinations.

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<th>OR (%)</th>
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<td>(mean)</td>
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*References cited in Kjær et al.*

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obtained. Some attempts in this direction are already ongoing; for instance, an important approach to enhance the efficacy of monoclonal antibodies-based protocols in the therapy of this malignancy (52) utilizes the ability of IFNs to up-regulate carcinoembryonic and other tumor-associated antigens (53).

Lung cancer

Although chemo- and radiotherapy do have activity in lung cancer, the results of these therapeutic options are unsatisfactory. Therapeutic regimens that are currently used in advanced non-small cell lung cancer (NSCLC) yield the average OR rates of 20-30%, while median survival may be as low as 6-8 months. Small-cell lung cancer (SCLC), which distinguishes itself from NSCLC by more aggressive clinical course and median survival less than 3 months in the absence of treatment, has greater responsiveness to chemotherapy, but median survival remains 12-14 months.

In the search of new systemic strategies against lung cancer, biologic agents such as IFNs have been reconsidered for the treatment programs. Clinical studies that include IFNs are heterogeneous in regard to the IFN type and other biochemotherapeutics used in combination therapy; they frequently dealt with small sample series, and patients groups are often unmatched by stage of disease and category of responses.

IFNs in advanced non-small cell lung cancer (NSCLC)

The IFN monotherapy is inactive in this disease; the responses were rare and no impact on survival was seen (54).

Clinical experiences with IFNs as adjunctive treatment of NSCLC are limited. The summarized data of trials that used IFN in combination with other agents are presented in Table 3 (55-72). It is evident that addition of IFNs to conventional chemotherapy confers little or no benefit; these combinations are usually accompanied by increased toxicity. When IFNs were combined with radiotherapy (RT), different results have been reported. The IFNβ-therapy preceding RT gave encouraging response rate in the McDonald’s study (65); concurrent treatment with IFNα and RT did not provide any advantage over RT alone (64), while the concomitant treatment of NSCLC patients with IFNα and fractionated thoracic radiation was associated with severe, life-threatening toxicity without effect on survival (66).

In the studies using IFN in combination with retinoic acid (RA) or IL-2, no antitumor response was seen (Table 3). Multiagent regimens including chemotherapy, IFN and the thymic preparation thymosin α1, gave an improved response rate (71,72), which was associated with reduced toxicity. These promising results need to be confirmed in larger randomized trials.

<table>
<thead>
<tr>
<th>Study</th>
<th>Therapy</th>
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<th>PR</th>
<th>OR (%)</th>
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ChT-chemotherapy; RA-retinoic acid; Tα1-thymosin α1; RT-radiotherapy

IFNs in small-cell lung cancer (SCLC)

Similarly to NSCLC, the IFN trials in SCLC are heterogeneous, which makes the interpretation of the results difficult. The available data on this matter are presented in Table 4 (73-83). In most studies, IFNα was used as maintenance therapy for patients in whom complete (CR) or partial responses (PR) were achieved by induction chemo- and radiotherapy. In contrast to Mattson et al. (74,75), whose results were significantly in favor of IFNα therapy (in patients for whom other prognostic factors were favorable), other reports were negative or inconclusive (76,81,82). In the trials that used IFNγ, no beneficial effect on survival was observed (78-80). It is noteworthy that IFN-therapy was usually associated with toxic effects, which frequently required the discontinuation of treatment.

Presently, it seems that IFNs do not make a major progress in the treatment of lung cancer. Further investigations to define the active biochemotherapeutic combination and optimal dosing schedules are necessary.

Breast cancer

Numerous attempts to improve the efficacy of chemotherapy of metastatic breast cancer by the additions to, and substitutions of one or other chemotherapeutic agent/s in conventional regimens, have failed to produce further substantial improvement of response rate or response duration. Because of that, the biotherapy, including IFNs, in a combination strategy against breast cancer has been tried. However, limited number of clinical trials are available thus far and this approach is still in experimental area.

Encouraging data of initial reports concerning therapeutic potential of IFNα, have not been confirmed in subsequent clinical trials (84-88): in most patients, IFN therapy had negligible activity.

In few clinical studies, IFNα was used in combination with IL-2; minor objective response associated with considerable toxicity was reported (89-91).

In patients with subcutaneous metastases, the intraloskeletal therapy with IFNα+IFNγ has been tested in two small trials. Promising locoregional antitumor activity associated with extensive immunomodulation was found (92,93), but further follow-up studies are needed to confirm these results.

Another combination of biotherapeutics - IFNα and thymostimulin, was evaluated in
advanced breast cancer by Munno et al. (94). In clinical
terms, patients administering this combination
could complete chemotherapeutic cycles without interruptions; they had fewer
infections in comparison to patients receiving
different therapeutic regimens.

Generally, all these data show that IFNs,
used either as single agent or in combination
with other biotherapeutics, have no or very lim-
ited clinical activity in advanced breast cancer.

During the last few years, there is an
increasing number of trials using IFNs in combi-
nation with hormonotherapy in the treatment of
this malignancy. Such an approach is based on

the treatment of advanced breast cancer remains
investigational, and the optimal scheduling is
still undetermined.

Either alone or combined with different bio-
 therapeutics, IFN has also been tried, although
less frequently, in tumors other than the above-
mentioned ones. In several clinical trials IFNα,
usually combined with RA, was given to patients
with squamous cell carcinoma (SCC) of the
uterine cervix; such an approach is of special
interest, since both agents have been shown to
suppress the growth of human papilloma virus
type 16 (HPV-16)(109), which is related to cervi-
cal carcinoma. Moreover, IFN might correct the
RT-due, long-lasting depression of lymphocytes
(110,111). However, the results obtained in these
trials are very heterogeneous. The high OR rates
of 50% and 42% reported by Lippman et al.
(112,113) were not confirmed in later studies
(114,115).

The Lippman’s group also reported very
high (68%) objective response of patients with
inoperable SCC of the skin; again, IFNα was
combined with retinoic acid (116). The high
response rates seen in these initial trials were
not obtained in other squamous tumors (head
and neck, oesophagus), in which this regimen
(117-119), or the combination of IFN with IL-2
(120,121), was used. Further studies integrating
such therapy with other treatment modalities
are warranted in cervix and skin cancers.

Interferons were also tried as local-intraves-
ical therapy in superficial bladder cancer. The
average OR rate was 40% (122,123). Intravesical
instillation of IFN lowers the relapse rate from
70-80%, seen after surgery alone, to 30-50%. It is
noteworthy that this treatment has few and usu-
ally mild side effects, which is in contrast to the
routine local BCG therapy; however, the latter
has significantly higher response rates (60-70%).
Because of that, an ongoing multi-center trial
(123) uses low doses of both agents in the thera-
py of superficial bladder cancer.

The local (intra- and perilesional) or sys-
temic IFN therapy was tried, with some success,
in patients with various other solid tumors: hon-
drosarcoma (124), malignant pleural mesothel-
oma (125,126), glioma (127), prostatic cancer
(128) and AIDS-related Kaposi’s sarcoma
(129,130). This latter entity is of special interest,
since it is the most common complication of HIV
infection and AIDS; therefore, all biological
activities of IFN (antiviral, antitumor and
immunological), may be of relevance. It is
agreed that IFN monotherapy may be effective
in a proportion of patients (those with CD4 cell
number > 150 cells/mm³)(131). However, the
doses necessary to achieve a significant antitu-
mor effect are often poorly tolerated. The thera-
py with IFN and zidovudine (132-135) resulted
in tumor regression in a substantial percentage

### Table 4. Interferons in small cell lung cancer patients responsive to induction chemotherapy.

<table>
<thead>
<tr>
<th>Study</th>
<th>IFN type</th>
<th>Number of patients</th>
<th>Median time to progression (months)</th>
<th>Median survival (months)</th>
<th>2-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kohne 1992</td>
<td>IFN-α</td>
<td>25</td>
<td>13.5</td>
<td>16.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mattson 1992</td>
<td>IFN-α</td>
<td>91</td>
<td>11</td>
<td>18*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ChT</td>
<td>59</td>
<td>11</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>87</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Mattson 1997</td>
<td>IFN-α</td>
<td>91</td>
<td>10</td>
<td>10*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ChT</td>
<td>59</td>
<td>10</td>
<td>2*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>87</td>
<td>10</td>
<td>2*</td>
<td></td>
</tr>
<tr>
<td>Kelly 1993</td>
<td>IFN-α</td>
<td>64</td>
<td>9</td>
<td>13</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>control</td>
<td>68</td>
<td>10</td>
<td>16</td>
<td>35</td>
</tr>
<tr>
<td>Glisson 1993</td>
<td>IFN-α</td>
<td>14</td>
<td>10</td>
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<td></td>
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<tr>
<td>Jett 1994</td>
<td>IFN-γ</td>
<td>51</td>
<td>6.9</td>
<td>13.3</td>
<td>27*</td>
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<tr>
<td></td>
<td>control</td>
<td>49</td>
<td>8.1</td>
<td>18.8</td>
<td>33</td>
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<tr>
<td>Bitran 1995</td>
<td>IFN-γ</td>
<td>41</td>
<td>3.6</td>
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<tr>
<td>van Sandwijk</td>
<td>IFN-γ</td>
<td>59</td>
<td>8.9</td>
<td>17</td>
<td></td>
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<td>1997</td>
<td></td>
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<tr>
<td>Tummaroello</td>
<td>IFN-α</td>
<td>14</td>
<td>12</td>
<td>15</td>
<td>28*</td>
</tr>
<tr>
<td>1997</td>
<td>control</td>
<td>12</td>
<td>7</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>* Zarogoulidis*</td>
<td>IFN-α</td>
<td>42</td>
<td>11.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>ChT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>IFN-α+ChT</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>ChT</td>
<td>39</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Prior 1997*</td>
<td>IFNα+ChT</td>
<td>43</td>
<td>7.6</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ChT</td>
<td>34</td>
<td>5.4</td>
<td>**</td>
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</table>

* p<0.01 in comparison to control
** p<0.02 in comparison to control
# Stanojlovic-Bakić N.
of patients, but was usually associated with dose-limited toxicity. Generally, this disease remains a challenging problem; larger studies using IFN combined with antiretroviral treatment and chemotherapy are warranted.

CONCLUSIONS AND FUTURE DIRECTIONS

Although IFNs have been tried in the therapy of solid malignancies other than RCC and MM for several years, it can be stated presently that this approach is still in experimental area. Despite the wide variety of clinical trials using IFNs either as monotherapy or in combination with other BRMs, no clear-cut enhancement of therapeutic efficacy of standard treatment has been substantiated. However, it seems that some combinations, such as IFN and hormone therapy for breast cancer, and IFN+retinoic acid in squamous cell carcinomas, deserve further investigation. The disappointing results of IFN therapy may be primarily due to its use mainly in advanced cancer. As it has been known for several years, the biotherapy might be more effective in the early stages of tumor development. Therefore, the optimal effects of IFN therapy may be expected during the early evolution of cancer (136), and in pre-malignant lesions as well (137,138). The kinetics of tumor cell populations influence the expression of specific receptors, which is a common denominator of the action of BRMs. Thus, the response of human tumors to IFN strongly depends on the tumor cell growth kinetics (136,137): the stationary cell populations are killed, whereas the fast growing ones are only reversibly inhibited. This may be the reason for different sensitivity of primary tumors and metastases (139).

In future investigations of therapeutic potential of IFNs in solid malignancies, the key question to be addressed is the better understanding of biological mechanisms of specific tumor sensitivity, i.e., why some tumors of the same histologic type are responsive and some are not. Furthermore, the mechanisms of resistance of sensitive tumor types also have to be resolved. Such research may lead to better defining the biological features related to tumor responsiveness (140, 141).

In addition, several other points remain to be elucidated: the relative contribution of antiviral, antitumor and immunologic effects of IFNs in exerting the beneficial effect in some malignant lesions, the defining predictive factors for clinical response and the optimal therapeutic schedule, the reduction of toxicity, the treatment duration, new indications and new drug combinations - all are expected to be resolved in near future.

Acknowledgements
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