·Review·

Adjuvant interferon therapy for malignant melanoma: the debate

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[Abstract] Based on the results of the Kirkwood high-dose interferon alpha-2b (HDI) adjuvant therapy trial of the Eastern Cooperative Oncology Group 1684, the US Food and Drug Administration (FDA) approved HDI as the postoperative adjuvant therapy for high-risk melanoma. Unfortunately, controversies continue regarding the use of interferon (IFN) as adjuvant therapy for melanoma owing to the inconsistent results of subsequent trials. Numerous trials of adjuvant interferon therapy demonstrated a benefit in terms of relapse-free survival (RFS), but without confirmed significant effect on overall survival (OS). The optimal timing, dose, and type of interferon are not yet defined. Therefore, adjuvant interferon treatment is preferentially applied in the randomized clinical trials in specialized centers. Decisions about the appropriateness of adjuvant interferon alfa-2b treatment for patients should be made on an individual basis, after discussion with the patient, including an explanation of the potential benefits and side effects of interferon therapy. Moreover, we also need to use available regimens reasonably, seek feasible and predictable prognostic factors to serve patients with individualized therapy.

Key words: Interferon, melanoma, adjuvant therapy, clinical trial

Malignant melanoma (MM) is a malignant tumor derived from melanocytes, with the characteristics of high malignancy, easy metastasis, and poor prognosis. MM mainly occurs in the white race and has a high incidence in North Europe, North America, and Oceania. There are about 160 000 new cases of MM worldwide per year [1], and the incidence is still increasing. Although the incidence of MM in Chinese people (1/100 000) is significantly lower than those in the Western countries, it has the fastest increase of incidence, with about a 3% –5% annual incremental rate (based on the statistical data of the 8 areas of Beijing)[2].

The early stage MM can be cured by radical surgery. However, once the distant metastasis occurs, the median survival time is only about 6 to 12 months, and the 5-year survival rate is less than 5% [3,4]. Therefore, an effective adjuvant therapy is very important for reducing the metastasis of high-risk patients. Previously, multiple strategies such as chemotherapy, biological therapy, and radiation therapy have been used as adjuvant therapy for MM[5]. However, so far, interferon-α (IFN-α) is still the only drug which has been proved to improve the overall survival (OS)(Figure 1)[6].

There are a lot of clinical trials concerning interferon in treating the high risk stage IIB-IIIC MM patients, with different doses and time. The doses of interferon were 1×10^6–3×10^6 units of low-dose interferon (LDI), 5×10^6–10×10^6 units of intermediate-dose interferon (IDI), and 15×10^6–20×10^6 units of high-dose interferon (HDI). In addition, the treatment time of interferon also varied from 1 month to 5 years. The reproducibility of the results was poor due to the varied experimental designs. A decade after the approval of interferon treatment for MM by the USA Food and Drug Administration (FDA), which interferon treatment regimen could bring the maximal risk-benefit ratio has not yet reached a consensus. Many countries have still no uniform treatment recommendation for the adjuvant therapy of melanoma[7,8].

The hot spot of the academic debate on interferon treatment mainly contains the following three aspects: (1) Whether interferon treatment is valuable? (2) Which is the

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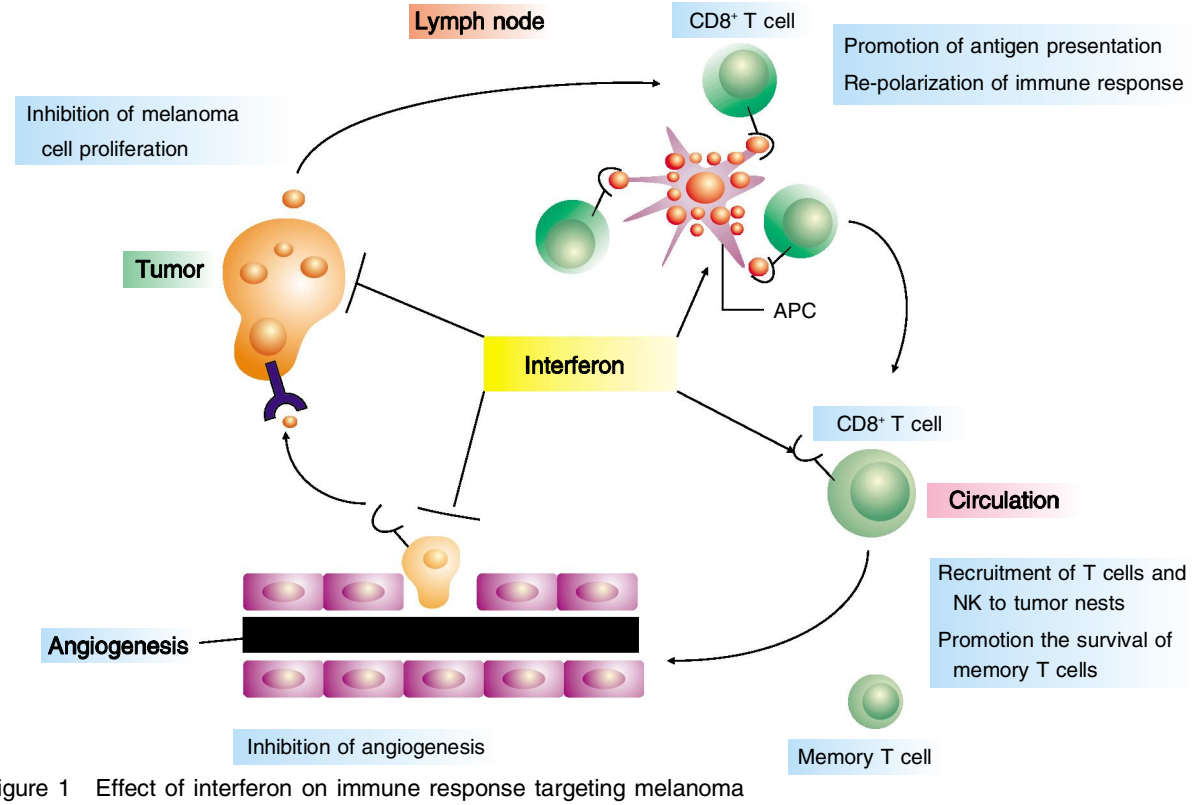

Figure 1 Effect of interferon on immune response targeting melanoma

Interferon-α (IFN-α) showed multiple effects on melanoma. Firstly, IFN-α has the potential of promoting antigen presentation and re-polarizing the immune response toward Th1 response. Secondly, IFN-α helps the recruitment of T cells and NK to tumor tissue and promotes the survival of memory T cells. Thirdly, IFN-α could inhibit the angiogenesis of melanoma. Finally, IFN-α might directly inhibit the proliferation of melanoma cells.

standard adjuvant therapy? (3) Is there a preponderant crowd? In the present article, we tried to answer the above debate through analyzing the data of multiple clinical trials and elucidating the reasons of the debate.

Therapeutic Regimens of Interferon

High-dose interferon (HDI)

HDI treatment model was original from a series of the ECOG studies supervised by Kirkwood *et al.*[9-11] In these studies, interferon therapy was divided into the induction stage and the maintenance stage. The dosage of interferon in the induction stage was up to 20 × 10^6 units / (m^2·d), with 5 continuous days per week for 4 weeks. The dosage of interferon in the maintenance stage was 10 × 10^6 units / (m^2·d), used every other day, 3 times per week for 48 weeks. The total treatment period was up to 13 months. Based on the OS benefit from the ECOG1684 trial[9], interferon was approved to be applied as adjuvant therapy for high-risk MM by FDA in 1996. Subsequently, the value of HDI adjuvant therapy was further explored by the ECOG1690 and ECOG1694 trials[10,11]. Unfortunately, OS benefit was not obtained in the patients of both HDI group and LDI group in the ECOG1690 trial[10]. Only the relapse-free survival (RFS) of the patients in HDI group was significantly prolonged than the observation group. In addition, although OS and RFS benefits were obtained in some patients of HDI group in the ECOG1694 trial, the experimental design was widely criticized and the results were not widely accepted because the control group used the GMK vaccine but not blank control. Due to the flaws of the series of ECOG studies and the inconsistent results, the rank of HDI in the adjuvant therapy is challenged. Moreover, even if the OS benefit of HDI was confirmed, the serious toxicity and low response rate make it necessary to find an effective treatment method with a low toxicity.

Optimized interferon therapeutic regimen

HDI could benefit to OS in the ECOG1684 trial, but it had high toxicity, and the 3–4 grades of toxicity were more common. About 37% of the patients in the trial group required the dosage reduction or delayed treatment due to the excessive toxicity[12]. At present, many clinical trials were optimized by reducing the dose and extending the treatment time.

Low-dose interferon (LDI)

Previously, multiple trials, including French, Austrian and AIM-HIGH trials, were carried out to explore the effect of LDI adjuvant therapy for melanoma[13-17]. RFS benefit was obtained in some trials, but no OS benefit was obtained. However, the LDI trial by Garbe *et al*.[18] in 2008 showed that LDI benefited to both RFS and OS. In this trial, the OS benefits of LDI group, LDI combined with DTIC group and blank control group were compared. The results showed that as compared with the blank control group, LDI benefited not only to RFS but also to OS, whereas LDI combined with DTIC did not obtain any benefit, suggesting that DTIC combined with LDI may weaken the effect of LDI, but the exact mechanism is still unclear. The authors considered that DTIC maybe inhibited the immune function of interferon. In addition, DTIC maybe promoted the proliferation and metastasis of the residual melanoma cells after killing some melanoma cells through the cytotoxicity effect. Another possible reason was that the disproportional primary tumor ulceration in two groups affected the final results. Therefore, the reference value of this trial is limited. In the clinical trial by Grob *et al*.[13], LDI had a certain role in extending the RFS, the toxicity could be tolerated, and the cost was relatively low, so some European countries (such as Germany, Switzerland, France, and so on) have approved LDI as adjuvant therapy [6]. The treatment time of interferon in multiple clinical trials was largely different. Hauschild *et al*. [19] found that extend LDI treatment to 5 years could not improve the RFS and OS of the patients who received LDI treatment for 18 months. Therefore, the LDI treatment time is still recommended for 1.5 years.

Intermediate-dose interferon (IDI)

Although LDI reduced the probability of severe toxicity, the OS benefit was also vanished[13-17] (except for the trial by Garbe *et al*. [18]). In the EORTC 18952 trial[20], 1418 stage IIB-III melanoma patients underwent IDI for 1 or 2 years. The results suggested that IDI treatment for either 1 or 2 years did not bring distant metastases-free interval (DMFS) benefit or OS benefit. In addition, it was pointed out that the DMFS and OS after 2 years of IDI treatment were slightly better than those after 1 year of IDI treatment, suggesting that longer interferon treatment could be explored.

Modified high-dose interferon (modified-HDI)

The RFS curves and OS curves in the ECOG trial were separated at an early stage[9], suggesting that one month of HDI in the induction stage is very important. Because the toxicity of the standard doses of interferon was severe, the HeCOG group carried out a clinical trial to compare the 1-month HDI treatment (Group A) and 13-month interferon treatment (Group B)[21]. The trial was a non-inferiority trial. The results showed that 1-month modified-HDI treatment [15×10^6 units / ($m^2 \cdot d$) for 5 days per week followed by 2 days of intermission for 4 weeks] was not worse than the 13-month interferon treatment (the dose and usage of interferon at the induction stage was the same with Group A, and the dosage at the maintenance stage was 10×10^6 units / d, every other day for 3 times per week for 48 weeks).

Pegylated-interferon (peg-IFN)

As mentioned above, LDI only brought RFS benefit, whereas the EORTC 18952 trial suggested that prolonged interferon treatment maybe would bring OS benefit. Therefore, the EORTC 18991 trial[22] enrolled 1256 stage III melanoma patients and compared the RFS and OS benefits of 5-year peg-IFN treatment group (n = 627) and the observation group (n = 629), with a 3.8-year median follow-up time. The results showed that 5-year interferon treatment only brought the RFS benefit [hazard ratio (HR) = 0.82, 95% confidence interval (CI): 0.71-0.96, P = 0.01], but not OS benefit. However, it's worth noting through sub-group analysis that only N1 (lymph node micrometastasis) patients obtained RFS benefit (HR = 0.73, 95% CI: 0.53-1.02, P = 0.016), suggesting that 5-year peg-IFN had a better effect on the patients with low tumor load. In addition, 31% of the patients in the trial group failed to complete a 5-year treatment due to the high toxicity. The median treatment time at the maintenance stage was only 12 months. Therefore, the completion of the trial is not ideal, and promoting this trial has a very limited sense (Table 1).

Drug combination

LDI can only bring the RFS benefit[13-17] (except for the trial by Garbe *et al*.[18]). Therefore, some researchers tried to increase the therapeutic efficacy through combining with other drugs. However, combining with DTIC chemotherapeutics or other drugs such as IL-2 and isotretinoin did not significantly improve the RFS and OS benefits[5].

Meta analysis

The rank of interferon in the adjuvant therapy for melanoma is under a long-standing debate. There are dozens of clinical trials with different doses and treatment time, and the results are also different. For the numerous trials, meta analysis is required to clarify the role of interferon. Large-scale of meta analysis mainly include the meta analysis on the ECOG1690 and ECOG1684 trials by Kirkwood *et al*. [23], the meta analysis by Wheatley et al. in 2003 and 2007 respectively[24-25], and the meta analysis by Mocellin *et al*. which was published in 2010[26]. These meta analysis results are different, but all of them suggested that interferon could bring RFS benefit regardless of the dose. Differently, OS benefit was not obtained in two of these analyses[23, 24], but obtained in other two meta analyses. In the meta analysis by Wheatley *et al*. in 2007 [25] which

Table 1 Clinical trials of adjuvant interferon therapy for high-risk melanoma

Trial	Eligibility	Patients	Time	Treatment (arm: patients)	RFS (*P* value)	OS (*P* value)
ECOG 1684 (Kirkwood, 1996)	IIB–III	280	13m	HDI: 143 Control: 137	0.0023	0.0237
ECOG 1690 (Kirkwood, 2000)	IIB–III	608	13m vs. 24m	HDI(13 m): 203(1) LDI(24 m): 203(2)	0.03*	0.744*
				Control: 202	0.17#	0.672#
ECOG 1694 (Kirkwood, 2001)	IIB–III	774	13m	HDI: 385 GMK: 389	0.006	0.04
French CGM (Grobe, 1998)	II	499	18m	LDI: 245 Control: 244	0.035	0.059
Austrian MMCG (Pehamberger, 1998)	II	311	12m	LDI: 154 Control: 157	0.02	NS
AIM HIGH (Hancock, 2004)	IIB–III	674	24m	LDI: 338 Control 336	0.3	0.6
Scottish (Cameron, 2001)	IIB–III	94	6m	LDI: 46 Control: 48	> 0.1	> 0.2
WHO-16 (Cascinelli, 2001)	III	426	3y	LDI: 218 Control: 208	0.50	0.72
DeCOG (Garbe, 2008)	III	441	2y	LDI: 146(1) LDI+DTIC:148(2)	0.018*	0.0045*
				Control: 147	0.97#	0.76#
EORTC 18952 (Eggermont, 2005)	IIB–III	1388	25m vs. 13m	IDI (25m): 556 IDI (13m): 553	0.17§	0.21
				Control: 279		
HeCOG (Gogas, 2007)	IIB–III	353	1m	HDI(13m): 176 HDI(1m): 177	0.90	0.49
EORTC 18991 (Eggermont, 2008)	III	1256	5y	Peg–IFN: 627 Control: 629	0.01	0.78

*, vs. control; #, vs. control; NS, not significant; §, distant metastases–free survival.

included the data of 13 clinical trials, patients obtained the event-free survival (EFS) (odds ratio=0.87; 95% CI: 0.81–0.93; *P* = 0.00006) and OS effects (odds ratio = 0.9; 95% CI = 0.84-0.97; *P* = 0.008) from interferon regardless of the dose and treatment time. In another meta analysis published in 2010[26] which included 14 randomized clinical trials from 1990 to 2008 and a total of 8122 peoples, it was concluded that interferon could significantly extend the disease-free survival (DFS) (HR = 0.82; 95% CI = 0.77–0.87; *P* < 0.001) and OS (HR = 0.89; 95% CI = 0.83–0.96; *P* = 0.002) (Table 2).

Table 2 Several meta analysis of adjuvant IFN therapy trials

Meta analysis	Trials involved	Patients	Results	
			Relapse (*P* value)	OS (*P* value)
Kirkwood (2004)	2 RCTs	713	RFS (*P* < 0.006)	*P* = 0.420
Wheatley (2003)	12 RCTs	5082	RFS (*P* < 0.001)	*P* = 0.100
Wheatley (2007)	13 RCTs	6067	EFS (*P* < 0.001)	*P* = 0.008
Mocellin (2010)	14 RCTs	8122	DFS (*P* < 0.001)	*P* = 0.002

RCTs, randomized controlled trials; OS, overall survival, RFS, relapse-free survival; EFS, event-free survival; DFS, disease-free survival.

Hot Spot of the Academic Debate on Interferon Adjuvant Therapy

Whether interferon treatment is valuable?

Multiple meta analyses indicated that interferon could bring RFS benefit. So far, only 3 clinical trials confirmed that adjuvant therapy with interferon could bring OS benefit, which were the registered ECOG1684 clinical trial with high-dose interferon[9]; the ECOG1694 trial[11], which had limited reference value even the OS benefit was obtained because the control group used the GM2 vaccine but not the blank control; and the stage III clinical trial carried out by Garbe *et al*. in 2008[18], in which LDI alone or in combination with DTIC was compared with the blank control. The results of this trial have been mentioned previously, and the authors can not explain why their results were different from those of other LDI trials. Although Wheatley reported the meta analysis results at the annual ASCO meeting in 2007 that interferon could bring OS benefit regardless of the dose and therapeutic regimen, the results are still controversial because this analysis included the ECOG2696 and ECOG1694 trials, in which the control group was GM2 vaccine group. Although there still no a consistent conclusion concerning the OS benefit from interferon therapy, we know that a 3% absolute OS benefit could be obtained from interferon therapy[26]. Compared with the adjunctive therapy for other tumors, a 3% OS benefit is still acceptable while no better therapy is available[27].

Which is the standard adjuvant therapy?

HDI can bring RFS and OS benefits, but the value of OS benefit has not been confirmed by other similar trials, and it brings high toxicity and poor tolerance. LDI has low toxicity and is acceptable, but only RFS benefit but no OS benefit (except for the clinical trial of Garbe in 2008[13]) was obtained. MDI was used only in the EORTC18952 trial[20], but both DMFS and OS were not extended. Only RFS benefit was obtained in peg-IFN treatment, although the treatment time was extended to 5 ye ars. Moreover, the median treatment time was only more than 1 year, and nearly 40% of the patients could not complete the whole treatment[22]. Therefore, promoting this trial has a very limited sense. The HeCOG trial[21] with a shortened treatment time adopted non-inferiority comparison, and the interferon dose in these two groups were largely adjusted. The interferon doses in the induction stage and the maintenance stage were reduced by 25% and 33% of the original standard doses, respectively. In addition, the expected 15% DFS statistical difference was not achieved in the previous clinical trials and meta analysis. Therefore, it is likely that this trial could not detect the difference between these two groups. The significance of this trial is that 1-month dose-modified interferon treatment is not worse than the 13-month interferon treatment under the same dose intensity. In addition, the combination therapy failed, and there was no other therapy which could replace interferon[28]. Currently, interferon was only recommended as a choice of adjuvant therapy in the clinical guidelines by the National Comprehensive Cancer Network (NCCN) in the USA and the European Society for Medical Oncology (ESMO)[7,8]. The interferon treatment can bring RFS benefit, but the optimal treatment time and dose were not designated. Therefore, there is no a standard model for interferon treatment at present.

We considered that patients should be encouraged to participate in clinical trials. In addition, after patients are fully informed, LDI treatment could be chosen for those elderly patients with poor tolerance or uncertain OS benefit; HDI treatment could be chosen for those young patients with good tolerance or expecting OS extension; 1-month dose-modified interferon treatment could be chosen for those patients with poor compliance (dosage and usage were referred to the HeCOG trial[21]).

Is there a preponderant crowd?

The patients with ulcer at the primary lesions

At the annual ASCO Meeting in 2007, Wheatley *et al.*[25] reported a meta analysis concerning the interferon adjuvant therapy for melanoma and suggested that the primary tumor with ulceration was a good indicator for predicting the EFS benefit from interferon treatment (95% CI: 0.82–0.94, odds ratio = 0.76, P = 0.0003) and OS (95% CI: 0.84–0.98, odds ratio = 0.77, P = 0.02). At the annual ASCO Meeting in 2009, Eggermont *et al.*[29] retrospectively analyzed 2644 patients in the EORTC18952 and EORTC18991 trials. They found that the RFS (P = 0.001), DMFS (P = 0.001), and OS (P = 0.001) of the patients with ulceration at primary tumors were significantly extended than the patients without ulceration. Therefore, the ulceration status may be a predictor for the efficacy of interferon therapy.

Tumor load

It was found in multiple trials that the tumor load may affect the prognosis of patients, but the results were not completely the same. Among the HDI trials, the ECOG1684 subgroup analysis showed that the patients with lymph node metastasis obtained most benefit[9]; the ECOG1690 subgroup analysis showed that the patients with 2–3 metastatic lymph nodes obtained most benefit[10]; whereas the ECOG1694 subgroup analysis showed that the patients without lymph node metastasis obtained most benefit[11]. In addition, Eggermont et al. retrospectively analyzed the EORTC18952 and EORTC18991 trials, and found the existence of the preponderant crowd in these two trials. In the EORTC18991 trial, the stage III N1 patients (accompanied by lymph node micrometastasis) obtained RFS benefit (HR = 0.73, 99% CI = 0.53–1.02, P = 0.016) and DMFS benefit (HR = 0.75, 99% CI = 0.52-1.07, P = 0.03), whereas the stage III N2 patients (accompanied with visible clinical lymph node metastasis) did not obtain RFS, DMFS, OS benefits[22,30]. These two trials suggested that the less the tumor load is, the better the therapeutic efficacy of interferon treatment is (IIB/C> IIIA> IIIB)[20,22,30].

At present, the predictive effect of staging on the therapeutic efficacy of interferon treatment is not yet clear. It has not been finally confirmed in the standard HDI group (in the 3 ECOG trials). However, in the peg-interferon group (2-year treatment group in the EORTC18952 trial, 5-year peg-interferon group in the EORTC18991 trial), the efficacy of interferon may be negatively correlated with the tumor load. We believe that the value of staging should be determined based on the different doses and therapeutic regimens.

Autoimmune response

Many trials revealed that the autoimmune reaction may be associated with whether the patients could benefit from interferon treatment. Initially, the paper that was published in the New England Journal of Medicine in 2006 by Gogas *et al.*[31] caused wide attention. In this study, they analyzed the autoimmune antibodies and vitiligo-like skin changes of 200 patients enrolled in the HeCOG trial, and found that, with a

median follow-up time of 45.6 months, 52 patients (26%) showed the anti-thyroid antibody or other autoantibodies or clinical manifestations, and that these patients had higher DFS and OS (P < 0.001) than other patients without autoimmune reactions. Dafni *et al.* [32] reported the further results of this clinical trial: with a median follow-up time of 82.6 months, the relationship between autoimmune reactions and the DFS, OS of the patients was consistent with the previous report, the DFS and OS of the patients with autoimmune reactions were significantly prolonged.

Multiple other reports showed the correlation between the autoimmune response and the patient's prognosis. For example, Stuckert *et al.* [33] retrospectively analyzed the autoimmune reactions in the ECOG2696 and ECOG1694 trials. Because ECOG2696 was of a stage II clinical trial with a small sample size, the DFS of the patients with autoimmune reaction in this trial had only the tendency of extension. In the ECOG1694 trial, the extension of both RFS (P = 0.178) and OS (P = 0.091) did not reach the statistical significance. Satzger *et al.* [34] retrospectively analyzed 134 patients who received a LDI treatment. They found that the RFS of the patients with autoimmune reaction (P = 0.048) was significantly prolonged, whereas the OS (P = 0.065) only had the tendency of extension. Bouwhuis *et al.* [35,36] analyzed the autoimmune reactions in the EORTC18952, Nordic IFN, and EORTC18991 trials. The conclusions varied based on different statistical methods, but it still suggested that the emergence of autoimmune reactions has little relation with the interferon treatment.

We considered that the regimen implementer should carefully observe the autoimmune reactions during the interferon treatment. Currently, it could be considered as a factor for good prognosis while no better prognostic factor is available. Its ultimate role still needs to be determined by a large-scale clinical trial. In addition, because the autoimmune reactions appear after treatment, it can not play a role during the procedure of screening patients.

Current Situation and Prospects

In summary, there is still no other alternative therapy to substitute the interferon treatment in the adjuvant therapy for MM. Multiple clinical trials and meta analyses have confirmed that interferon could prolong the RFS of patients, and the benefit of interferon treatment is independent of dose or treatment time. Although whether interferon could extend the OS of patients is still controversial, IFN can bring a 3% 5-year OS benefit has been obtained a broad consensus. Thus, patients should be encouraged to participate in clinical trials. In addition, after patients are fully informed, the available schemes should be reasonably applied. More efforts should be put to find the effective prognostic factors for guiding the treatment better.

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