11. Philip TO, Mathieu P, Chauvin F, *et al.* A 5-year study (1990–1994) on screening babies for neuroblastoma in France. Methodological aspects and preliminary observations. In Sawada T, Matsumura T, Kizaki Z, eds. *Proceedings of the 3rd International Symposium on Neuroblastoma Screening.* Kyoto Prefectural University of Medicine, 1994, 75–84.
12. Erttmann R, Schilling FH, Dohrmann S, *et al.* Two years experience of the German pilot study for the early detection of neuroblastoma. In Sawada T, Matsumura T, Kizaki Z, eds. *Proceedings of the 3rd International Symposium on Neuroblastoma Screening.* Kyoto Prefectural University of Medicine, 1994, 65–67.
13. Brodeur GM, Nakagawara A. Molecular aspects of neuroblastoma and its prognosis. In Sawada T, Matsumura T, Kizaki Z, eds. *Proceedings of the 3rd International Symposium on Neuroblastoma Screening.* Kyoto Prefectural University of Medicine, 1994, 159–164.
14. Miyagi Y, Nagashima Y, Tanaka Y, *et al.* Studies for the genes expressed in neuroblastoma detected by mass screening. In Sawada T, Matsumura T, Kizaki Z, eds. *Proceedings of the 3rd International Symposium on Neuroblastoma Screening.* Kyoto Prefectural University of Medicine, 1994, 148–151.
15. Kaneko Y, Maseki N, Sakurai M, *et al.* Chromosomes and screening for neuroblastoma. *Lancet* 1988, **1**, 174–175.
16. Schilling FH, Erttmann R, Ambros PF, *et al.* Screening for neuroblastoma. *Lancet* 1994, **344**, 1157–1158.
17. Kerbl R, Urban C, Starzl I, *et al.* Neuroblastoma with *MYCN* amplification detected by urine: mass screening in infants after the sixth month of life. *Med Ped Oncol* 1993, **21**, 625–626.
18. Estève J. Some remarks on power calculation for neuroblastoma screening. In Sawada T, Matsumura T, Kizaki Z, eds. *Proceedings of the 3rd International Symposium on Neuroblastoma Screening.* Kyoto Prefectural University of Medicine, 1994, 47–51.

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Clinical Strategies for the Treatment of Neuroblastoma

D. Niethammer and R. Handgretinger

Neuroblastoma is the most common solid extracranial tumour in childhood. In spite of intensive efforts of clinicians and scientists the prognosis for advanced disease is still poor. This paper presents a short review of the state-of-the-art in conventional treatment including surgery, chemotherapy, and radiation. This is followed by a review of the treatment attempts with high dose chemotherapy followed by autologous bone marrow or stem cell transplantation. One of the main problems with this approach is the contaminating tumour cells. Finally the various immunotherapeutic strategies are summarised which are used to remove minimal residual disease. Later, our new approach, combining various treatment modalities, is described.

Key words: neuroblastoma, clinical strategies, high dose chemotherapy, immune therapy
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INTRODUCTION

NEUROBLASTOMA IS the most common solid extracranial tumour in childhood. It shows a remarkable biological heterogeneity, ranging from spontaneous differentiation or regression to progression in spite of intensive multimodal therapy. According to clinical and radiological criteria, 4 stages were initially defined by Evans and associates [1]. Recently, the Forbeck classification has been introduced based on additional surgical and histological criteria [2]. The clinical outcome for lower stages of neuroblastoma is normally good, whereas the prognosis for advanced stage III and stage IV tumours is poor. Additional risk factors, such as elevated lactate dehydrogenase (LDH), resectability of primary tumour, age > 9 months at diagnosis, decreased white blood cell count, or the histological presence of undifferentiated tumour tissue, have been described [3]. Recently, additional biological features have been identified which may predict the clinical outcome [4–7]. Based upon DNA ploidy, chromosome 1p deletion, *MYCN* amplification, loss of heterozygosity (LOH), and expression of the high affinity nerve growth factor receptor p140^{trk} (*TRKA*) risk groups can be identified. Tumours within the "good risk group" are likely to differentiate or regress spontaneously, or respond favourably to chemotherapy. In the "bad risk group", aggressive multimodal therapy regimens or innovative therapeutic modalities are justified. All therapeutic modalities used in neuroblastoma should, therefore, be adapted to the stages and biological risk factors. This should prevent overtreatment of low risk neuroblastomas on the one hand, and undertreatment of high risk tumours on the other.

The aim of this review is to discuss risk-adapted therapeutic

Correspondence to Dr D. Niethammer at the Children's University Hospital, Department of Pediatric Hematology/Oncology, Rümelinstrasse 23, 72070 Tübingen, Germany.
Both authors are at the Children's University Hospital, Department of Pediatric Hematology/Oncology, Tübingen, Germany.

strategies in the treatment of neuroblastoma. Since most patients present with high risk tumours and very poor prognosis, most of this paper deals with the multimodal treatment of high risk neuroblastoma.

SURGERY

Primary surgery is the treatment of choice in patients with localised neuroblastoma. Histological and molecular characterisation of the resected tumour is necessary for the exact staging of the patient and for designing further therapeutic strategies. The molecular and cytogenetic characterisation should, at least, include ploidy, presence or absence of chromosome 1p deletion and status of *MYCN* amplification. In case of non-resectability, some courses of chemotherapy can be given followed by surgery. The aim should be the complete surgical resection of the tumour. However, this might not be necessary for the majority of intrathoracic neuroblastomas.

CHEMOTHERAPY

A number of trials have been performed in neuroblastoma in order to evaluate the role of chemotherapy. The German Society for Paediatric Oncology/Haematology (GPOH) initiated co-operative treatment protocols for neuroblastoma (NB) in 1979. Since then, four consecutive trials have been performed, starting in 1979 (NB 79, 82, 85 and 90). The event-free survival (EFS) for patients with stage IV disease in these trials was 0.04, 0.18, 0.19 and 0.37, respectively. A multivariate analysis showed disease-free survival (DFS) of 90% after 6 years, in the absence of identified risk factors (elevated LDH at diagnosis, age >9 months at diagnosis, primary tumour not resectable) for stage III patients. In the presence of all three risk factors, DFS was 22%. In stage IV neuroblastoma, identified risk factors were elevated LDH, histological grade 3 (after Hughes), primary tumour not resectable, and decreased white blood cell count (F. Berthold). The survival of patients without these risk factors was 37%, whereas the presence of elevated LDH and some of the other risk factors decreased the survival to 8%.

Other investigators have not reported significantly better results, although the chemotherapeutic regimens have been intensified [8–12]. In most of these studies, the initial responses were good. In the GPOH studies, 30–40% complete remissions (CR) and 60–70% partial remissions (PR) were obtained, and some tendency to prolong EFS and survival time was seen with dose intensification of the chemotherapy regimens or the introduction of a maintenance therapy. Clinical protocols investigating the role of intensified induction therapies, such as the OPEC/OJEC or rapid COJEC protocol, including the use of haematopoietic growth factors, have been initiated [13]. However, despite the high initial response rates, the long-term results for stage IV patients are still poor, and no clear correlation between initial response and survival can be seen.

RADIOTHERAPY

Neuroblastoma is a radiosensitive tumour [14] and therefore, local radiotherapy is used for treatment of stages III and IV. In stage III, the site of the primary tumour after surgery should be irradiated in patients with an expected EFS < 50%. Due to the high local relapse rate in patients with stage IV, the primary tumour site as well as single bone metastases should be irradiated. Irradiation should be given during concomitant chemotherapy. Some emergency situations may exist where irradiation might be helpful to stop tumour growth (i.e. imminent blindness owing to infiltration of the orbita, or paraplegia in case of intraspinal tumour, when a laminectomy cannot be performed).

MIBG (meta-iodobenzylguanidine) is a norepinephrine analogue which is selectively accumulated by the uptake-1 process in tumours of neural crest origin, such as neuroblastoma. When appropriately radiolabelled, MIBG can be used for scintigraphic imaging as well as treatment. For the latter, 131-Iodine has been linked to benzylguanidine. In a series of 47 patients treated with several courses of ^{131}MIBG, no permanent clinical benefit could be seen [15]. The role of MIBG in the conventional treatment of neuroblastoma is, therefore, not yet clear. Some authors suggest a frontline therapy with MIBG prior to chemotherapy [16]. However, further clinical results are necessary to assess the clinical benefit of this approach.

One of the side effects of high dose MIBG therapy is prolonged myelosuppression. MIBG has, therefore, been introduced into the myeloablative conditioning regimen prior to autologous stem cell transplantation. In a series of 7 patients, high dose MIBG was added to the conditioning regimen followed by autologous transplantation with peripheral stem cells [17]. A rapid and complete haematopoietic recovery was seen in these patients. It is difficult to judge the clinical benefit of high dose MIBG in this multimodal therapy regimen. However, there is a diagnostic value of the high dose MIBG prior to the myeloablative chemotherapy, since residual neuroblastoma tissue can be detected, which would not be seen with the conventional diagnostic MIBG scintigraphy [18].

Another therapeutic strategy for stage IV neuroblastoma is the use of radiolabelled antibodies directed against neuroblastoma cells. In a recent Phase I study, using 131-Iodine labelled anti-ganglioside GD2 antibody 3F8, 23 patients with refractory neuroblastoma were treated at various dose levels [19]. In 21 of the patients, a subsequent haematopoietic rescue with autologous bone marrow was performed. Some responses were seen in both soft tissue masses and bone marrow. However, longer clinical follow-up is necessary for the assessment of this treatment modality. The use of other antibodies, such as the chimeric anti-GD2 antibody ch 14.18 labelled with 186-Rhenium (R. Handgretinger, unpublished results) or the radiolabelled chimeric antibody chCE7 [20], is still in the preclinical evaluation phase.

HIGH DOSE CHEMOTHERAPY

While there is substantial experience of the use of high dose chemotherapy with subsequent stem cell rescue in stage IV neuroblastoma patients, its role is still not clear when compared with conventional therapy. Some reports favoured bone marrow transplantation (BMT) [21], whereas others failed to show a benefit of BMT compared with conventional therapy. However, dose intensification of induction and maintenance therapy has coincided, so that comparison with earlier historical data derived from less intensive chemotherapy might be misleading. When high dose chemotherapy was introduced for the treatment of stage IV neuroblastoma, haematological rescue with allogeneic bone marrow from siblings was initially performed. Owing to the higher morbidity and mortality rate associated with allogeneic BMT, there was no clinical benefit of allogeneic BMT [22]. Therefore, autologous stem cells are widely used for haematological rescue after high dose chemotherapy. In some clinical trials, double autograft protocols have been evaluated. This strategy was associated with severe side effects, and no clinical benefit was obtained [23]. Some investigators favour the use of total body irradiation (TBI) in the myeloablative regimen. However,

published data do not support this approach, since no improved outcome has been seen [24]. The role of purging autologous stem cells in order to remove contaminating tumour cells is not yet clear, since no randomised trials have been performed in order to answer this question. Several purging methods have been described, such as chemopurging [25] or immunomagnetic tumour cell depletion [26]. The disadvantage of most of the negative depletion methods is a prolonged haematopoietic recovery period after myeloablative therapy. In order to clarify the role of contaminating tumour cells, autologous bone marrow was transfected with marker genes prior to transplantation. Using this approach, Brenner and associates showed that relapses after high dose chemotherapy can originate from graft-contaminating tumour cells [27]. The risk of contaminating tumour cells was assumed to be lower when using peripheral blood stem cells (PBSC) as a stem cell source for autologous transplantation. However, using sensitive detection methods, tumour cells were still found in PBSC in a number of patients [28]. Therefore, the advantage of PBSC in terms of tumour cell contamination is not yet clear. However, one advantage of using PBSC compared with bone marrow is clearly the more rapid haematopoietic recovery [29], which is associated with a lower morbidity and mortality rate. Methods for tumour depletion of PBSC by positive stem cell selection methods (CD34 positive selection) have recently been introduced in the treatment of neuroblastoma. Preliminary results show a rapid haematopoietic recovery after autologous grafting with enriched CD34-positive progenitor cells (R. Handgretinger, unpublished results).

IMMUNOTHERAPY

Although improvements in survival of stage IV patients have been achieved by either intensive induction and maintenance chemotherapy or myeloablative therapy followed by autologous stem cell transplantation, the cure rate still remains poor. The tendency of stage IV neuroblastoma patients to relapse after achieving a complete remission is well known. Therefore, the aim of new therapeutic strategies should be to prevent relapse by an adjuvant therapy, which is also the purpose of maintenance therapy. Immunotherapy with monoclonal antibodies, cytokines, a combination of both, or other immunological approaches have been investigated in preclinical and clinical settings. Cytokines, such as interferon-beta and interferon-gamma, have already been investigated in combination with chemotherapy [30] or in a phase I trial in stage IV patients [31], respectively. No clinical benefit could be observed in these trials. Several trials with murine [32, 33] or chimeric [34] monoclonal antibodies, directed against the disialoganglioside GD2, have shown some clinical responses, including complete and partial remissions in resistant stage IV disease. The clinical role of lymphokine-activated killer (LAK) cells in combination with the infusion of the lymphokine interleukin 2 (IL-2) have been investigated by other authors [35, 36]. The side effects of these approaches, however, proved to be unacceptable. IL-2 was also administered in an adjuvant setting after ABMT [37]. Again, toxicity was high, and this approach was not recommended as an effective treatment strategy by the authors. Combinations of several factors, using either the chimeric monoclonal anti-GD2 antibody ch 14.18 in combination with the haematopoietic growth factor, granulocyte–macrophage colony stimulating factor (R. Handgretinger, unpublished data), or the murine anti-GD2 mAb 14.G2a in combination with IL-2, are in progress (P. Sondel, personal communication). Another approach could be the clinical use of genetically engineered fusion proteins consisting of monoclonal antibodies and cytokines. Some interesting results have been obtained in animal studies using a ch 14.18/IL-2 fusion protein [38].

It should be emphasised that immunotherapy of neuroblastoma is just beginning. It is clearly not a "magic bullet" for advanced or relapsed disease. However, this treatment modality could have a place in the context of conventional therapy of neuroblastoma with chemo- and radiotherapy. The optimal time for this therapeutic strategy may be the adjuvant setting at the stage of minimal residual disease.

CONCLUSIONS

The role of risk factors has been discussed extensively (this issue). It is clear that in the absence of "bad risk" biological factors, the intensity of therapy can be reduced to a certain extent. However, there are still many open questions regarding the treatment of high risk neuroblastoma patients. Intensive induction and maintenance therapy, including high dose chemotherapy, seem to improve the survival of the affected children. It is not yet clear, however, whether this approach will have a significant influence on the cure rate. In autologous stem cell transplantation, there is no evidence for a positive effect of the use of TBI, allogeneic BMT or autologous double-graft protocols. The effect of bone marrow purging or CD34 positive selection of PBSC on the clinical outcome still remains to be determined, although the data reported by Brenner and associates [27] argue for the further use of purging methods. The role of MIBG in the clinical setting is still unproven, and it remains an open question whether radiolabelled antibodies can do better than MIBG. The value of immunotherapeutic strategies, such as the use of antibodies, cytokines, a combination of both, or other immunological approaches, remains to be determined in clinical protocols. However, in order to answer these questions, randomised protocols are necessary. For this reason, large numbers of patients must be recruited for evaluation of the different therapeutic strategies. Therefore, international co-operative studies are necessary to answer at least some of the questions.

However, it can be anticipated, at least to a certain extent, that higher cure rates of stage IV neuroblastoma patients will only be achieved by a multimodality approach, combining all the described therapeutic strategies. In our hospital, we have, therefore, initiated a protocol consisting of induction chemotherapy according to the German national protocol followed by surgery. After cyclophosphamide and G-CSF-induced stem cell mobilisation, we positively select and cryopreserve CD34-positive haematopoietic progenitors. We then proceed to high dose MIBG therapy (in positive cases) and myeloablative chemotherapy, followed by rescue with autologous CD34-positive peripheral stem cells. After the transplantation, further adjuvant treatment with several courses of immunotherapy, using the chimeric mAB ch 14.18, are performed. In case of resistant metastasis, local radiotherapy is added. From the preliminary results, we can conclude that this multimodal approach is feasible without severe side effects. However, longer clinical follow-up is necessary to assess the effect on the cure rate of the patients.

1. Evans AE, D'Angio GJ, Randolph J. A proposed staging for children with neuroblastoma. Children's Cancer Study Group A. *Cancer* 1971, 27, 374–378.
2. Brodeur GM, Seeger RC, Barrett A, *et al.* International criteria for

diagnosis, staging, and response to treatment in patients with neuroblastoma. *J Clin Oncol* 1990, **18**, 368–389.
3. Berthold F, Harms D, Lampert F, Niethammer D, Zieschang J. Risk factors in neuroblastoma in infants. *Contrib Oncol*, 1990, **41**, 101–117.
4. Nakagawara A, Arima M, Azar CG, Scavarda NJ, Brodeur GM. Inverse relationship between *trk* expression and N-*myc* amplification in human neuroblastoma. *Cancer Res* 1992, **52**, 1364–1368.
5. Nakagawara A, Arima-Nakagawara M, Scavarda NJ, Azar CG, Cantor AB, Brodeur GM. Association between high levels of expression of the *trk* gene and favourable outcome in human neuroblastoma. *N Engl J Med* 1993, **328**, 847–854.
6. Christiansen H, Schestag J, Christiansen NM, *et al.* Clinical impact of chromosome-1 aberration in neuroblastoma. A metaphase and interphase cytogenetic study. *Genes Chrom Cancer* 1992, **5**, 141–149.
7. Strehl S, Ambros P. Fluorescence *in situ* hybridization combined with immunohistochemistry for highly sensitive detection of chromosome 1 aberrations in neuroblastoma. *Cytogenet Cell Genet* 1993, **63**, 24–28.
8. Finklestein JZ, Klemperer MR, Evans AE, *et al.* Multiagent chemotherapy for children with metastatic neuroblastoma: a report from Children's Cancer Study Group. *Med Pediat Oncol* 1979, **6**, 179–188.
9. Nitschke R, Cangir A, Crist W, Berry DH. Intensive chemotherapy for metastatic neuroblastoma: a Southwest Oncology Group Study. *Med Pediat Oncol* 1980, **8**, 281–288.
10. Carlsen NLT, Schroeder H, Bro PV, *et al.* Neuroblastomas treated at the four major oncologic clinics in Denmark 1943–1980: an evaluation of 180 cases. *Med Pediat Oncol* 1985, **13**, 180–186.
11. Pinkerton CR, Zucker JM, Hartmann O, *et al.* Short duration, high dose alternating chemotherapy in metastatic neuroblastoma (ENSG 3C induction regimen). The European Neuroblastoma Study Group. *Br J Cancer* 1990, **62**, 319–323.
12. Kushner BH, O'Reilly RJ, LaQuaglia M, Cheung NK. Dose-intensive use of cyclophosphamide in ablation of neuroblastoma. *Cancer* 1990, **66**, 1095–1100.
13. Pritchard J, Whelan R, Hill BT. Sequential cisplatinum and VM26 in neuroblastoma: laboratory and sequential (OPEC regimen) studies. *Prog Clin Biol* 1985, **365**, 545–556.
14. Deacon JM, Wilson PA, Peckham MJ. The radiobiology of human neuroblastoma. *Radiat Oncol* 1985, **3**, 201–209.
15. Klingebiel T, Berthold F, Treuner J, *et al.* Metaiodobenzylguanidine (MIBG) in treatment of 47 patients with neuroblastoma: results of the German neuroblastoma trial. *Med Pediat Oncol* 1991, **19**, 84–88.
16. De Kraker J, Hoefnagel CA, Caron H, *et al.* Targeted radiotherapy with iodine-131-meta-iodobenzylguanidine (MIBG) as first line treatment of neuroblastoma advanced disease patients. *Med Pediat Oncol* 1994, **3**, 179 (abstract).
17. Klingebiel T, Handgretinger R, Herter M, *et al.* Peripheral stem cell transplantation in neuroblastoma stage IV with the use of ^{131}I-MIBG. *Prog Clin Biol Res* 1994, **385**, 309–317.
18. Klingebiel T, Reuland P, Feine U, *et al.* High dose ^{131}I-Iodobenzylguanidine (MIBG) as a diagnostic instrument for neuroblastoma stage IV. *Med Pediat Oncol* 1991, **19**, 416.
19. Cheung NKV, Yeh SDJ, Kushner BH, *et al.* Phase I study of radioimmunotherapy of neuroblastoma using iodine 131 labeled 3F8. *Prog Clin Biol Res* 1994, **385**, 328.
20. Novak-Hofer I, Amstutz HP, Haldemann A, *et al.* Radioimmunolocalization of neuroblastoma xenografts with chimeric antibody chCE7. *J Nucl Med* 1992, **33**, 231–236.
21. Pritchard J, Germond D, Jones D, deKraker J, Love S. Is high dose melphalan of value in treating advanced neuroblastoma? Preliminary results of a randomized trial by the European Neuroblastoma Study Group. *Proc Am Soc Clin Oncol* 1986, **5**, 205.
22. Matthay KK, Seeger RC, Reynolds CP, *et al.* Comparison of autologous and allogeneic bone marrow transplantation for neuroblastoma. *Prog Clin Biol Res* 1994, **385**, 301–307.
23. Zucker JM, Philip T, Bernard JL, *et al.* Single or double consolidation initial therapy in metastatic neuroblastoma: first results of LCME 3 study in 40 patients. *Bone Marrow Transplant* 1991, **7** (Suppl. 2), 91.
24. Vitale V, Franzone P. The role of TBI in conditioning regimens for children. *Bone Marrow Transplant* 1991, **7** (Suppl.3), 32–34.
25. Beaujean F, Hartmann O, Benhamou E, Lemerle J, Duedari N. Hemopoietic reconstitution after repeated autologous transplantation with mafosfamide-purged marrow. *Bone Marrow Transplant* 1989, **4**, 537–541.
26. Kemshed JT, Heath L, Gibson FM, *et al.* Magnetic microspheres and monoclonal antibodies for the depletion of neuroblastoma cells from bone marrow: experiences, improvements and observations. *Br J Cancer* 1986, **54**, 771–778.
27. Brenner MK, Rill DR, Holladay MS, *et al.* Gene marking to determine whether autologous marrow infusion restores long-term haematopoiesis in cancer patients. *Lancet* 1993, **342**, 1134–1137.
28. Moss TJ, Cairo M, Santana VM, *et al.* Clonogenicity of circulating neuroblastoma cells: implications regarding peripheral blood stem cell transplantation. *Blood* 1994, **83**, 3085–3089.
29. Handgretinger R, Klingebiel T, Baden B, *et al.* Stem cell mobilization, collection and transplantation in patients with pediatric tumors. *Cancer Res Therapy and Control* 1992, **3**, 43–48.
30. Berthold F, Burdach S, Kremens B, *et al.* The role of chemotherapy in the treatment of children with neuroblastoma stage IV: the GPO (German Pediatric Oncology Society) experience. *Klin Pädiatr* 1990, **202**, 262–269.
31. Evans A, Main E, Zier K, *et al.* The effects of gamma interferon on the natural killer and tumour cells of children with neuroblastoma. *Cancer* 1989, **64**, 1383–1387.
32. Cheung NKV, Lazarus H, Miraldi FD, *et al.* Ganglioside GD 2 specific monoclonal antibody 3F8: a phase I study in patients with neuroblastoma and malignant melanoma. *J Clin Oncol* 1987, **5**, 1430–1440.
33. Handgretinger R, Bader P, Dopfer R, *et al.* A phase I study of neuroblastoma with the anti-ganglioside GD2 antibody 14.G2a. *Cancer Immunol Immunother* 1992, **35**, 199–204.
34. Handgretinger R, Anderson K, Lang P, *et al.* A phase I study of neuroblastoma with the human/mouse chimeric anti-ganglioside GD2 antibody ch 14.18. *Eur J Cancer* 1995, **31**, 261–267.
35. Negrier S, Michon J, Floret D, *et al.* Interleukin-2 and lymphokine-activated killer cells in 15 patients with advanced metastatic neuroblastoma. *J Clin Oncol* 1991, **9**, 1363–1370.
36. Favrot MC, Michon J, Floret D, *et al.* Interleukin-2 immunotherapy in children with neuroblastoma after high-dose chemotherapy and autologous bone marrow transplantation. *Pediat Hematol Oncol* 1990, **7**, 275–284.
37. Michon J, Negrier S, Coze C, *et al.* Administration of high-dose recombinant interleukin 2 after autologous bone marrow transplantation in patients with neuroblastoma: toxicity, efficacy and survival. A Lyon–Marseille–Curie-East of France Group study. *Prog Clin Biol Res* 1994, **385**, 293–300.
38. Sabzevari H, Gillies SD, Mueller BM, *et al.* A recombinant antibody—interleukin 2 fusion protein suppresses growth of hepatic human neuroblastoma metastases in severe combined immunodeficiency mice. *Proc Natl Acad Sci USA* 1994, **91**, 9626–9630.