Managing Hodgkin Lymphoma

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Hello, my name is Franco Cavalli. I am the Scientific Director of the Oncology Institute of Southern Switzerland and President of the International Conference on Malignant Lymphomas, which takes place every second year in Lugano. I am here today to discuss the management of refractory and relapsed Hodgkin lymphoma, but not only, we will have also something about the first-line treatment.

Let us start. As the cure rate for Hodgkin lymphoma is approaching 90%, it has become at least as important to be able to decrease the treatment-related long-term side effects as it is to further increase the therapeutic activity of the first-line treatment. In fact, we know that after 10 to 15 years, treatment-related cardiopulmonary events and second neoplasm are more frequent than relapses of the lymphoma. PET/CT today represents most probably, and at least in the near future, the best possibility to achieve both goals: to decrease the long-term toxicity and to improve their therapeutic outcome.

As it was stated in the report prepared by the committee, which I have to discuss the role of PET in lymphomas at the Lugano conference, PET-guided treatment is today at least in Hodgkin lymphoma already a reality. Based on current data, we can, in fact expect that, thanks to the PET-guided treatment, we will be able to avoid, at least in 40% of the patients with early Hodgkin lymphoma, radiotherapy. While in advanced Hodgkin lymphoma, we will be able to spare at least to four-fifths of the patients, a more intense chemotherapy since ABVD would be enough to achieve PET negativity and only the 20% of the patients who will still be PET positive will then need an intensification by BEACOPP.

This is very important also for the relapsed patients since we know that high-dose chemotherapy and autologous transplant are able to cure 30% only of the patients who have been primarily treated with BEACOPP, but 60% of those who have been primarily treated with ABVD.

So, let us see the overall management of relapsed patients. Well, there are two special situations in which a specific treatment can be used. This is first the case in patients who have a very limited nodal relapse, which can be encompassed in an involved field of radiotherapy in a section of the body which has not been previously eradiated. Those patients should be treated with radiotherapy alone. The oldest special situation is represented by very late relapses, relapses after 10-15 years, which are very infrequent

but they occur. In that situation, the patient might be managed as though it would be the management of primary case; but in the overall majority of relapsed patients, the treatment of choice today is salvage treatment first, and if the lymphoma proves to be still chemo-sensitive, then the patient will have to be moved to a high-dose chemotherapy and reinfusion of autologous stem cells. It is important also to note that a moderate PET positivity after salvage treatment is not something which would prevent people to move the patients to the high-dose chemotherapy and the auto transplant.

But, alas, a few patients will still relapse after high-dose chemotherapy and auto transplant, and how should we manage them? Well, in the past, we had very few possibilities. Today, different drugs have proven to be efficacious. There are mTOR inhibitors, which have shown an interesting anti-tumor activity. Histone deacetylase inhibitors have also shown an interesting activity, but everybody today agrees that as a drug which has shown the most promising and the most interesting and consistent therapeutic activity is brentuximab. Brentuximab is very efficacious in those patients, and people have been very surprised to see how many patients, even after auto transplant, can still respond when they further relapse to brentuximab.

On top of that, the drug if correctly administered has very manageable toxicity and which can be easily foreseen. Now, those data have convinced people to move brentuximab earlier in the treatment of patients with relapsed Hodgkin lymphoma. At the Lugano meeting, the Memorial Sloan-Kettering Group presented data, Dr. Moskowitz presented them, in which patients who were relapsing, they were first treated with brentuximab alone, the idea being to avoid if possible the salvage chemotherapy always is the philosophy of trying to undertreat the patients to avoid if possible an intense chemotherapy in order to decrease as much as possible the long-term negative side effects.

So in that study, one-fourth of the patients went into a complete response with brentuximab alone and could then go on to the high-dose chemotherapy and the auto transplant and could so be spared the negative effect of intense chemotherapy. But brentuximab has proven to be efficacious also in the so-called primary refractory patients. In fact, by using PET-guided treatment, the number of primary refractory patients have decreased since most of them will respond after ABVD when they are switched to BEACOPP, but there are still those who do not respond even to BEACOPP, and different small studies have demonstrated that the important percentage of those patients will respond to brentuximab. It is, therefore, understandable that everybody is trying today to incorporate brentuximab into the first-line treatment.

This has proven not to be so easy. In fact, the combination of ABVD with brentuximab demonstrated too high pulmonary toxicity, and it was so correctly decided that this combination should be abandoned. On the other side, the results of the German HD13 trials are helping us perhaps in finding the right avenue about how to incorporate brentuximab in the first-line treatment. In that study, ABVD was compared to similar combinations either without bleomycin or without dacarbazine. It very soon demonstrated that by avoiding dacarbazine, the therapeutic outcome worsened significantly. In the case of bleomycin, the difference was much smaller; but at the end of the trial, ABVD proved superior to the combination without bleomycin. Therefore, the conclusion that researchers have now drawn is that we should develop a treatment which will include AVD (Adriamycin, vinblastine and dacarbazine) drop bleomycin and use instead of that brentuximab. So, this trial is ongoing. The number of patients who have been treated is still too limited, but there are great hopes in the lymphoma community that this combination will prove first feasible and then probably and possibly more efficacious than the traditional ABVD. Would that be the case, then we would have the possibility to make another jump forward in the treatment of Hodgkin lymphoma. Already now, as it has been shown by the Vancouver data, ABVD which in the past gave a complete response in the order of 70% is achieving today a complete response rate in the order of 90%. If AVD plus brentuximab will be proven to be more efficacious, we would most probably at the end not be very far from a complete response rate in the order of 100%, and that is the hope of all physicians who are treating patients with Hodgkin lymphoma.