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Does chemotherapy prevent HCV-related hepatocellular carcinoma? Cons

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Abstract

The accuracy and the reliability of well-recognized clinical, virologic, histologic, and molecular risk factors for hepatocellular carcinoma (HCC) are still insufficient. Thus, accurate risk prediction of cancer development in individual patients with the aim of selecting high risk cohorts of patients for HCC chemoprevention programs remains an elusive goal. Future directions in chemoprevention of HCC will be in the development of molecular risk models and of new chemopreventive agents. Studies examining multiple genes and proteins (genomics and proteomics) in the same HCCs will be required to evaluate this possibility thoroughly. A strategy aiming at preventing chronic liver disease of any etiology (HCV and HBV infection, alcohol, obesity, others) may be required to prevent HCC in low and intermediate incidence areas, and hence, worldwide. In the setting of secondary chemoprevention, literature data pooling suggests a slight preventive effect of interferon (IFN) on HCC development in patients with HCV-related cirrhosis. The magnitude of this effect is low, and the observed benefit might be due to spurious associations. The preventive effect is limited to sustained virological responders to IFN. So, there is no sound evidence to support a recommendation for widespread use of IFN to prevent HCC in HCV-related cirrhosis. In the setting of tertiary chemoprevention, the risk of recurrence of HCC may be reduced by IFN treatment in selected patient populations. Further large-scale multicenter randomized controlled trials may prove useful to evaluate the benefit on overall survival.
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1. Introduction

Although early diagnosis and effective treatments are paramount in controlling the death rate of patients with hepatocellular carcinoma (HCC) [1], the importance of cancer prevention has gradually emerged because advanced (large or locally invasive) HCC is difficult to cure [2]. Because the basic mechanism of all cancer development results from accumulation of epigenetic and genetic alterations in cells, the current concept of multistage carcinogenesis has promoted chemoprevention to the stage of a new medical science [3]. Therefore, HCC (chemo)prevention remains a major issue in the long-term management of cirrhotic patients, especially in compensated cirrhosis of viral aetiology, in which HCC is the first complication to occur and a major cause of liver-related death [4].

Chemoprevention may be defined as the use of natural or synthetic agents to reverse, suppress, or prevent premalignant lesions from progressing to invasive cancer [5]. Chemoprevention of HCC may be classified into three categories:

1. *primary*, preventing cancer in healthy subjects at high risk for etiologic factors known to cause chronic liver disease;
2. *secondary*, preventing cancer in those with premalignant conditions, for example, HCC prevention in patients with cirrhosis;
3. *tertiary*, preventing recurrence in patients cured of an initial cancer.

A prevention program for HCC should fulfil the following prerequisites:

1. identification of the risk factors for HCC;
2. determination of the pathogenetic mechanisms of liver

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carcinogenesis as well as of the genetic markers that identify the early events in the carcinogenetic process and possibly availability of animal tumor models;
3. finally, evaluation of the available data from epidemiologic and clinical studies on candidate (chemo)preventive agents.

2. Primary prevention

Because vaccination against HCV is yet unavailable and there is only a low probability of a vaccine against HCV being developed in the near future, other preventive methods are required to reduce the burden of HCV-related liver disease. Counselling is needed for primary prevention of new infection by rigorous implementation of infection control practice to prevent nosocomial and iatrogenic HCV transmission and secondary prevention of HCV transmission from infected persons to other persons [6]. However, the impact of any prevention program on HCV spread is relatively low because the majority of the infected patients are not under medical care. Although screening of the whole population is not recommended, it is important to test for HCV all persons with risk factors for HCV infection. A strategy aiming at preventing chronic liver disease of any etiology (alcohol, obesity, others) may be required to prevent HCC in low- and intermediate-incidence areas, and hence, worldwide. The incidence of HCC might be further reduced by eliminating aflatoxin from the food supply in areas of the world where agricultural products are stored under conditions that favour the growth of *Aspergillus flavus* and *Aspergillus parasiticus*. A recent case-control study conducted in Sudan clearly demonstrated that reduction of aflatoxin contamination of foods may be a useful public health strategy in HCC prevention [7]. Other risk factors, like anabolic or sex steroids, smoking habits, and perhaps plant-derived or chemical agents have not been considered, because their impact on HCC epidemiology is doubtful or very small, and available data are sparse and somewhat conflicting.

3. Secondary prevention

The role of interferon (IFN) in preventing HCC in HCV related cirrhosis is controversial. It has been argued that long-term suppression of viral replication could reduce hepatocyte turnover and lessen the risk of dysplasia and cancer. In 1995, a small randomized controlled trial (RCT) showed a decrease in the incidence of HCC in patients with HCV cirrhosis compared with untreated controls [8]. In the wake of this study, several controlled trials [9–27] were performed. These studies, often assessed retrospectively, collected cohorts of a relatively small size and having a marked degree of heterogeneity, making it difficult to assess the actual level of benefit obtained by IFN treatment. Moreover, these studies have been subjected to many criticisms because of several methodological flaws, their results being largely inconsistent. This can be explained, at least in part, by differences in design, stage of disease, duration of follow up, type of IFN, and schedule of treatment. The main reason for these discrepancies, however, most likely derives from the many limitations of retrospective studies, such as susceptibility, intervention, and selection biases, that may make the results unreliable. Finally these studies were not primarily designed, powered and conducted to assess the benefit of IFN on HCC prevention.

Hitherto, a number of important questions still remain unsolved by the available studies:
- Is the risk of HCC in viral cirrhosis reduced by IFN therapy?
- If a risk reduction truly exists, does the benefit apply to all patients with HCV cirrhosis?
- Is a sustained response to IFN required to reduce the incidence of HCC?
- Does the preventive effect of IFN on HCC development start before the onset of severe fibrosis or cirrhosis?

Three meta-analyses on aggregate data [28–30] were performed to evaluate whether IFN reduces the incidence of HCC in patients with HCV-related cirrhosis. In the last published [30], IFN seemingly decreased HCC rate in all but one of 20 studies included in the meta-analysis, a significant difference being observed in 13 studies.

The rate difference (RD) between IFN-treated patients and controls of each trial ranged from -33.3% to $+3.9\%$. The pooled estimate of the treatment effect was significantly in favour of a preventive effectiveness of IFN (RD, -12.2%; 95% CI, -8.4% to -16.1%, $P < 0.00001$). A remarkable heterogeneity among the studies ($P < 0.0001$) was found. The most prominent heterogeneity was in the difference of magnitude of the treatment effect on the risk of cancer ("quantitative heterogeneity"). Large differences were observed in the baseline risk of HCC among the different trials: the HCC rate in the untreated group ranged from 6.8% to 73%.

All meta-analyses [28–30] clearly showed that the heterogeneity in HCC incidence in patients who received IFN is the most relevant feature of the studies. The inconsistency among these trials is not surprising if one considers all potential biases in the selection of patients with different demographic and clinical characteristics, different timing of referral and diagnostic criteria, true differences in case mix, risk factors for HCC development, severity of the underlying cirrhosis and dose and length of IFN treatment.

An attempt to explain the wide variability in the risk of HCC development was made by stratifying studies according to variables that described the patients studied (patient-level covariates) and the study design features (study-level covariates). A significant heterogeneity in IFN benefit among studies remained even after stratifying by study- and patient-level covariates. However, heterogeneity in the prevention effect of IFN on HCC development disappears in the stratum of sustained responders, implying that viral clearance seems to influence the clinical benefit.

A meta-analysis [30] clearly showed that the overall effect of IFN on HCC development was influenced by the Japanese studies, which had the highest incidence of HCC in untreated

patients. This may be explained by the intensiveness of the screening programs. Genetic and dietary factors, different strains of HCV, age-specific distribution of infection or HBV occult infection and different molecular characteristics and biological behaviour of the tumour may also account for the difference in HCC incidence observed between European and Japanese patients.

Firm conclusions, drawn on the results of direct comparisons between treated and untreated cirrhotic patients, are seriously hampered by the fact that the majority of the studies included in the meta-analyses were non randomized controlled trials (NRCT) and only three small RCTs were originally designed to perform this comparison. NRCTs are subject to many problems that reduce their internal and external validity. Their lack of precision and reliability causes inherent biases towards false positive results [31]. When assessing NRCTs, the most important bias is the likelihood of inappropriate selection of patients, which can lead to incorrect results and spurious associations. Therapeutic guidelines cannot be derived from NRCTs unless the observed benefit of treatment is large, the treated group strictly comparable to external controls, and the clinical course of untreated patients predictable by a reliable prognostic model. None of the NRCTs of IFN for HCC prevention in viral cirrhosis fulfils these methodological standards.

So, the available evidence from meta-analyses is sufficient to conclude that IFN may prevent or delay the development of HCC in patients with HCV-related cirrhosis. However, the magnitude of the overall effect is low and the observed benefit might be due to spurious associations. The preventive effect is stronger among sustained responders to IFN, which intrinsically represent a small proportion of all cirrhotic patients.

After the meta-analyses, 3 observational cohort studies, two prospective studies conducted in Japan [32] and in Taiwan [33] and one retrospective study conducted in Italy [34], have clearly confirmed that the efficacy of IFN in the chemoprevention of HCC is exclusively linked to the achievement of a sustained viral eradication, while no benefit in reducing HCC development was observed in non-responder patients.

Recently, the effectiveness of long-term maintenance therapy with pegylated-IFN at low dose in non-responder patients with advanced fibrosis or HCV-related cirrhosis was evaluated by 3 RCTs: the HALT-C trial [35], the Epic-3 trial [36] and the COPILOT trial [37]. Patients in these studies were quite homogeneous in terms of recruitment criteria, stage of liver disease at entry, follow up and treatments. The outcomes assessed were death, hepatic decompensation as defined by Child-Pugh score progression, HCC, and, for non-cirrhotic patients, an increase in hepatic fibrosis.

Not surprisingly, in all the 3 RCTs the proportion of cirrhotic patients who developed clinical outcomes was similar in the treatment and control group. The 3 studies show that the natural history of cirrhosis was not significantly affected by low-dose PEG-IFN maintenance treatment as both overall, event free survival and HCC development did not differ between treated and untreated patients. So, no benefit of maintenance therapy in reducing the progression of fibrosis, hepatic decompensation, mortality, or in preventing the development of HCC was observed, despite the improvement of inflammatory markers (alanine aminotransferase and necroinflammatory histologic findings) and the reduction of viral load. It seems reasonable, therefore, to recommend caution when treating cirrhotic patients to reduce the risk of cancer with long-term maintenance IFN regimens.

The negative results of these large multicentre RCTs were fully expected, based on the following considerations:

First, the hypothesis that a long-term suppression of HCV replication in the absence of a complete viral eradication could slow or block the mechanisms of carcinogenesis has low biological plausibility. In contrast to the data regarding carcinogenesis by HBV, there is currently no sound evidence in the literature that the risk of developing HCC is correlated with the levels of HCV replication.

Second, our previous meta-analysis [38] had already clearly demonstrated that the histological improvement of fibrosis was clearly observed only in patients with a sustained virological response to therapy while in nonresponders we did not find any significant regression of fibrosis.

Third, previous evidence from literature data pooling clearly suggested that the preventive effect of IFN on HCC development in patients with HCV-related cirrhosis was observed only among sustained responders to IFN.

Fourth, the low doses of PEG-IFN used in the 3 RCTs make the probability of demonstrating a significant clinical benefit very unlikely.

Finally, considering the difficulties in planning and conducting long-term randomised clinical trials, a prospective trial aimed at assessing the efficacy of IFN in preventing HCC should have been conducted in a selected population at high risk for HCC development.

4. Tertiary chemoprevention

The 3-year survival rate of patients with HCC undergoing surgical or percutaneous ablation remains low, because of the high risk of intra-hepatic recurrence even though treatment has been considered curative by imaging technique. A plateau in the effectiveness of ablative treatment may well have been reached, and further improvement in survival from a single-modality approach seems unlikely.

Cammà et al. [39] who followed a large cohort (more than 200) of patients with small (<5 cm) HCC in compensated cirrhosis treated by radiofrequency thermal ablation (RFTA), reported that the 3-year recurrence rate of new lesions was 34%, quite similar to that of a previous study on percutaneous ethanol injection (PEI) (41%) of the same group [40], and also similar to that found in the study by Lencioni et al. [41], in which the 2-year recurrence rate of patients treated by radiofrequency thermal ablation was 36%. Therefore, all these data underscore, from a practical point of view, the need for adjuvant therapy (tertiary prevention) in the effort to prolong

survival and reduce recurrence rates. In the past, different anticancer agents have been evaluated for tertiary prevention of HCC recurrence, including retinoids [42], intra-arterial I-131 [43], adoptive immunotherapy [44], and finally IFN [45–49]. Recently, sorafenib, an oral multi-kinase inhibitor targeting both tumor cells and the tumor vasculature is being evaluated in the setting of tertiary chemoprevention. Two large multinational randomized, double blind, placebo-controlled trials are currently in progress to evaluate the efficacy (overall survival and cancer-free survival) and the tolerability of sorafenib versus placebo as adjuvant treatment in subjects with HCC following potentially curative treatment (surgical resection or local ablation) or palliative treatment (transcatheter arterial chemoembolization – TACE).

5. Interferon

The potential activity of IFN in the setting of secondary chemoprevention has led to the treatment of patients with IFN in the adjuvant setting. Since the first RCT of IFN adjuvant therapy appeared in 2000 [45], four other RCTs have been published [46–49]. Studies have indicated that IFN decreases the rate of HCC recurrence, and the results of our meta-analysis, totalling 196 patients, consistently show a statistically significant benefit on HCC recurrence. IFN was superior to no treatment in all trials, reaching statistical significance in all but one study. The pooled estimate of the treatment effect was significantly in favour of a beneficial effect of IFN on HCC recurrence (RD, −43%; 95% CI, −65% to −20%, $P < 0.0001$). No significant heterogeneity was found among the five trials. The NNT, i.e. the number of patients with HCC receiving potentially curative treatments needed to treat with IFN to prevent one cancer recurrence, was 2. However, the key clinical question is whether all patients with HCC receiving potentially curative treatments should and could be treated with IFN or whether adjuvant treatment should be administered only to a selected group of patients who clearly stand to benefit. Unfortunately, there is no reliable predictive model capable of identifying patients with HCC receiving potentially curative treatments at high risk of developing HCC recurrence. Furthermore, all the RCTs in the tertiary setting have been conducted in the eastern populations limiting the external validity of these studies and therefore making the transferability of the results to different populations questionable. Further large-scale multicenter RCTs designed and conducted also in western populations may prove useful to substantiate the benefit on recurrence and overall survival.

Recently, Mazzaferro and coworkers published a RCT [50] on a group of 150 early or intermediate HCV-related HCC patients undergoing resection and stratified into 80 HCV-pure (hepatitis B anticore antibody [anti-HBc]-negative) and 70 HCV mixed (anti-HBc-positive) groups, then randomized to IFN-α (3 million units 3 times weekly for 48 weeks [$n = 76$]) versus control ($n = 74$). While no treatment effect was apparent in the mixed HCV + HBV population and on early recurrences, there was a significant benefit on late recurrences in HCV-pure patients adherent to treatment. Authors concluded that IFN does not affect overall prevention of HCC recurrence after resection, but it may reduce late recurrence in HCV-pure patients receiving effective treatment.

6. Acyclic retinoids

Retinoids, acting on nuclear receptors, retinoic acid receptor (RAR) and retinoid X receptor (RXR) have potential for cancer chemoprevention through their action as regulators of cell growth and differentiation [51]. Retinoids may inhibit or reverse the carcinogenic process in various types of cancers, including the liver, in experimental models of oncogenesis. A preventive approach to HCC using a synthetic retinoid analog, acyclic retinoid, has theoretical interest, because post-translational modification of RXR by phosphorylation impairs its function, leading to uncontrolled hepatocyte growth. In vitro acyclic retinoid suppresses the phosphorylation of nuclear retinoid X receptor α (RXRα), restores its function in the presence of its endogenous ligand, 9-cis RA, and thereby induces apoptosis of the cancer cells. HCC in cirrhotic patients contains lower levels of endogenous retinoids, and may be insensitive to retinoic acid because of a malfunction of RXRα [50]. In HCC tissues, there is an accumulation of phospho-inactivated RXRα, which functions as a dominant negative receptor and interferes with transactivation by remaining normal RXRα. Acyclic retinoid prevents phosphorylation of RXRα and restores its function and enhances the sensitivity of HCC cells to IFNs-α and -β, thereby promoting apoptosis induced by these interferons. This could lead to eradication of (pre)malignant clones ("clonal deletion") from the cirrhotic liver.

Clinical use of polyprenoic acid, an orally absorbable acyclic retinoid, has been exploited in the context of tertiary prevention of HCC recurrence after surgical or PEI tumor ablation in 89 patients with cirrhosis [52]. Treatment with polyprenoic acid significantly reduced the incidence of recurrent or new cancer lesions. After a median follow-up of 38 months, 12 patients in the polyprenoic acid group (27%) had recurrent or new HCCs compared with 22 patients in the placebo group (49%, $P = 0.04$). These promising results still await confirmation by other controlled studies.

7. Summary

The accuracy and the reliability of well-recognized clinical, virologic, histologic, and molecular risk factors for HCC are still insufficient; thus, accurate risk prediction of developing cancer in individual patients remains an elusive goal. Future directions in chemoprevention of HCC will be in the development of new molecular risk models and of new chemopreventive agents. The design of targeted molecular therapies may need to be tailored to the specific molecular phenotype of a specific HCC. Studies examining

multiple genes and proteins (genomics and proteomics) in the same HCCs will be required to evaluate this possibility thoroughly.

In the setting of *secondary chemoprevention*, literature data pooling suggests a slight preventive effect of IFN on HCC development in patients with HCV-related cirrhosis. The magnitude of this effect is low, and the observed benefit might be due to spurious associations. The preventive effect is more evident among sustained responders to IFN.

In the setting of *tertiary chemoprevention*, although different agents have been evaluated including retinoids, intra-arterial I-131, adoptive immunotherapy, and finally IFN, there is no sound evidence to support the recommendation for widespread use of these agents to prevent HCC recurrence after curative or palliative treatments. The risk of recurrence of HCC seems reduced by IFN treatment in selected oriental populations only. However, the results are on the whole inconclusive or conflicting and they were not replicated in most cases. The lack of conclusive evidence of benefit from the previous therapeutic approaches highlights the urgent and ongoing need for more effective and safe adjuvant agents assessed in large-scale multicenter RCTs. Sorafenib is being evaluated in 2 RCTs designed to assess the effectiveness of this drug in improving overall survival of patients with HCC undergoing surgical resection, RFTA or TACE. It is, therefore, necessary to wait for the results of these RCTs to implement efficient programs of tertiary chemoprevention in clinical practice.

Conflicts of interest

The authors have received a fee from Bayer HealthCare for their contribution to this supplement. Bayer HealthCare played no role in the preparation, review, or approval of the manuscript. The authors have no other conflict of interest to report.

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