IMPACTFACTOR

nature REVIEWS CLINICAL ONCOLOGY

Localised non-bulky Hodgkin lymphoma – future questions

Bertrand Coiffier and Olivier Casasnovas

Late toxicities from radiation therapy are frequent in patients with Hodgkin lymphoma and can hamper survival. These late toxicities should decrease with modern radiation therapy, but results are not mature and so the importance of this decrease is still unknown. Hence, all studies in Hodgkin lymphoma must report long-term outcome.

This article was first published in ***Nature Reviews Clinical Oncology*** vol. 9 no.3, and is published with permission.
 doi:10.1038/nrclinonc.2012.7

In a recent publication, Meyer et al.[1] presented a 12-year follow-up of patients with localised non-bulky Hodgkin lymphoma included in a study that compared chemotherapy to a radiation-based treatment.[1] Inclusion criteria in this study – previously published with a short follow-up period[2] – were not-too-low risk patients (stage IA with one involved node and erythrocyte sedimentation rate [ESR] <50 mm were excluded) but not-too-high risk (patients with tumour diameter >9 cm, a tumour larger than one-third of the chest wall diameter or with intra-abdominal disease were excluded).[2] The study design was quite complicated and divided the patients into a chemotherapy arm and a radiation arm. After randomisation, patients in the chemotherapy arm received doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD); patients with a complete remission or unconfirmed complete remission after two cycles received four cycles in total, and the remaining patients received six cycles in total. Patients assigned to the radiation arm with at least one unfavourable risk factor (>39 years old, ESR >49 mm, more than three disease sites, or mixed cellularity or lymphocyte-depleted histology) received two cycles of ABVD before radiotherapy, whereas those patients with no risk factor received only radiotherapy (subtotal nodal radiation therapy). The study was opened to enrolment in January 1994 and terminated in April 2002, but only 405 of the 450 patients had completed enrolment. The decision to terminate enrolment was taken by the Data and Safety Monitoring Board because by that time the radiation protocol was outdated. This trial was a complicated study with too many possible biases and difficult-to-interpret results that would likely have had little effect on the existing pool of Hodgkin lymphoma trial data. The first results with a 4.2-year median follow-up period showed a significantly better progression-free survival (PFS; or freedom-from-disease progression as it was called in the study) for patients randomised to the radiation arm, with a similar overall survival in both arms but a slight increase of death from causes other than Hodgkin lymphoma in the radiation arm.[2]

This study was saved by the late analysis, even though 14% of the

patients were lost to follow up;[1] late results (median follow-up period 11.3 years) showed a lower 12-year PFS (87% vs 92%; hazard ratio [HR] 1.91; *P*=0.05) but an improved 12-year overall survival rate (94% vs 87%; HR 0.50; *P*=0.04) for the patients in the chemotherapy arm compared with the radiotherapy arm. This longer overall survival was related to a lower number of patients dying from causes other than Hodgkin lymphoma (12 deaths in the ABVD arm versus 24 in the radiation arm). These numbers will likely continue to increase because the number of secondary cancers is much higher in the radiation-based arm than the chemotherapy arm (23 vs 10). These results raise several questions: first, what is a good balance between chemotherapy and radiotherapy in patients with localised Hodgkin lymphoma? Second, is it possible to reduce the intensity of therapy in some patients? Third, when can results from a randomised study be considered definitive in patients with Hodgkin lymphoma? Finally, what is the best endpoint for future studies in patients with Hodgkin lymphoma?

The current treatment for localised Hodgkin lymphoma – a short course of chemotherapy plus low-dose involved-field radiotherapy – cures over 90% of patients.[3,4] To increase this cure rate, deaths after relapse or from other causes need to be decreased or avoided. The treatment of relapsed patients has improved recently with the use of high-dose therapy with stem-cell transplants and new drugs. The ABVD regimen was associated with few severe late complications; secondary myelodysplastic syndrome (MDS) or acute myeloid leukaemia (AML) are rare and the dose of doxorubicin is usually too low to induce cardiac failure.[5] By contrast, MDS and AML are more frequent with combined therapy, and secondary solid tumours increase over time after radiotherapy.[6] The 30-year incidence of secondary cancers with mantle radiation therapy is around 30% but decreases by 60% to 12% with involved-field radiation therapy. The long term follow-up of another trial – EORTC/GELA H10 – will give insights on the risk of a secondary cancer after involved-node radiation therapy. Cardiovascular complications are also more frequent after radiotherapy, even though they are less common now with the standard use of involved-field radiation therapy.[7]

Is it possible to reduce the use of radiotherapy or to reserve it for a subgroup of patients with localised Hodgkin lymphoma? To date, two studies comparing results of chemotherapy alone versus the combined modality have been reported with a short follow-up period; these studies demonstrated either no PFS benefit[8] or a marginally better PFS[9] for the combined modality and the same overall survival for both treatment modalities.[8,9] To a certain extent, the Meyer et al.[1,2] study also compared both modalities, as 73% of the patients included in the radiation arm received a combination of chemotherapy plus radiation. However, long-term outcome favours the chemotherapy arm, the extended radiation arm being hampered by an excess of death due to late toxic effects.[1]

On the basis of these three studies,[1,2,8,9] there is no clear evidence that we can safely omit a modern radiotherapy treatment in all patients with localised non-bulky Hodgkin lymphoma because PFS results are controversial and data on long-term overall survival with current combined treatments are unavailable.

Recently, response-adapted therapy has emerged as a new concept that is supported by the development of functional imaging. In this therapy design, patients achieving complete remission as determined by ^{18}FDG PET assessment after two chemotherapy cycles will not receive radiotherapy, but those without a complete remission will. To generalise this idea, randomised studies must show that these patients with early complete remission will not have a shorter survival than those receiving radiotherapy. Preliminary results of PET relevance to identify patients eligible for radiotherapy are in favour of this hypothesis, at least in advanced-stage Hodgkin lymphoma.[10] However, the majority of these studies are ongoing and definitive results have not yet been published. Involved-field radiation therapy remains the standard treatment for these patients until such results demonstrate that radiotherapy is not necessary in early responders. Furthermore, an additional issue to address is establishing suitable rules for interpreting interim PET scan results.

The trial published by Meyer et al.[1,2] is also remarkable because results were modified from the early[2] to the later[1] report. Although PFS results did not change, overall survival changed from the same in both arms to being better in the chemotherapy arm, because of late toxic events in the radiotherapy arm. Clearly, for diseases in which overall survival is very good, such as localised Hodgkin lymphoma,

Practice points

- Radiotherapy is associated with late toxic effects
- Long-term follow up (>10 years) should be mandatory in Hodgkin lymphoma trials
- Chemotherapy alone might be sufficient treatment for selected patients

results must not be reported early on and a minimum of 10 years is necessary to allow the analysis of the late effects and deaths caused by late toxic effects.

It is too frequently the case that study reports from trials in patients with Hodgkin lymphoma or non-Hodgkin lymphomas are published with less than five years of follow up. These early results are important, particularly if there is a difference in overall survival, or if a potential change for clinical practice is reported, but they must be called 'preliminary' and followed by the publication of mature results.

This recommendation for the publication of mature results leads to the evaluation of endpoints of studies that assess the first-line treatment of treatment-naive patients. Assessment of PFS allows the evaluation of the efficacy of the tested therapy, but not late toxicity. When there is a large difference between the two arms (larger than 20%), the early results are usually confirmed by late results; however, when the difference is small (less than 10%) results must be called preliminary and need to be confirmed by other studies and/or by mature results.

In summary, our first goal is to cure patients with cancer, but when long-term survival is over 90%, we need to look at the possible toxic effects of treatment on survival. All randomised studies showing a benefit in the experimental arm must be reported with a median follow-up longer than 10 years to allow this assessment to be completed.

References

1. RM Meyer et al. ABVD alone versus radiation-based therapy in limited-stage Hodgkin's lymphoma. *NEJM* http://dx.doi.org/10.1056/NEJMoa1111961
2. RM Meyer et al. (2005) Randomized comparison of ABVD chemotherapy with a strategy that includes radiation therapy in patients with limited-stage Hodgkin's lymphoma: National Cancer Institute of Canada Clinical Trials Group and the Eastern Cooperative Oncology Group. *JCO* 23, 4634–42
3. A Engert et al. (2010) Reduced treatment intensity in patients with early-stage Hodgkin's lymphoma. *NEJM* 363:640–652
4. JO Armitage. (2010) Early-stage Hodgkin's lymphoma. *NEJM* 363:653–662
5. D Hodgson. (2011) Late effects in the era of modern therapy for Hodgkin lymphoma. *Hematology Am Soc Hematol Educ Program* 2011:323–329
6. AJ Swerdlow et al. (2011) Second cancer risk after chemotherapy for Hodgkin's lymphoma: a collaborative British cohort study. *JCO* 29:4096–4104
7. BM Aleman et al. (2003) Long-term cause-specific mortality of patients treated for Hodgkin's disease. *JCO* 21:3431–39
8. DJ Straus et al. (2004) Results of a prospective randomized clinical trial of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) followed by radiation therapy (RT) versus ABVD alone for stages I, II, and IIIA nonbulky Hodgkin disease. *Blood* 104:3483–89
9. H Eghbali et al. (2005) Comparison of three radiation dose levels after EBVP regimen in favorable supradiaphragmatic clinical stages I-II Hodgkin's lymphoma: preliminary results of the EORTC-GELA H9-F trial [abstract]. *Blood* 106:a240
10. A Engert et al. (2011) Reduced intensity of chemotherapy and PET-guided radiotherapy in patients with advanced stage Hodgkin lymphoma: The GHSG HD15 final results [abstract]. *Ann Meeting Am Soc Hematol* a589

Author affiliations

Bertrand Coiffier, Department of Haematology, Centre Hospitalier Lyon-Sud, Pierre-Bénite, France; Olivier Casasnovas, Department of Haematology, Hôpital le Bocage, Dijon, France

First-line bevacizumab for ovarian cancer – new standard of care?

➜ Susana Banerjee and Stan Kaye

Demonstration of the clinically significant activity of bevacizumab in advanced-stage ovarian cancer has attracted a great deal of interest. Here, we summarize the two positive phase III trials that led to EMA approval of bevacizumab as first-line therapy and discuss the optimum use of the drug in this disease.

This article was first published in ***Nature Reviews Clinical Oncology*** on 28 February 2012, and is published with permission. doi:10.1038/nrclinonc.2012.28

In December 2011, two positive phase III trials[1,2] that assessed bevacizumab in patients with ovarian cancer were reported in the *New England Journal of Medicine*; these results led to the EMA approval of the drug as first-line treatment in combination with carboplatin and paclitaxel for this disease.[3] Bevacizumab is currently the most widely tested antiangiogenic agent for the treatment of cancer. Bevacizumab is a monoclonal antibody that targets the VEGF pathway, which has a critical role in ovarian function as well as in the spread of ovarian cancer.[4] Therefore, positive results from clinical trials assessing bevacizumab in this notoriously difficult-to-treat disease have been eagerly anticipated.

The first study (GOG-0218) was reported by Burger et al.[1] and was a double-blind, three-arm, placebo-controlled study in 1873 patients with newly diagnosed stage III (incompletely resected with residual disease >1 cm) or stage IV epithelial ovarian cancer. Patients were randomly assigned to one of three treatments: combination chemotherapy (carboplatin–paclitaxel), carboplatin–paclitaxel chemotherapy plus concurrent bevacizumab, or carboplatin–paclitaxel

chemotherapy plus concurrent and maintenance bevacizumab. The bevacizumab dose was 15 mg/kg for up to 22 cycles (15 months total). After a protocol amendment, stage III patients with macroscopic residual disease of ≤1 cm were also included. Nevertheless, all patients enrolled had advanced-stage disease and their overall outlook was worse than those patients assessed in the second study, ICON7.[2]

Perren et al.[2] published the results from the ICON7 study. The trial randomly assigned patients to one of two arms: 1528 patients received carboplatin–paclitaxel chemotherapy with or without concurrent and maintenance bevacizumab. Bevacizumab was given at 7.5 mg/kg (half the dose used in GOG-0218) for a total of 18 cycles (12 months total). In this trial, 9% of patients had high-risk, early-stage disease (FIGO stage I or IIA, clear cell or grade 3 histology) whereas 30% were at the highest risk for progression (FIGO stage IV, or stage III and >1 cm residual disease).

The primary endpoint in both trials was progression-free survival (PFS), which was evaluated using RECIST and Gynecologic Cancer Intergroup (GCIG) CA125 criteria in GOG-0218; only RECIST criteria were included in the assessment in ICON7. Despite key differences, for both studies the primary endpoint was met for concurrent and maintenance bevacizumab. In GOG-0218, median PFS was extended by 3.8 months (14.1 months vs 10.3 months; $P<0.001$).[1] In the ICON7 trial, the median PFS was 17.3 months in the chemotherapy-alone arm compared to 19.0 months with the addition of bevacizumab (HR 0.81; $P=0.004$).[2]

In GOG-0218, an additional analysis was carried out that did not take account of CA125 progression (that is, only interpreting the response based on RECIST criteria); in this analysis, the median PFS was six months longer in the group receiving bevacizumab (concurrent and as maintenance) compared to the chemotherapy-alone control arm (12 months vs 18 months; HR 0.645; $P<0.001$).[1] However, this analysis, which was required by the regulatory agencies, has been criticised owing to the bias associated with unequal censoring in the two arms.

In ICON7, the magnitude of PFS improvement is relatively modest (1.7 months);[2] however, a preplanned analysis demonstrated that the benefit of bevacizumab is greater in patients defined to be at the highest risk of progression. The 3.6-month improvement in PFS seen in this subgroup using restricted means analysis (restricted means 14.5 months vs 18.1 months; HR 0.73; $P=0.002$) is similar to the difference in PFS reported in GOG-0218 for the equivalent arms (3.8 months).

For the assessment of the effects of bevacizumab treatment on overall survival, final mature data are awaited. However, in ICON7, an improvement in overall survival with bevacizumab in the high-risk group was particularly noteworthy (28.8 months vs 36.6 months; HR 0.64, 95%CI 0.48–0.85; $P=0.002$).[2] The demonstration of a survival benefit of almost eight months in patients with a poor prognosis is very encouraging.

Toxic effects were as expected, with hypertension grade ≥2 being common (23% of patients in the GOG-0218 study; 18% of patients in the ICON7 study) but generally well controlled. Overall, bevacizumab treatment was well tolerated. Although bowel perforations had been reported in earlier bevacizumab trials,[5] these perforations were rare events in GOG-0218 (<3% of the patients) and ICON7 (1% of the patients). However, the incidence was higher with bevacizumab therapy compared to control arms.

Based on these new trial results, is it possible to say that bevacizumab is the new standard of care? To answer this, several questions need to be addressed. First, which patients should be offered bevacizumab? Although both studies met their primary endpoints for the whole trial population, it could be argued that given the overall survival benefit seen in high-risk patients in ICON7,[2] women with stage IV or stage III >1 cm residual disease should be considered for first-line treatment. The OCEANS study,[6] in which patients with recurrent platinum-sensitive disease were treated with bevacizumab in combination with chemotherapy (carboplatin with gemcitabine), provides a new dimension to this issue. This study reported a significant improvement in PFS with the addition of bevacizumab (8.4 months vs 12.4 months; HR 0.48; $P<0.0001$) and strongly suggests a role for bevacizumab in this setting of recurrent disease.[5] Therefore, a reasonable proposal for patients optimally debulked and thus at a lower risk of early relapse would be to reserve bevacizumab until first recurrence.

The second question is what is the optimal dose of bevacizumab? The licensed dose of bevacizumab, based on the PFS data of GOG-0218, is 15 mg/kg.[3] However, when comparing PFS improvement in a similar patient population (high-risk) in ICON7, there is no difference in PFS improvement between the groups receiving 15 mg/kg and 7.5 mg/kg. The 7.5 mg/kg dose is likely to be more cost-effective and, so far, this is the dose which is associated with an overall survival benefit.

Based on the available data, should bevacizumab maintenance be extended

Practice points

The addition of bevacizumab given concurrently with chemotherapy and continued as maintenance treatment significantly increases progression-free survival as first-line therapy for ovarian cancer, in particular for those patients at high risk of progression.

until disease progression? The maximal treatment effect, as indicated by the greatest separation of PFS curves in GOG-0218 and ICON7, coincided with the end of planned bevacizumab treatment. When bevacizumab is discontinued, the impression is that the disease returns promptly and this is in keeping with observations in other cancers.[7] Results from the OCEANS study,[6] seemingly superior to the GOG-0218 and ICON7 results, were achieved when bevacizumab was continued until disease progression. Taken together, these findings suggest that bevacizumab therapy until disease progression is warranted.

A fourth question is: should bevacizumab be given in combination with chemotherapy (in addition to maintenance) for first-line therapy? The lack of PFS difference between the chemotherapy-alone control arm and the concurrent bevacizumab arm in GOG-0218 would suggest that the main impact of bevacizumab is as maintenance treatment post chemotherapy. However, the significantly increased response rates (48% vs 67%; $P<0.0001$) in the subset of patients with measurable disease following debulking surgery in the bevacizumab arm of the ICON7 trial, and in the OCEANS study (57% vs 79%; $P<0.0001$), indicates clearly that bevacizumab enhances chemosensitivity, and its omission from concurrent treatment may be unwise.

Finally, does the extent of benefit reported so far justify the cost? For those patients with the worst initial outlook, a PFS improvement of four months translates into almost double the time without chemotherapy before the first recurrence. This improvement does represent an important clinical benefit and patient selection is therefore paramount. The identification of a group of patients likely to benefit most from bevacizumab treatment could tip the balance towards a cost-effective therapy.

These important studies by Burger et al.[1] and Perren et al.[2] demonstrate that the anti-VEGF strategy has real potential in ovarian cancer. In addition to bevacizumab, other agents targeting this pathway are in active development[4] and future trials will undoubtedly clarify the best strategy to use all these approaches for the benefit of our patients.

Details of the references cited in this article can be accessed at www.cancerworld.org

Competing interests:
Stan Kaye declares an association with Roche. See the article online for full details of the relationship. Susana Banerjee declares no competing interests

Author affiliations
Susana. Banerjee, the Royal Marsden NHS Foundation Trust, London, UK; Stan Kaye, the Institute of Cancer Research and Royal Marsden Hospital, Sutton, UK