Diagnostic and Therapeutic Approaches in Italian Hospitals: Adjuvant and Metastatic Therapy in Melanoma

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Key Words

Melanoma · Adjuvant treatment · Interferon · Chemotherapy

Abstract

Melanoma incidence and mortality rates are rising in Italy, indicating that more effective treatments are required both in the adjuvant and metastatic settings. We analyzed clinical practices in the adjuvant and metastatic settings by conducting a nationwide survey of clinicians responsible for managing melanoma treatment and follow-up in a representative sample of Italian hospitals. 95% of participating hospitals completed the panel of questions on adjuvant and metastatic treatment, making it likely that these results give a realistic picture of treatment and follow-up of melanoma patients in Italy. In low-volume hospitals (<25 new melanoma diagnoses yearly) adjuvant therapy was significantly

more used than in large-volume hospitals for patients in stage III and IV (82 versus 66% and 56 versus 30%, respectively), and only 11% of patients were enrolled in clinical trials. In the metastatic setting dacarbazine was the preferred first-line treatment (32%) followed by polychemotherapy (23%); 12% of patients were enrolled in clinical trials and less than 10% received interleukin-2, usually subcutaneously. The information provided by this study was used by the Italian Melanoma Intergroup to improve the quality of care and to redirect financial resources. Copyright © 2013 S. Karger AG, Basel

Introduction

Incidence and mortality rates of malignant melanoma are continuously rising in Italy despite a stabilization of mortality rates in women and a slowing of the increase in

mortality for men. Surgical resection with appropriate margins is still the treatment of choice in patients with early-stage non-metastatic melanoma. Rising mortality rates clearly indicate that early diagnosis is not enough and more effective treatments are required both in the adjuvant and metastatic settings. Ten-year survival rates in patients treated with radical resection vary from 77 to 27%; survival depends on lesion thickness (Breslow), mitotic index, presence or absence of ulceration, microscopic or macroscopic involvement of regional lymph nodes, and the number of lymph nodes involved [1, 2]. In the past 15 years numerous studies, including several meta-analyses and systematic reviews, have analyzed the impact of adjuvant therapy with interferon (IFN), levamisole, bacillus Calmette-Guérin, various vaccines, chemotherapy or biochemotherapy [3]. When we conducted this survey, the only drug with a documented effect on recurrence-free survival and, to a lesser extent, on overall survival (OS) was recombinant IFN- α . The efficacies of chemotherapy, IFN- γ and vaccines have never been documented; on the contrary, in many studies vaccines were even harmful. The sometimes conflicting results have led to a lack of uniformity in clinical practice. A recent meta-analysis of data on 6,066 randomized patients in 14 clinical trials of IFN- α [4] found an 18% increase in 5-year disease-free survival (DFS) and an 11% reduction in the risk of death, though no optimal dose and/or duration was identified.

In Italy, recombinant IFN- α -2a is registered and reimbursed by the National Health Service at the dose of 3 MU s.c. 3 times a week for 12–18 months in patients with primary melanomas ≥ 1.5 mm and no lymph node metastases, while patients with lesions ≥ 4 mm or radically removed lymph node metastases are administered IFN- α -2b at 20 MU/m²/day, 5 days/week for 4 weeks followed by 10 MU/m²/day s.c. 3 times a week for 48 weeks. Pegylated IFN (Peginterferon- α -2b) is not registered in Italy for melanoma, despite evidence that it prolongs DFS, especially in patients with ulceration and microscopic nodal metastases [5]. No study to date has included patients with radically removed transit metastasis (stage N2c).

Systemic treatment of metastatic disease is even more controversial. Despite findings of increased overall response and longer time to progression in some studies, neither polychemotherapy nor biochemotherapy have been shown to increase OS compared to dacarbazine (DTIC) or temozolomide alone, and the former are significantly more toxic [6, 7]. In addition to limited efficacy, DTIC itself has never been compared to supportive therapy alone, and therefore there is no formal evidence of its

effectiveness. Only recently has an increase in OS in metastatic disease been reported using a new immunomodulating drug, ipilimumab [8, 9], and for melanoma harboring BRAF mutations a new BRAF inhibitor, vemurafenib [10]; however, those results were not available when this survey was performed and neither of these drugs is licensed in Italy.

We conducted this survey to analyze the clinical practice for the treatment of melanoma in the adjuvant and metastatic settings at hospitals throughout Italy.

Methods

Briefly, a nationwide survey of clinicians responsible for the diagnosis, therapy or follow-up phases of melanoma care in Italian hospitals was conducted. Italian hospitals with ≥ 200 beds ($n = 285$) were subdivided into 145 hospitals with 200–399 beds and 140 hospitals with ≥ 400 beds and a proportionally stratified random sample ($n = 120$ centers), stratified by number of beds and geographic distribution, was selected. Two or three clinicians were interviewed at each center, resulting in approximately 250 interviews and a predicted margin of error – 95% confidence level – of 7.7%.

Based on the findings, centers were grouped by number of new melanoma diagnoses per year into low- and high-volume centers, around the median value of 25. Variables were analyzed in the total sample/total Italian hospitals, and comparisons were made between high- and low-volume centers using Pearson's χ^2 test and the zeta test at 95% confidence level. Detailed methods are presented elsewhere in this issue [11].

Results

Adjuvant Therapy

A sample of 114 hospitals was divided according to the number of new melanoma diagnoses per year into high-volume centers ($n = 55$; >25 diagnoses/year) and low-volume centers ($n = 59$; ≤ 25 diagnoses/year), 25 diagnoses being the median value. Treatment decision-making was multidisciplinary in 92% of centers. Medical oncologists administer treatments and manage patients in adjuvant and metastatic settings in 89% of centers. A medical oncologist has a dominant role in 95% of low-volume centers ($p = 0.008$ vs. high-volume centers).

Adjuvant treatment was offered to 18% of patients in stage IIA, 37% in stage IIB and IIC, 75% in stage IIIA, 74% in stage IIIB, 71% in stage IIIC and 44% in stage IV. More low-volume centers administered adjuvant treatment to stage IV radically resected patients (56 vs. 30%; $p < 0.0001$); low-volume centers reported significantly higher values also for stages IIA, IIIB and IIIC ($p = 0.02$, 0.005 and 0.04, respectively) (table 1).

Table 1. Adjuvant therapy proposed to patients with melanoma according to disease stage; centers are grouped according to yearly melanoma diagnoses into high-volume (>25) and low-volume (≤25) centers

Examination schedule used	Type of center		
	high-volume (n = 55)	low-volume (n = 59)	all (n = 114)
Mean number of patients receiving adjuvant therapy	16.1	5.0	10.5
Patients receiving adjuvant therapy by disease stage			
IIA	11%	24%*	18%
IIB	33%	41%	37%
IIC	31%	43%	37%
IIIA	74%	76%	75%
IIIB	66%	82%**	74%
IIIC	65%	77%***	71%
IV	30%	56%****	44%

* p = 0.02; ** p = 0.005; *** p = 0.04; **** p = 0.003.

Table 2. Therapeutic strategies for high-risk patients with melanoma in Italian hospitals; centers are grouped according to yearly melanoma diagnoses into high-volume (>25) and low-volume (≤25) centers

Strategy	Type of center		
	high-volume (n = 55)	low-volume (n = 59)	all (n = 114)
Stage II			
Low-dose IFN for 1–3 years	43%	43%	43%
High-dose IFN for 1 year	20%	34%*	27%
Clinical trial	18%	14%	16%
Chemotherapy	2%	0%	1%
Not indicated	17%	9%	13%
Stage III			
Low-dose IFN for 1–3 years	8%	18%	50%
High-dose IFN for 1 year	65%**	36%	16%
Clinical trial	10%	11%	13%
Chemotherapy	7%	24%**	10%
Radiotherapy	0%	5%	3%
Not indicated	11%	6%	8%

* p = 0.04; ** p = 0.001.

When asked the question, ‘what are the priorities on the basis of which adjuvant therapy is administered?’, the high-volume centers indicated DFS as their first priority followed by OS, whereas the low-volume centers put OS as their first priority followed by DFS; in both high- and

low-volume centers quality of life (QOL) is the third priority, followed by toxicity and cost. Low- and high-volume centers gave the same reasons for not offering treatment, indicating as first priority QOL followed by toxicity, OS, DFS and cost. This choice was conditioned by patient age and comorbidities in 70% of centers, while factors such as patient expectations, willingness, and potential interference with work, logistics and daily life affected choice in less than one third, with no significant difference among groups.

When asked which type of adjuvant therapy was administered, there were no differences between the centers in stage II, where low-dose IFN therapy for 1–3 years was administered in 43% of centers. High doses for 1 year were administered in 20% of high-volume centers and 34% of low-volume centers (p = 0.04); 17% of high-volume centers versus 9% of low-volume centers did not indicate which treatment was administered (table 2). Regarding stage III, there was a significant difference in the use of high-dose IFN therapy, which was administered in 65% of high-volume centers versus 36% of low-volume centers (p = 0.001); the opposite tendency was found for chemotherapy, administered in 24% of low-volume centers versus 7% of high-volume centers (p = 0.001).

Overall, 5% of low-volume centers administered adjuvant radiotherapy to stage III patients versus 0% of high-volume centers. High-dose IFN was administered, regardless of stage, in 77% of patients, and there were no differences in the reported incidence of toxic effects among centers. Fatigue was the most frequently reported side effect (62%), followed by hepatotoxicity (59%), flu-like syndrome (51%), myelotoxicity (41%), mood disorders (26%), autoimmunity (11%) and fever (2%).

Metastatic Disease

Overall, 11% of centers did not treat patients with metastatic melanoma, with no difference between high- and low-volume centers. In first line, DTIC monotherapy was chosen most frequently in one third of centers (32%), with no differences among centers, while polychemotherapy was chosen in 23% of centers; participation in a clinical trial (12%) was the third choice. Biochemotherapy, fotemustine and temozolomide, alone or in combination, were administered at approximately 10% of centers, showing no substantial difference between high- and low-volume centers. Interleukin-2 alone was administered in 8% of the low-volume centers compared to 1% of the high-volume centers (not significant) and it was generally given s.c. in low doses.

Second-line therapy was administered at 89% of centers, with no difference between groups, and the most widely used drug was fotemustine, administered in 43% of high-volume centers and 29% of low-volume centers ($p = 0.09$), followed by temozolomide (20%), polychemotherapy (16%) and DTIC (9%). There was a significant difference between low- and high-volume centers in administration of DTIC as second-line therapy: 15 versus 3%, respectively ($p = 0.02$). 11% of high-volume centers and 5% of low-volume centers participated in clinical trials. There was also a difference between groups regarding use of interleukin-2 in second-line therapy: 7% of low-volume centers and none of the high-volume centers ($p = 0.03$).

Radiotherapy was administered in 60% of centers with no significant difference between groups. It was mainly administered to patients with brain metastases (93%), and the percentages were similar across centers. Radiotherapy for bone metastases was used more often in low-volume centers (90 vs. 67%; $p < 0.0001$), as was palliative therapy for hemorrhagic lesions (26 vs. 3%; $p = 0.004$). Palliative treatment of symptomatic lesions was administered in 54% of centers and was associated with symptomatic cutaneous lesions in 15% of centers.

Adjuvant lymph node basin radiotherapy in patients at high risk of recurrence was performed in 26% of all hospitals, and more often in low-volume centers (32 vs. 22%; $p = 0.24$).

Discussion

The high number of participating hospitals and their wide distribution in the country make these results provide a realistic picture of treatment and follow-up of melanoma patients in Italy.

There is a propensity to work in multidisciplinary teams. Half of the centers always base treatment decisions on multidisciplinary discussion, while 42% do this for particular cases. Therapy is offered and managed by medical oncologists both in the adjuvant setting and in advanced disease. However in 20% of high-volume centers and 12% of low-volume centers, adjuvant treatment is managed by dermatologists, despite the absence of a recognized dermatology-oncology specialization in Italy. Adjuvant therapy is offered in stages IIA through IV, more often in low-volume centers (difference only significant for stage IV). Medical oncologists deal prevalently with patients at high risk of recurrence and death, and may have a different perception of death risk and less concerns

about treatment toxicity, resulting in a propensity to offer adjuvant treatments more often than dermatologists, who generally follow lower-risk patients.

Considering the risk of recurrence and death, it was surprising that stages IIB and IIC tend to receive less treatment than stage IIIA. The 5-year survival rate for stage IIC is 45% and 10-year survival is 32%; in stage IIIA 5-year survival varies from 63 to 70%, and 10-year survival varies from 57 to 63% [1]. The 12-month high-dose IFN studies conducted by the Eastern Cooperative Oncology Group (ECOG) 1684 [12], 1690 [13] and 1694 [14] revealed no differences in benefit between stage II and III. Meanwhile, stage IIC was the only subgroup to benefit from treatment in the European Organization for Research and Treatment of Cancer (EORTC) study 18952 [15], which used low doses (5 MU) for 25 months or intermediate doses (10 MU) for 12 months. Thus the therapeutic approach is not consistent with the evidence and can only be explained as a misperception of the risk, though this is difficult to understand given that the reduced treatment in stage IIB and IIC is even more pronounced in high-volume centers.

Another unexpected finding is the tendency to propose adjuvant therapy in stage IV in about half of the low-volume centers and in a third of the high-volume centers. No study supports this approach, and this attitude seems to be based more on clinician fears than on scientific evidence, moreover considering that the main reasons for adjuvant therapy were an increase in DFS and OS, while those against it were toxicity and impact on QOL.

Nevertheless, treatments that have not been shown to change DFS or OS were administered, such as adjuvant chemotherapy. These decisions are more likely based on expectations than evidence. Likewise, risk of impaired QOL is the main reason for not offering adjuvant therapy, but at the same time the patient's expectations, interference with work, and logistics are considered in less than 30% of cases. Since the only prospective study [16] evaluating QOL during treatment with adjuvant IFN was published 2 years after this survey was done, these findings may represent worries transferred by the physicians to their patients.

Cost was the least important factor in treatment decision-making, presumably because treatments are fully covered by the National Health Service. Few adjuvant treatments were given in the context of clinical trials, and more in stage II than in stage III, and interestingly, with no difference between high- and low-volume centers.

The significant difference in the use of high-dose IFN therapy in stage III between high- and low-volume cen-

ters may result from confidence acquired through practice that leads to increased use of the drug, or to experience acquired through participation in clinical studies using high doses. Toxicity with the high-dose IFN therapy was as expected, except for a low reporting of fever (2%), probably included in 'flu-like syndrome'. The 11% incidence of autoimmunity in patients treated with IFN is lower than that reported in the literature [17], and it was impossible to verify whether this was the clinical incidence or a prospective autoimmunity monitoring.

Radiotherapy is rarely used as adjuvant therapy. However, this response is contradicted by the response to the specific question on the use of radiotherapy, to which high-volume centers responded that they use it in 22% of patients at high risk of lymph node recurrence and low-volume centers in 32%. These percentages are higher than expected based on the lack of randomized trials clearly supporting a survival benefit from adjuvant radiotherapy after lymphadenectomy at high risk of relapse [18, 19]. However, various guidelines, including those of the Italian Association of Medical Oncology, recommend adjuvant radiotherapy in patients with extra-nodal involvement, more than 4 lymph nodes involved, or diameter >4–6 cm, especially if located in the head or neck.

Treatment of metastatic disease showed a similar approach among high- and low-volume centers with only two (non-significant) differences: more participation in clinical studies in high-volume centers and a use of interleukin-2 <10% and mainly in low-volume centers. Dose and route of administration were not investigated.

Considering temozolomide, fotemustine and DTIC together, about half of the patients received monotherapy, while one third received polychemotherapy or biochemotherapy with no difference between groups. This answer shows that despite its higher toxicity without increased efficacy, biochemotherapy [20] is still used in one out of three patients. Despite the low efficacy, chemo-

therapy is used more than experimental treatments, even if those represent a better option both for the patients and clinicians. Overall, 11% of centers do not manage stage IV patients, suggesting referral to other centers, and this should further facilitate enrolment in clinical trials.

Soon two new drugs, ipilimumab and vemurafenib, that have OS benefits in metastatic patients, will be reimbursed in Italy for second-line treatment of metastatic disease and for treatment of patients with melanomas harboring BRAF mutations. This should completely change treatment for metastatic disease, even if their high cost will affect the use that will be strictly regulated by AIFA (Italian Medicines Agency).

The Italian Melanoma Intergroup used this survey to improve the quality of care and redirect financial resources. The first action was to implement education and collaboration between dermatologists, medical oncologists and surgeons organizing multidisciplinary educational masters in all Italian regions. The second was to revise and divulge new national guidelines in collaboration with the Medical Oncology Association and regional agencies. The third was to implement the construction of regional melanoma multidisciplinary networks aimed at increasing melanoma knowledge and facilitating the referral and accrual in clinical studies. Fourth we started in 2011 a national melanoma registry collecting all new melanoma cases and treatments, and this will provide us rapid and prospective information on the efficacy of the implemented actions.

Disclosure Statement

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